Submission on behalf of the British Transplantation Society

for the

National Institute for Health and Clinical Excellence Health Technology Appraisal entitled:

Machine perfusion systems and solutions for cold (static) storage of donated kidneys

Summary

Effective preservation of kidneys following removal from an organ donor is essential for safe transplantation. The British Transplantation Society welcomes the appraisal of preservation technology by NICE. In this submission the BTS aims to provide some practical background to the practice of organ retrieval and preservation as it currently happens.

The BTS would like to make three recommendations for NICE in undertaking this appraisal:

1. Careful consideration should be taken of the implications that any recommendations regarding the preservation of kidneys might have on the preservation of other organs for transplantation, in particular the liver and pancreas.

2. The appraisal should not consider the preservation of kidneys from live donors.

3. The appraisal should await publication of the full results of the European and UK studies of machine perfusion.

[redacted]

1 Background

In this submission the British Transplantation Society aims to inform the Appraisal of the current practice in the UK, and how renal preservation techniques impact on the preservation of other organs in particular liver and pancreas. The Society has no view as to the most appropriate method for storage of donated kidneys, but wishes to identify important considerations that need to be taken into account by the Appraisal Committee. The Society makes no attempt to review the available literature on the subject. We do provide data from UK Transplant that aims to illustrate current practice and outcomes. UK Transplant is a section of NHS Blood and Transplant that is charged with coordinating transplantation in the UK. It keeps records of all the transplants performed in the UK, and we are grateful for their cooperation and in particular to [redacted] for providing the analyses that we requested.

1.1 The donation process

There are two types of organ donor, live donors and deceased donors.

1.1.1 Live kidney donors

In live donation the kidney is removed from a live person and transplanted quickly into the recipient with a short period of ischaemia of just minutes or hours. There is little evidence about the best method of storing live donor kidneys because they usually have immediate excellent function no matter how stored. Most centres flush the kidney with either Marshall's solution (Soltran) or UW solution (ViaSpan) and place the kidneys in ice-cold solution until transplantation.

The Society recommends that the appraisal does not consider storage of kidneys from Live Donors.

1.1.2 Deceased kidney donors

A deceased organ donor is one who has been certified as dead either by brain stem criteria (Donation after Brain Death, DBD) or following cardiac arrest (Donation after Cardiac Death, DCD). A DBD donor (also know as a heart-beating donor) has blood flowing to the kidneys up to the moment of retrieval. A DCD donor (also referred to as a non-heart-beating donor) has no blood flowing from the time of cardiac arrest to the time of retrieval, often many minutes.

1.1.3 Extended Criteria Donors

There is a great shortfall in organs for transplantation, and survival on dialysis is poorer than survival following transplantation. Therefore transplant clinicians will use kidneys that they believe will function well in the recipient, but acknowledge that some kidneys will function better than others. Hence a kidney from a fit 18 year old who died from a head injury would be expected to work better than one from an elderly hypertensive diabetic who died from an intracerebral haemorrhage. The term "extended criteria donor" (ECD) has been used to identify a donor with an anticipated poor outcome. An ECD has been defined as a donor over the age of 60, or one over 50 with a history of hypertension, death by intracranial haemorrhage, or a baseline creatinine over 1.5mg/dL (133µmol/L).

It is possible that ECD donor kidneys are more prone to ischaemic damage than non-ECD kidneys, and might be more sensitive to preservation techniques than "standard" criteria donors. It is noteworthy that DCD kidneys are not defined as ECD kidneys.

1.2 The ischaemic period

The process of renal transplantation involves removing a kidney from the donor and transplanting it into a recipient. This entails a period when the kidney is deprived of its blood supply, termed ischaemia. During ischaemia the metabolism of the kidney proceeds; lack of oxygen supply causes aerobic cellular metabolism to switch to an energy-greedy anaerobic metabolism. As ischaemia progresses the energy resources of the organ are depleted and cellular damage occurs. The damage sustained during the ischaemic period manifests as delayed return to function of the organ following transplantation, and occasionally as a failure to resume any worthwhile function. Other factors also contribute, such as donor age and cause of death. The process of ischaemia can be slowed dramatically by cooling the organ to 4°C, at which point anaerobic metabolism proceeds at a very slow rate.

1.3 Organ preservation

Preservation is necessary to allow time for identification of the appropriate recipient, transport of the kidney to the recipient, preparation of the recipient for surgery, and implantation of the kidney. This can be achieved either through static cold storage or utilisation of cold machine perfusion.

1.3.1 Preservation solutions

Two solutions are used commonly in the UK, Marshall's Hypertonic (hyperosmolar) Citrate Solution (Soltran, Baxters) and University of Wisconsin Solution (UW solution, ViaSpan, Bristol Myers Squibb). Other solutions are available, but are more widely used in Europe and the USA. These include Histidine-Tryptophan-Ketoglutarate solution (HTK solution, Custodiol) and Celsior, both of which have some efficacy as liver preservation solutions.

Typical usage would involve 8 litres of preservation solution per donor, allowing for fluid required to flush the organs and fluid in which to pack the organs for storage.

1.3.2 Preservation machines

The Organ Recovery Systems (ORS) LifePort machine is the most commonly used machine in the UK and contains a single kidney; the Waters RM3 machine is less commonly used and can perfuse two kidneys at once. The ORS LifePort can be set up and left to run unattended; the RM3 requires more supervision with attendant costs. Preservation solutions used for machine perfusion are the University of Wisconsin Machine Preservation Solution (**not** the same as ViaSpan), currently marketed by ORS as KPS1. The donor kidney is first flushed *in situ* during retrieval before removal and placing in the machine perfusion preservation solution. The aortic flush solution could be any other preservation solution, but in the UK would typically be UW solution or Marshall's solution.

1.4 Implications of kidney preservation solutions on other donor organs

In the organ donor at the time of retrieval, the donor aorta is cannulated and cold preservation fluid is passed through it into the abdominal organs that will be used for transplantation, namely the kidneys, liver, pancreas and occasionally intestine. The heart and lungs are preserved using different solutions. Whatever solution passes through the aorta to perfuse the kidneys will also perfuse the other organs. While Marshall's is a good kidney preservation solution it is not safe for extended preservation of the liver or pancreas or intestine.

2 Current practice

In the UK in the last financial year (2006-07) there were 793 solid organ donors; 634 DBD and 159 DCD. Table 1 shows the usage of organs per donor. The majority of donors donate liver and kidneys; one third also donate a pancreas.

Table 1. Solid organ donors in the UK, 1/4/06 to 31/3/07.
Source: UK Transplant Activity Report 2006-2007

	Donation after Brain Death	Donation after Cardiac Death
Total number of donors	634	159
Kidney donors	609	156
Liver donors	586	50
Pancreas donors	239	5

Where a donor donates kidney and liver but not pancreas it is common for Marshall's solution to be used, with the liver flushed after removal with UW solution to wash out the Marshall's and replace it with a liver preservation fluid. The pancreas cannot be flushed on the back table to replace the Marshall's with UW, therefore where a pancreas is donated UW solution is used as the aortic flush solution. The liver then needs no further back table flushing and the total volume of preservation fluid used is thus reduced.

Table 2 illustrates that in the UK livers for transplantation are preserved in UW solution, whether from DCD or DBD donors. Table 3 shows that the majority of kidneys for transplantation are initially preserved with Marshall's solution (74%), with the remainder using UW solution (23%). DBD kidneys are allocated nationally so most kidneys are transported remote from the retrieving centre; such kidneys tend not to be machine perfused (Table 4). In contrast both kidneys from DCD donors are retained locally for transplantation in an effort to reduce the ischaemic time. Machine perfusion is more commonly used for DCD kidneys.

Table 2. Preservation solution usage for liver transplants in the UK (2000-2007)
Source: UK Transplant

	Preservation solution		
	UW Solution	Others / Not reported	Total
Donor Type			
DBD donors (Heart beating)	4918	53	4971
DCD donors (Non-Heart beating)	166	4	170
All	5084 (98.9%)	57 (1.1%)	5141

Table 3. Preservation solutions used for kidney transplants in the UK (2000-2007)
Source: UK Transplant

	Donor Type						All Deceased Donors	
	Extended Criteria DBD Donors		Standard Criteria DBD Donors		DCD (Non-Heartbeating) Donors			
	N	%	N	%	N	%	N	%
Preservation Solution								
Marshall's	3158	84	3758	72	567	48	7483	74
UW Solution	488	13	1354	26	497	42	2339	23
Other solution	82	2	97	2	64	5	243	2
Not reported	29	1	19	(0.4)	60	5	108	1
Total	3757	100	5228	100	1188	100	10173	100

Note: More Standard criteria kidneys are perfused using UW solution because these donors are more likely to be pancreas donors, which necessitates the use of UW rather than Marshall's solution.

Table 4. Reported cold machine perfusion usage for kidney transplants in the UK (2000-2007)
Source: UK Transplant

	Donor Type						All Deceased Donors	
	Extended Criteria DBD Donors		Standard Criteria DBD donors		DCD (Non-Heartbeating) Donors			
	N	%	N	%	N	%	N	%
Donors Machine Perfused								
Yes	14	(0.4)	15	(0.3)	112	9	141	1
No	3179	85	4371	84	480	40	8030	79
Not reported	564	15	842	16	596	50	2002	20
Total	3757	100	5228	100	1188	100	10173	100

Note: Very few kidneys were subject to machine preservation, although it is possible that many of the "not reported" group were machine preserved, making comparisons unreliable.

3 Effect of preservation method on outcome of kidney transplants in the UK

For the purposes of this submission, [redacted] and colleagues at UK Transplant modelled the effects of different variables on outcome of kidney transplants in the UK between 2000 and 2007. During this period 10173 first and repeat kidney only transplants were performed in adult and paediatric patients. Excluding cases with no follow-up (n=376) or where cold ischaemic time was missing (n=139) or where UW or Marshalls were not used/confirmed (n=269), 9389 transplants were analysed.

Table 5. Cox regression model for one year graft survival[1] of all deceased donor kidney only transplants in adult and paediatric patients in the UK, 2000-2007

Factor	Factor Level [baseline]	p-value	Hazard Ratio	95% Hazard Ratio Confidence Limits	
Preservation solution	[UW]		1.00		
	Marshalls	0.75	1.03	0.84	1.27
Machine perfusion	[No]		1.00		
	Yes	0.42	1.28	0.70	2.34
	Unknown	0.68	0.96	0.79	1.17
Donor type	[Standard criteria DBD (HBD)]		1.00		
	Extended criteria DBD (HBD)	0.08	1.23	0.98	1.54
	DCD (NHBD)	0.14	1.25	0.93	1.67
Donor Age	Linear	<0.0001	1.02	1.01	1.02
HLA mismatch level	[1 – 000]		1.00		
	2 – 0DR & 0/1Bmm	0.41	1.10	0.88	1.37
	3 – (0DR & 2B) or (1DR & 0/1Bmm)	0.15	1.19	0.94	1.51
	4 – (1DR & 2B) or (2DRmm)	0.08	1.32	0.97	1.80
Cold ischaemic time (hrs)	Linear	0.0007	1.02	1.01	1.03
Effects of recipient age, year of graft and graft number were also accounted for					

[1] Censored for death with functioning graft

Observations from these results:

- Comparing with standard criteria DBD donors as the baseline group, DCD donor kidneys had similar outcome (Relative Risk (RR) = 1.2, p=0.14), while extended criteria DBD donor kidneys had inferior outcome that reached significance only at the 8% level (RR=1.2). This is after accounting for donor age, which was fitted as an additional linear effect because it was highly significant despite being partially taken account of in the ECD criteria. The weak effect of ECD is attributable to a combination of weak effects with regard to hypertension, cerebrovascular accident and serum creatinine, none of which were more important prognostic factors than the others.

- Machine perfusion was not significantly related to outcome (RR for machine perfusion versus no machine perfusion = 1.3, p=0.4). But note the extent of missing data for machine perfusion (Table 4).

- There was no significant difference between UW and Marshalls (RR for Marshalls = 1.03, p=0.8).

In addition, an interaction term was fitted for preservation solution * HLA levels 3-4 as there appeared to be an association between HLA mismatch and preservation solution. This showed a significantly inferior outcome for HLA levels 3 and 4 vs 1 and 2 only when UW was used.

A similar interaction term for preservation solution * NHBD (yes/no) was non-significant.

There was also some evidence that the cold ischaemic time effect was stronger (and only significant) in the Marshall's group.

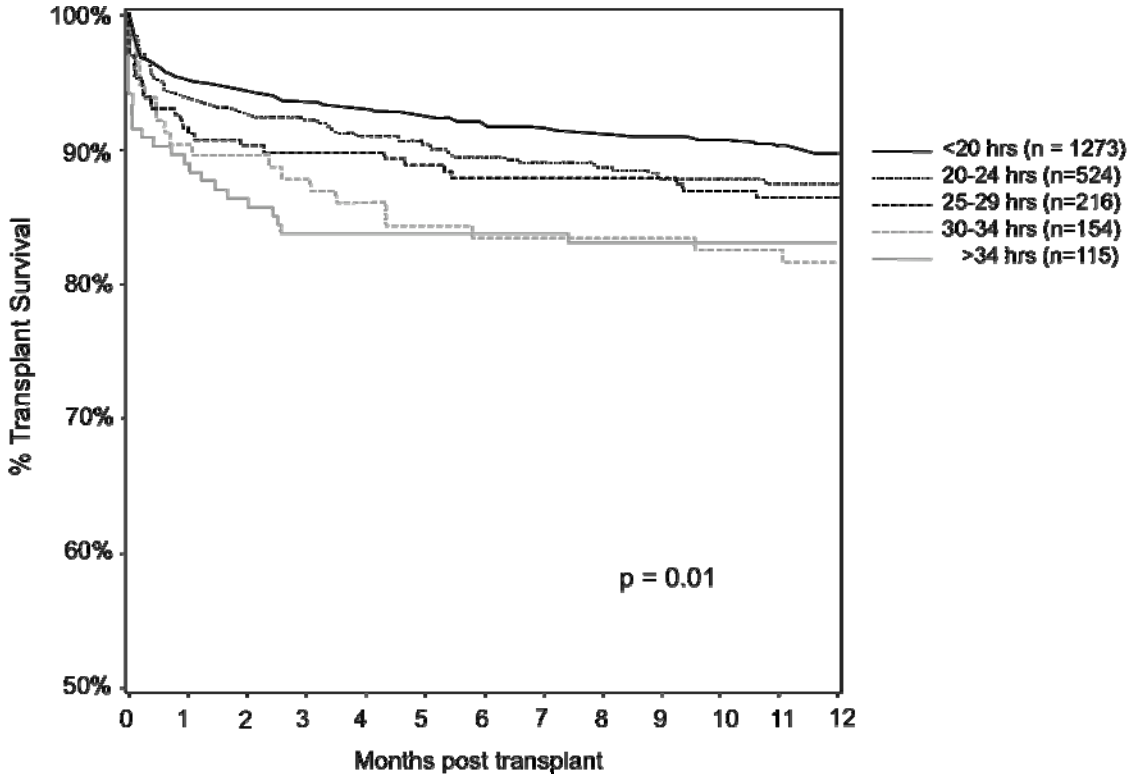
4 Important considerations in performing an appraisal of cold preservation of kidneys

4.1 Preservation time

4.1.1 Effect of ischaemic time on graft outcome in the UK

Increasing ischaemic time has a deleterious impact on kidney transplants. In particular contemporary UK data show that ischaemic times over 20 hours are associated with significantly poorer outcome (figure 1), (approximated by a simple linear effect in table 5).

Figure 1. Transplant survival[1] for kidneys in the UK 1/2000 to 6/2002 according to cold ischaemic time
Source: UK Transplant

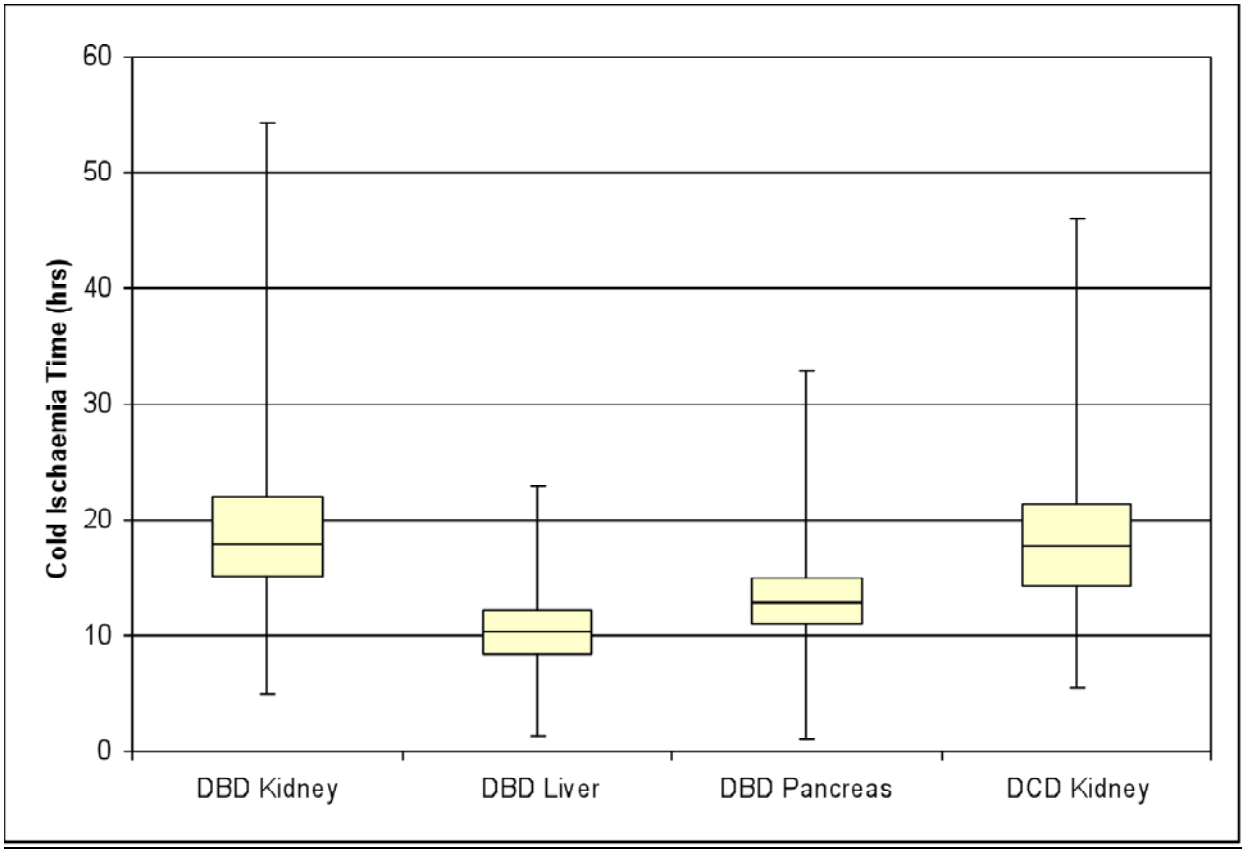


[1] Death with function counted as graft failure

4.1.2 Current ischaemic times for deceased donor organs in the UK

In evaluating preservation solutions it is important to evaluate their efficacy within the range of preservation times normally encountered in the UK. Hence just because one solution is as effective as another for 12 hours cold ischaemia does not mean they are as efficacious over 24 hours. Figure 2 details the ischaemic times commonly encountered for the different abdominal organs in the UK. Appendix 1 contains the raw data. The appraisal should consider efficacy of preservation at the ischaemic times currently experienced in the UK.

Figure 2. Box and whisker plot showing median, interquartile range (boxes) and range of cold ischaemic times for different solid organs in the UK, 2000-07.
Source: UK Transplant



4.2 Contemporaneous and historic data

Much of the data relating to machine perfusion, and comparing Marshall's solution with UW solution, relates to transplant practices in the 1980s and early 1990s. This was an era when renal transplant survival was much inferior to today, with 70% one year graft survival compared to the 90% figure of today. The whole practice of transplantation has changed and evolved, and great care should be exercised before using historic data to influence current practice. For example in a recent review of machine preservation[1] data spanning 30 years were considered, although the authors commented on the limitations of such data.

With respect to machine perfusion there are two large studies due to report within the next 12 months that should provide reliable evidence upon which the appraisal should base its recommendations. One is from Eurotransplant looking at both DBD and DCD donor kidney transplants, the other from the United Kingdom looking solely at DCD donor kidney transplants.

The society recommends that the NICE await publication of the full results from the European and UK studies of machine perfusion before completing the appraisal of these technologies.

[1] The clinical and cost-effectiveness of pulsatile machine perfusion versus cold storage of kidneys for transplantation retrieved from heart-beating and non-heart-beating donors. Wight J, Chilcott J, Holmes M, Brewer N. Health Technology Assessment 2003; 7(25).

4.3 Implications of the Ministerial Taskforce on Organ Donation

On 16th January 2008 the Secretary of State for Health, Mr Alan Johnson, announced that the recommendations of the Organ Donation Taskforce first report, "Organs for Transplants", had been accepted and would be implemented. Recommendation 10 stated

> *"A UK-wide network of dedicated organ retrieval teams should be established to ensure timely, high-quality organ removal from all heartbeating and nonheartbeating donors. The Organ Donation Organisation should be responsible for commissioning the retrieval teams and for audit and performance management.*

The implications of this recommendation are that retrieval of organs will be commissioned by UK Transplant. This would mean that the practicalities of moving machines around the country would become easier, since they may no longer be the property of the purchasing hospital, but rather purchased as part of the commissioned retrieval service.

5 Appendix 1.

Table 6. Cold Ischaemic Times (hrs) for Adult & Paediatric Kidney only transplants from Heartbeating Donors in the UK in 2000-2007

Year of Transplant	Total Number of Transplants	Total Number of transplants with valid CIT	Median	Interquartile Range	Minimum	Maximum
2000	1276	1198	18.7	15.9 - 23.1	6.2	47.2
2001	1277	1267	18.8	16.0 - 23.2	6.3	50.1
2002	1201	1196	18.5	15.8 - 22.9	5.5	54.4
2003	1134	1119	18.6	15.9 - 22.5	5.1	48.1
2004	1211	1207	18.4	15.8 - 22.6	5.3	45.4
2005	996	988	17.4	14.8 - 21.1	6.8	48.0
2006	991	983	16.4	13.8 - 19.9	5.2	43.8
2007	899	834	16.5	14.1 – 20.0	6.3	44.2
All Years	**8985**	**8792**	**18.0**	**15.3 – 22.0**	**5.1**	**54.4**

Cold Ischaemia Times have been taken as valid in the range 5 hours to 60 hours

Table 7. Cold Ischaemic Times (hrs) for Adult & Paediatric Liver only transplants from Heartbeating Donors in the UK in 2000-2007

Year of Transplant	Total Number of Transplants	Total Number of transplants with valid CIT	Median	Interquartile Range	Minimum	Maximum
2000	651	634	11.0	8.8 – 13.1	2.8	21.2
2001	662	645	10.8	8.8 – 12.9	2.1	20.0
2002	681	654	10.5	8.6 – 12.6	2.2	19.7
2003	606	592	10.6	8.7 – 12.4	2.5	20.5
2004	676	621	10.7	8.7 – 12.3	1.4	20.4
2005	555	549	9.6	7.8 – 11.5	2.0	23.0
2006	584	581	9.8	8.1 – 11.4	2.2	17.6
2007	556	463	9.6	7.7 – 11.2	1.9	16.7
All Years	**4971**	**4739**	**10.4**	**8.4 – 12.2**	**1.4**	**23.0**

Cold Ischaemia Times recorded as less than 1 hour have been coded as missing

Table 8. Cold Ischaemic Times (hrs) for Adult & Paediatric Pancreas & Kidney/Pancreas transplants from Heartbeating Donors in the UK in 2000-2007

Year of Transplant	Total Number of Transplants	Total Number of transplants with valid CIT	Median	Interquartile Range	Minimum	Maximum
2000	32	0				
2001	47	28	11.8	10.0 – 13.8	2.3	19.0
2002	60	37	12.8	11.5 – 14.3	6.2	23.0
2003	54	35	13.0	11.0 – 15.0	1.1	22.0
2004	79	51	13.2	12.0 – 15.0	8.9	21.3
2005	116	104	13.5	11.2 – 15.8	1.7	23.6
2006	160	153	13.0	10.8 – 15.0	6.0	23.0
2007	219	156	12.4	10.7 – 15.2	4.0	33.0
All Years	**767**	**564**	**12.9**	**11.0 – 15.0**	**1.1**	**33.0**

Cold Ischaemia Times recorded as less than 1 hour have been coded as missing

Table 10. Cold Ischaemic Times (hrs) for Adult & Paediatric Kidney transplants from Non-heartbeating Donors in the UK (2000-2007)

Year of Transplant	Total Number of Transplants	Total Number of transplants with valid CIT	Median	Interquartile Range	Minimum	Maximum
2000	47	44	18.6	14.9 – 21.1	8.5	27.9
2001	56	56	17.4	13.8 – 22.9	7.0	41.3
2002	85	85	19.1	16.0 – 24.0	6.8	33.5
2003	112	112	18.1	14.0 – 23.0	8.7	30.5
2004	147	144	17.4	14.5 – 21.9	8.6	42.4
2005	200	200	18.0	14.9 – 22.0	5.8	36.4
2006	250	248	17.6	13.8 – 20.5	5.5	46.0
2007	291	270	16.9	13.7 – 20.7	6.3	39.0
All Years	**1188**	**1159**	**17.8**	**14.3 – 21.4**	**5.5**	**46.0**

Cold Ischaemia Times have been taken as valid in the range 5 hours to 60 hours