

The cost effectiveness of organ retrieval using *in situ* normothermic regional perfusion (NRP) for liver transplantation

What were we asked to look at?

A consultant surgeon and a commissioning team from NHS Blood and Transplant (NHSBT) asked us to look at the cost effectiveness of employing normothermic regional perfusion (NRP) during liver graft retrieval in organ donors following circulatory death.

Why is this important?

The number of successful liver transplantations is limited by a shortage of viable donor organs. Waiting list pressure has led to the use of grafts at higher risk of failure. Livers donors after circulatory death (DCD) are one such high risk category and have been associated with poor transplant outcomes. Standard retrieval techniques can damage donor livers which could make them unsuitable for transplantation or increased complications post-transplantation. Our analysis assesses whether the incremental cost of using NRP to retrieve donor livers is economically justified in view of its potential to improve liver outcomes.

What was our approach?

We conducted a cost-effectiveness analysis of the costs and transplantation outcomes associated with NRP retrieval of liver grafts compared with standard retrieval. The analysis is based on data from two UK transplant centres.

What next?

NHSBT will use the findings of this work to inform their business case for expanding the provision of NRP on a UK-wide level.

Key findings

- The use of normothermic regional perfusion (NRP) during organ retrieval offers several advantages including increasing the time available for a successful retrieval, improved quality and function of organs donated after circulatory death (DCD organs), and decreased risk of graft failure.
- Based on data available from two UK transplant centres, NRP appears to dominate standard DCD retrieval. This means that NRP is less costly and more effective in terms of the number of surviving patients, than standard DCD retrieval. This is primarily because, compared to standard DCD, the additional equipment and staffing costs associated with NRP retrieval are recovered through lower rates of re-transplantation and fewer post-transplant complications.
- The model estimated that for every 100 NRP retrievals, there would be four cases of death due to post-transplant complications, 69 cases of graft survival and 0.1 cases of death after re-transplantation at a total cost of approximately £2.38 million. In comparison, for every 100 standard DCD retrievals, there would be six cases of death due to post-transplant complications, 62 cases of graft survival and 0.67 cases of death after re-transplantation at a total cost of approximately £3.55 million.
- The model was sensitive to small increases to the proportion of patients experiencing post-transplant complications, but was not sensitive to the additional costs of implementing NRP.
- The key sources of uncertainty were the small sample sizes upon which the clinical evidence was based, limited data on the probability of death associated with many of the post-transplant complications and structural limitations of the model which necessitated simplifying assumptions.

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Introduction

The ability to perform transplant surgery on patients who require it depends on the availability of suitable donor organs. Deceased patients can be classed as donors due to brain death (DBD) or donors due to circulatory death (DCD). While DCD organ donation increases the total number of liver transplants that can be performed, patients transplanted with DCD livers are more likely to experience post-transplant graft failure and/or mortality (compared with patients transplanted with a DBD liver)¹.

In current clinical practice, DCD retrieval entails the immediate perfusion of organs with cold fluids and solutions. Time is imperative during DCD organ retrieval, but hasty retrieval also increases likelihood of surgical damage to the organ, which may affect organ functionality in the transplant recipient, or in some cases may render the organ unsuitable for transplantation at all.

Normothermic regional perfusion (NRP) is intended to increase the availability and viability of DCD organs, and therefore has the potential to improve patients' lives for those who receive transplants and those who might otherwise die because no viable organ is found in time for them. This Evidence Synthesis examines the cost effectiveness of DCD liver retrieval using NRP compared to the current standard (cold) retrieval procedure; in terms of cost per surviving transplant recipient.

Health technology description

NRP is a technique to restore the circulation to the abdominal and cardiothoracic organs following circulatory arrest for the purpose of transplantation. The system warms and oxygenates the donor's own blood and circulates it around their body, ensuring the organs are well perfused so that they do not deteriorate. NRP continues for around two hours after death following which the organs are cooled down and removed. NRP is an alternative to (cold) perfusion of the organs immediately after death.

NRP uses a machine to perfuse the donor, with disposable consumables, drugs and fluids. In addition, the retrieval team will use a machine to monitor the donor's blood gases, and another machine to test the liver and kidney function. The latter requires a member of the team to run the organ function tests every 30 minutes, so one member of staff is required to oversee this function, freeing up the organ preservation practitioner to oversee perfusion.

NRP is expected to impact upon:

- *Timeliness* - time is of the essence in DCD organ retrievals which can lead to increased rates of surgical damage, impacting on the organ function and in some cases of severe, non-repairable damage, leading to an organ being rendered unsuitable for transplantation. NRP extends the timeframe of a DCD organ retrieval; this makes it comparable to the length of a DBD organ retrieval.
- *Quality* - Once NRP has been initiated, cell deterioration is reversed with no expected subsequent adverse effects on organ quality. This means a DCD liver retrieved using NRP is comparable to a DBD liver in terms of quality. This is expected to impact on the likelihood of patients experiencing complications associated with DCD livers, such as ischaemic cholangiopathy (IC) and primary non-function (PNF).
- *Assessment* - NRP enables the retrieval surgeon to assess blood gas and biochemical markers that indicate the quality of the organ and whether the function will be affected. Better assessment may lower the risks of transplanting an unsuitable organ, and of re-transplantation or death due to complications.
- *Availability of Organs* - Improving the quality and function of livers means that livers - which were previously deemed non-transplantable due to poor function - can be utilised. Currently around 6% for patients who receive a 'standard' (ie non-NRP) DCD liver are re-listed onto the waiting list within one year after the procedure. Using a technique with lower rates of re-transplantation also means the organs that would have needed to be used in re-transplantation are available to other recipients on the waiting list. In addition, NRP enables transplant centres to consider donors with warm ischaemic time (time from systolic <50 mmHG to aortic perfusion) up to 60 minutes instead of the current 30 minute limit.
- *Efficiency* - Although there are costs associated with NRP (higher consumables and workforce costs), these need to be compared with the costs of re-transplantation and treating post-transplant complications. Re-transplantation takes a significant toll on the recipient, and leads to fewer organs available for transplantation.

Clinical effectiveness

Due to the quick turnaround time requested by the topic referrers it was not possible to undertake a formal literature search. Instead, clinical effectiveness data was acquired from a UK based cohort study as detailed below.

UK based cohort study

A service evaluation of the NRP programme was conducted at two UK transplant centres (Edinburgh and Cambridge) beginning in 2011. SHTG were supplied (academic in confidence)

results of an aggregate analysis based on prospective data from these two pilot centers until June 2017. The results of this analysis have since been published.²

The study used prospectively collected data collated from the UK Transplant Registry and hospital records of patients undergoing transplantation using livers recovered from DCD donors after a period of NRP. The retrospective analysis assessed whether NRP was associated with improved outcomes for livers transplanted from DCD donors. NRP was considered when trained staff were available at the transplant center and only in cases of controlled circulatory death (i.e. planned withdrawal of life-sustaining treatments from critically ill patients). Hence, the findings of this study may not apply to the wider use of NRP retrieval outwith the hospital environment and in donors experiencing uncontrolled circulatory death.

NRP was performed on 70 DCD donors from which 43 livers were transplanted. These were compared with 187 non-NRP DCD donor livers transplanted at the same two UK centres over the same period. Livers from 27 NRP donors were not used for reasons including abnormal liver appearance, rising alanine transaminase levels and prolonged withdrawal period. Differences in donor demographics and timings are presented in Table 1.

Table 1 – Donor demographics and donation data

	Comparator cohort (n=187)	NRP liver cohort (n=43)	P value
Mean Age (SD)	50 (11-76)	41 (16-69)	.1317
Cause of death; n (%)			.5358
<i>Head injury</i>	23 (12%)	10 (23%)	
<i>Hypoxia</i>	69 (37%)	12 (28%)	
<i>Cerebrovascular accident</i>	90 (48%)	20 (47%)	
<i>Other</i>	5 (3%)	1 (2%)	
Cold ischemic period; mins (95% CI)	444 (395-493)	382 (303-502)	.0035
Preservation period; mins (95%CI)	444 (395-493)	510 (423-631)	.0008
Transplant centre performing donor organ recovery; n (%)	102 (55%)	40 (93%)	<.0001

Liver recipients in each cohort were of similar age, severity of liver disease and had similar indications for transplantation. Key differences in recipient outcomes were as follows:

- Based on the two centres' data and taking into account their significant experience in using NRP, DCD livers from donors where NRP was used were more likely to be transplanted than when NRP was not used. Only five (12%) of the NRP livers suffered damage during retrieval compared to 48 (26%) of the non-NRP livers.
- No recipients of NRP livers developed IC (vs. 27% for non-NRP livers, $p < 0.0001$) or experienced primary non-function (vs 7% for non-NRP livers, $p = 0.1347$). A logistic regression model found that NRP was a significant factor ($p < 0.0001$) in not developing IC. Whilst this is clinically positive it does mean that, based on this data, it is not possible to predict the odds that transplant recipients will develop IC in the future.
- NRP was associated with a reduction in early allograft dysfunction (12% for NRP vs 32% for non-NRP livers, $p = 0.0076$), 30-day graft loss (2% NRP livers vs. 10% non-NRP livers, $p = 0.0559$) and fewer anastomotic strictures (7% vs. 27% non-NRP, $p = 0.0069$).
- Graft survival at ninety days post-transplantation was significantly better with NRP (98% vs 89% in the comparator group). At one year post-transplantation, graft survival with NRP was still superior (96% vs 88% in the comparator group), but the difference was not statistically significant (from supplied academic in confidence data).

Data from this study suggests that NRP during DCD organ retrieval leads to superior liver outcomes compared to conventional organ recovery. The study findings were limited by the lack of randomisation and the potential for bias due to heterogeneity in donor characteristics.

Safety

No safety issues related to NRP were identified for this Evidence Synthesis.

Patient and social aspects

NRP has the potential to increase the availability of organs for transplantation. This could lead to patients spending less time on the transplant waiting list.

Cost effectiveness

SHTG developed an economic model to assess the cost-effectiveness of NRP for liver transplantation. The comparator was standard non-NRP method of retrieval from DCD donors (hereafter referred to as 'standard DCD retrieval').

Methodology

A decision-tree approach was considered appropriate given the quality of the available evidence, the short follow-up time, and the rapid turnaround request by the topic referrer. The model was designed to estimate the following for a cohort of patients transplanted with NRP liver grafts compared to patients transplanted with grafts using the standard DCD retrieval process:

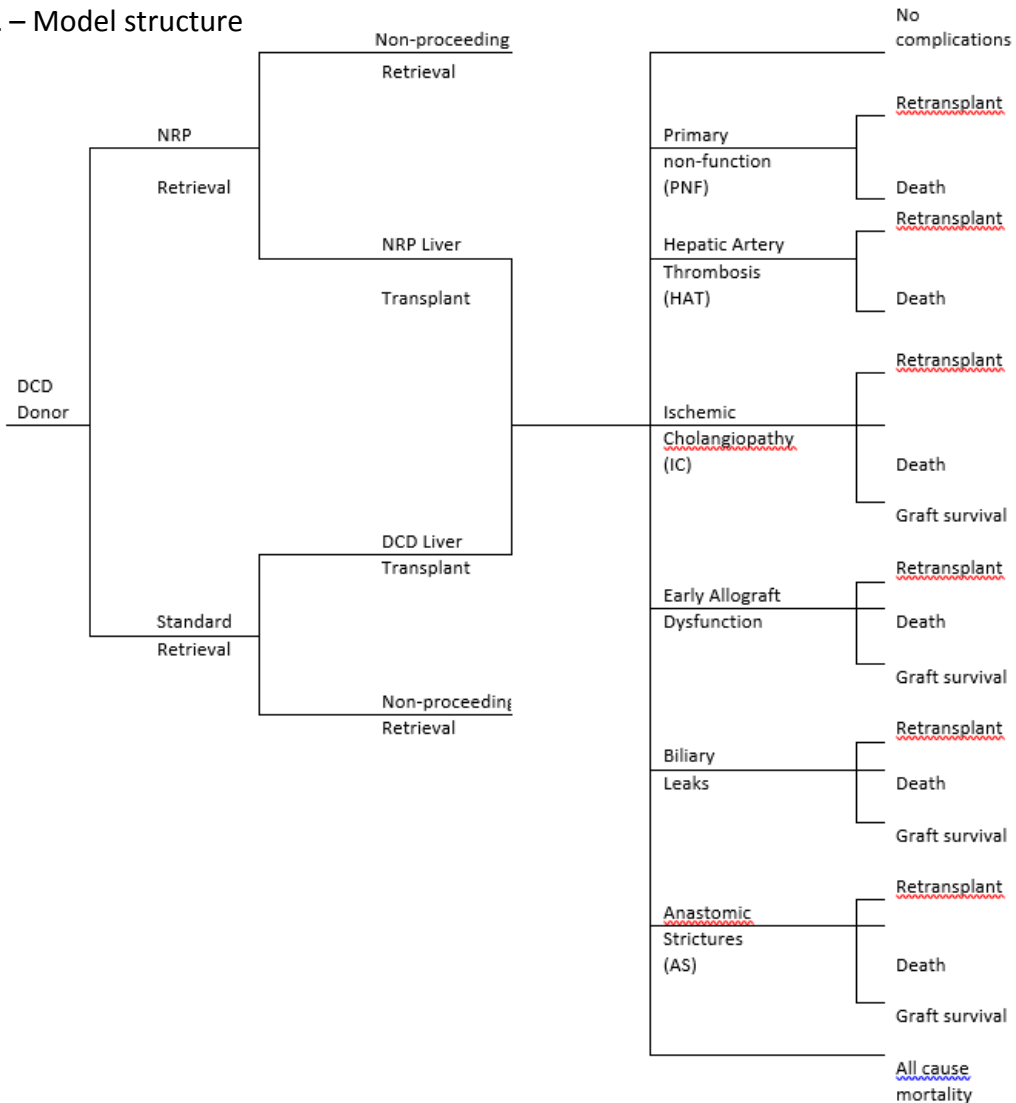
- The difference in costs per surviving patient between the two methods.
- The difference in the number of recipients developing post-transplant complications (up to 1 year) and the number of deaths arising from graft failure.
- The difference in costs associated with post-transplant complications between NRP graft recipients versus standard DCD graft recipients.
- The difference in graft survival rates and re-transplants amongst recipients of NRP and non-NRP livers.

The structure of the model is presented in Figure 1. The model inputs were described in the clinical effectiveness section of this report. The model also incorporated some key simplifying assumptions which were used to either inform its structure or the input parameters for the base case analysis. These are listed below:

- The proportion of call-outs which result in non-proceeding retrievals (i.e. liver grafts being retrieved but not transplanted due to damage or other reasons) is the same for both NRP and standard DCD (25% in the base case analysis). This is a conservative estimate and as per the study data, the probability of an unsuccessful retrieval is likely to be lower when NRP is employed (11.6% vs 25.7% livers damaged during retrieval using NRP and non-NRP respectively).
- All successfully retrieved livers are assumed to be transplanted into recipients with no grafts being discarded.
- The types of post-transplant complications associated with NRP and standard DCD retrieval are assumed to be the same. The probabilities of developing complications varies by type of retrieval (based on joint data from the two NORS centres).
- The base case analysis could not account for overlap in complications. This is because the aggregate level data could not differentiate patients who had multiple complications from patients who only had one type of complication. In other words, a patient with three different types of complications would have been considered as three different patients each developing one type of complication. This inflation in the number of patients meant that the number of recipients having 'no complications' in the standard DCD retrieval arm was zero.

- With the exception of PNF and Hepatic Artery Thrombosis (HAT), the probability of death due to other complications is assumed to be 0.05 as it is difficult to attribute the cause of death to specific complications.
- The base case analysis does not directly account for differences in length of hospital stay between NRP and non-NRP transplant recipients. The post-retrieval costs associated with the transplant procedure and procedures to treat subsequent complications are based on 'Non-elective inpatient' figures reported in the NHS National Schedule of Reference Costs (2017/18)³. Hence it is assumed that the cost of stays is included within individual procedure costs.
- The equipment cost for the technology was annuitised over a technology lifetime of 10 years and the cost of consumables for NRP retrieval were quantified per donor. The workforce costs were calculated per retrieval, given that some call-outs would result in a non-proceeding retrieval but staff would still require payment for attending call-outs.

Figure 1 – Model structure



Results

In the base case analysis, the cost per surviving patient was estimated to be £33,556 when using NRP versus £50,586 when using standard DCD retrieval. The rate of re-transplantation amongst NRP recipients was 1.91 per 100 grafts compared to 8.45 per 100 amongst the standard DCD graft recipients. The model predicted that for every 100 NRP retrievals, there would be four cases of death due to post-transplant complications, 69 cases of graft survival and 0.1 cases of death after re-transplantation. The total costs associated with NRP in the model, including the costs of treating post-transplant complications, were approximately £2.38 million.

In comparison, for every 100 standard DCD retrievals, there would be six cases of death due to post-transplant complications, 62 cases of graft survival and 0.67 cases of death after re-transplantation. The total costs associated with standard DCD in the model were approximately £3.55 million. The difference between NRP and standard DCD in the expected number of surviving graft recipients was 0.864 per 100 patients. The resulting incremental cost effectiveness ratio (ICER) is a negative integer value; which suggests that implementing NRP would be an economically dominant strategy, which could lead to savings per additional surviving patient (at 1 year outcomes) compared to standard DCD .

Based on data available from the two pilot sites, NRP appears to dominate standard DCD retrieval. This means that NRP is less costly and more effective in terms of the number of surviving patients, than standard DCD retrieval. This is primarily because, compared to standard DCD, the additional costs associated with NRP retrieval are recovered through lower rates of re-transplantation and fewer post-transplant complications.

Treatments that are both less costly and more effective than standard practice are rare. The base case results are potentially problematic given the model is based on a dataset involving small numbers of patients involved in the two pilot NRP sites.

The uncertainty surrounding the parameters was explored through one-way sensitivity analysis, by changing each model parameter input to be 10% lesser and greater than the initial base case value. Table 2 lists the parameters that the model is most sensitive to and shows the % change in value for each parameter required to change the conclusions of the analysis. The threshold value reflects the point at which comparatively fewer patients survive in the NRP arm due to an increase in survival in the standard DCD group.

The observation that very small increases to the proportion of patients experiencing complications has the power to change the conclusions of the model necessitates further

consideration. For the most sensitive values, a counter-intuitive situation has emerged. The impact of increasing the probabilities of developing post-transplant complications in the standard DCD cohort is that greater numbers of patients experience adverse events, but this consequently also results in greater rates of survival in the standard DCD patients. This is likely a competing risks issue, because the more rare adverse events that occur in the standard DCD group (i.e. PNF, HAT) have higher death rates, so having a higher probability of patients who experience the more common events with lower death rates leads to better survival in this group. There is a flip in the difference in survival between the NRP and DCD groups so that comparatively more people survive in the standard DCD group. Thus whilst NRP remains less costly, it is also less effective than standard DCD retrieval.

Table 2 – Parameter uncertainty explored through one-way sensitivity analysis

Parameter	NRP - Base case value	DCD retrieval – Base case value	DCD retrieval – Threshold value	% change needed to alter conclusions
Probability of ischaemic cholangiopathy	0.02	0.251	0.264	5%
Probability of anastomotic strictures	0.121	0.269	0.283	5%
Graft survival post ischaemic cholangiopathy	0.926	0.947	0.995	5%
Probability early allograft dysfunction	0.116	0.322	0.335	4%
Death from early allograft dysfunction	0.05	0.05	0.018	35%
Death from anastomotic strictures	0.05	0.05	0.011	22%

The interpretation of the uncertainty around the probabilities of death following early allograft dysfunction and death from anastomotic strictures (AS), both in the standard DCD

group, is more intuitive. Decreasing the probability of death from these complications will increase survival in the standard DCD group. Hence, survival between the groups now favours standard DCD rather than NRP and NRP as a strategy, while remaining less costly is now also less effective.

The model is also sensitive to the assumption that NRP results in an equivalent or lower proportion of non-proceeding retrievals compared to standard DCD (i.e. retrievals resulting in a transplant). Even a small increase in the probability that a retrieval does not proceed from 0.25 to 0.26 changes the conclusions as the number of surviving patients will be lower in the NRP group. This is likely to be driven by the fact that there is not a big difference in survival between the groups, so in a hypothetical cohort of 100 patients, even a small decrease in the availability of livers for transplant has the capacity to drive the modelled conclusions.

The cost of a NRP liver transplant (including the costs of in-patient stay) would have to be severely underestimated for it to change the conclusions of the model. For example, an 80% increase in costs for the NRP group would result in an ICER of £15.5K per additional surviving patient, which is still well below the conventional ICER threshold range of £20K to £30K used to demonstrate cost-effectiveness.

To further probe uncertainty around the small sample size underpinning the input parameters, an assumption was made of equivalence between the groups for all probabilities of post-transplant complications simultaneously (i.e. probabilities of IC, graft survival following IC, AS, early allograft dysfunction in the standard DCD group are *all* the same as for NRP). This changed the conclusions with a difference in costs of £22K and a difference in survival of 0.87. Therefore the ICER for NRP was £25K per additional surviving patient.

An alternate scenario analysis using a greater sample size was also conducted, whereby the probabilities of developing complications were based on combined data from the two UK pilot sites plus unpublished results from a larger Spanish trial provided to us in academic confidence. Whilst the difference in total costs between NRP and standard retrieval was not substantially different to that of the base case analysis, the expected number of surviving patients with NRP was much higher (2.85 per 100 patients), again showing that NRP dominated standard DCD retrieval.

Conclusion

The base case results of the economic model indicate that NRP is both less costly and leads to better outcomes, in terms of fewer post-transplant complications and better graft survival, compared to standard DCD retrieval.

The key sources of uncertainty around these findings relate to the small sample size from the two UK NRP sites upon which the probabilities of developing post-transplant complications are based, limited data on the probability of death associated with post-transplant complications (excluding PNF and HAT) and sensitivity around the proportion of NRP retrievals that are non-proceeding. Nevertheless, the model employed conservative assumptions and it is likely that NRP would continue to dominate standard DCD retrieval if the model is refined using better quality data.

Equality and diversity

Healthcare Improvement Scotland is committed to equality and diversity in respect of the nine equality groups defined by age, disability, gender reassignment, marriage and civil partnership, pregnancy and maternity, race, religion, sex, and sexual orientation.

The process for producing evidence syntheses has been assessed and no adverse impact across any of these groups is expected. The completed equality and diversity checklist is available on www.healthcareimprovementscotland.org

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The economic model was circulated to the topic referrers and colleagues involved with NRP implementation at NHS BT for verification of assumptions and input parameters. It was also reviewed by analysts at the Department of Health and Social Care who intend to undertake their own cost-effectiveness and budget impact analysis.

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