

Impact case study (REF3)

Institution: University of Cambridge		
Unit of Assessment: UOA1		
Title of case study: Saving lives and reducing healthcare costs through a comprehensive programme to increase organ transplantation.		
Period when the underpinning research was undertaken: January 2000 to present		
Details of staff conducting the underpinning research from the submitting unit:		
Name(s):	Role(s) (e.g. job title):	Period(s) employed by submitting HEI:
ML Nicholson	Professor of Transplant Surgery	March 2015 to present
SA Hosgood	Senior Research Associate	March 2015 to present
GJ Pettigrew	Reader in Surgery	October 2013 to present
CJE Watson	Professor of Transplantation	December 1998 to present
JA Bradley	Professor of Surgery	August 1997 to December 2016
Period when the claimed impact occurred: August 2013 to present		
Is this case study continued from a case study submitted in 2014? No		
1. Summary of the impact (indicative maximum 100 words)		
<p>65,000 people in the UK have end stage renal failure, for whom a kidney transplant would offer a better quality of life. Historically, many donor kidneys are rejected with little empirical evidence because they are perceived to be 'unsuitable for use' or from 'high-risk' donors. A similar problem exists for livers, with a third of deceased donor livers being unused, while patients are dying through lack of a transplant. A systematic programme of research led by the University of Cambridge has provided data demonstrating the quality and safety of organs that would previously have been rejected by many centres. They have pioneered techniques to allow rejected organs to be kept viable for assessment and successful transplantation. Their research has contributed to a 25% increase in the number of kidney transplants in the UK between 2013/14 and 2019/20, optimised usage of donor kidneys via a UK fast track scheme, informed national and international guidance on the allocation and safety of organs for transplantation, improved informed consent practice for transplant recipients across the UK and spearheaded new technology to improve availability of donor organs.</p>		
2. Underpinning research (indicative maximum 500 words)		
<p>The NIHR-funded Access to Transplant and Transplant Outcome Measures (ATTOM) Study, of which Cambridge researchers were lead members, studied 6,844 kidney transplant and dialysis patients between 2011 and 2016. ATTOM confirmed that kidney transplants provide far greater quality of life and healthcare savings than long-term dialysis treatment, and highlighted dramatic variations in kidney transplant rates across UK, owing to a lack of standard practice for selecting donor organs and recipients [1]. Concern about the use of kidneys from donation after circulatory death (DCD) patients – donors from whom life-support was withdrawn – further limited available organs for transplantation. Cambridge University-led research has focused on assessing the quality and safety of kidneys deemed 'unsuitable or high-risk' for transplantation, providing an evidence-base for increasing the number of safe organs available for transplant.</p>		
<p>Demonstrating the suitability of DCD kidney transplants: Cambridge University-led research has been pivotal in demonstrating the equivalent value of DCD relative to the more common brain-death donor (DBD) kidney transplants. Their study of 8,289 first-time kidney transplant recipients in all 23 UK centres between 2000 - 2007 identified equal 5-year graft survival rates between recipients of DCD (n=793) and DBD transplants (6,759; hazard ratio 1.01, 95% CI 0.83 to 1.19, p=0.97) [2]. Importantly, they also showed DCD donor kidneys tolerate cold storage less well than DBD donor kidneys, highlighting this as a critical consideration for organ allocation policy [3]. To provide histological evidence that DCD and DBD kidneys are equivalent, Pettigrew led an assessment of 243 DCD and 128 DBD 'time zero' kidney biopsies; demonstrating that the severity of chronic kidney injury and transplant outcome is equivalent for DCD and DBD kidneys and that the absolute injury score rather than donor source was predictive of graft outcome [4].</p>		
<p>Demonstrating the safety of organs from 'increased-risk' donors: The reluctance of centres to transplant organs from donors considered to be high-risk for transmitting disease to recipients, has also significantly reduced the availability of organs for transplantation. Historically, these</p>		

practices have been established with little empirical evidence. In a study of 17,262 potential donors in the UK (2003 to 2015), Cambridge researchers showed that no significant difference was observed in graft outcome among recipients receiving organs from increased risk behaviour (IRB) and non-IRB donors [5]. Cambridge also co-led a large national study that confirmed no cancer transmission to recipients receiving 133 organ transplants from donors with a previous malignant disease [6]. These studies have transformed understanding of organ suitability, confirming that the risk-benefit ratio favours transplantation of organs from donors previously viewed as 'high-risk' compared to declining organs and continuing with the risk of death on the waiting list.

Improving the quality of transplanted kidneys and livers

Ex vivo normothermic perfusion (EVNP): Approximately 15% of kidneys are declined for transplantation each year because of concerns of poor quality, e.g. inadequate perfusion. Cambridge researchers have pioneered EVNP of kidneys to restore function *ex vivo* (after organ recovery), to enable assessment of viability and to provide an opportunity to "recondition" kidneys, as well as being an alternative means of preservation. To provide proof-of-principle, kidneys from a 35-year-old DCD donor that had been declined by all UK transplant centres were subjected to one-hour EVNP after which standard criteria confirmed they were suitable for transplantation. Transplantation was completed into two recipients without complication, both of whom benefited from long term graft health [7]. This was expanded to a subsequent study in which of eight kidneys declined because of poor cold perfusion in the donor, five were successfully transplanted after EVNP, with four having immediate function [8]. 22% of DBD livers are also declined. Cambridge researchers have pioneered EVNP assessment of marginal livers, developed viability criteria, and demonstrated the ability to transplant livers declined by all centres [9].

In situ normothermic regional perfusion: Only 27% of DCD livers are used, because they have a higher chance of not working (4% vs 0.8% for DBD), and of being lost early through bile duct problems. Cambridge researchers pioneered a programme of *in situ* (i.e. prior to organ recovery) normothermic regional perfusion (NRP) in DCD donors before the liver is removed, enabling its assessment but also minimising ischaemic damage [10]. This technology also improves outcomes for kidneys and increases utilisation of pancreases.

3. References to the research (indicative maximum of six references)

Evidence of research quality: *Research published in peer-review journals. Research was supported by competitively won grants.

- [1] *Pruthi R, ...**Watson C**, ... Roderick PJ; ATTOM Investigators. Variation in Practice Patterns for Listing Patients for Renal Transplantation in the United Kingdom: A National Survey. *Transplantation*. 2018;102(6):961-968.
- [2] *Summers DM, ... **Watson CJ, Bradley JA**. Analysis of factors that affect outcome after transplantation of kidneys donated after cardiac death in the UK: a cohort study. *Lancet*. 2010;376(9749):1303-11.
- [3] *Summers DM... **Watson CJ, Bradley JA**. Effect of donor age and cold storage time on outcome in recipients of kidneys donated after circulatory death in the UK: a cohort study. *Lancet*. 2013;381(9868):727-34.
- [4] *Kosmoliaptsis V, ... **Bradley JA, Torpey N, Pettigrew GJ**. Baseline donor chronic renal injury confers the same transplant survival disadvantage for DCD and DBD kidneys. *Am J Transplant*. 2015;15(3):754-63.
- [5] *Trotter PB, ...**Watson CJE**, ...Bradley JA. Deceased Organ Donors With a History of Increased Risk Behavior for the Transmission of Blood-Borne Viral Infection: The UK Experience. *Transplantation*. 2017;101(7):1679-89.
- [6] *Desai R... **Watson CJ**, ... Neuberger J. Estimated risk of cancer transmission from organ donor to graft recipient in a national transplantation registry. *Br J Surg*. 2014;101(7):768-74.
- [7] ***Hosgood SA**, ... **Nicholson ML**. Successful transplantation of human kidneys deemed untransplantable but resuscitated by normothermic machine perfusion. *Am J Transplant* 2016;16:3282-3285.

- [8] ***Hosgood SA, ... Nicholson ML.** Normothermic machine perfusion for the assessment and transplantation of declined human kidneys from donation after circulatory death donors. *Br J Surg* 2018;105:388-394.
- [9] ***Watson CJ ... Butler AJ.** Normothermic perfusion in the assessment and preservation of declined livers before transplantation: hyperoxia and vasoplegia—important lessons from the first 12 cases. *Transplantation* 2017;101 (5): 1084–1098.
- [10] ***Watson CJ...**, Oniscu GC. *In situ* normothermic perfusion of livers in controlled circulatory death donation may prevent ischemic cholangiopathy and improve graft survival. *Am J Transplant.* 2019;19(6):1745-58..

Key competitively awarded funding

1. Blood and Transplant Research Unit for Organ Donation and Transplantation. National Institute of Health Research (NIHR). PI: Nicholson GBP3.8M (2015-20).
2. Kidney Research UK Project Grant: Reconditioning by ex-vivo normothermic perfusion in donation after cardiac death kidney transplantation. PI: Nicholson GBP740,551 (2015-21).
3. NIHR Programme Grant. Variations in access to best care for renal replacement therapy patients across the United Kingdom (ATTOM study). PI: Watson GBP1.9M (2011-2017).
4. NIHR Research for Patient Benefit funded PITHIA study. PI: Pettigrew GBP350,000 (2018-2021).

4. Details of the impact (indicative maximum 750 words)

There are currently (2020) around 6,000 people on the UK Transplant Waiting List. Of those, approximately 600 are awaiting a liver transplant, and approximately 4,600 awaiting a kidney transplant. Cambridge University, through its transplant personnel, continues to be at the forefront of national transplantation research and has an international reputation for excellence [A]. Research has led to the following impacts:

Impact on the health and wellbeing of people

Increasing access to kidney transplantation nationally: Watson, Chair of the National Health Service Blood and Transplant (NHSBT) Kidney Advisory Group, led a team to design an updated policy for kidney allocation [A]. From September 2019 a new national kidney offering scheme was introduced in the UK, which addresses some of the inequities resulting from the previous 2006 kidney allocation scheme. Recognising Cambridge University research showing the good long-term outcomes of DCD kidneys [2], this scheme now allows for offering of DCD kidneys as well as DBD kidneys.

Development of the UK Kidney Fast-Track scheme (KFTS): Having identified that usable kidneys were being declined by transplant centres, in 2012 Cambridge led the development of a national fast-track offering scheme to rapidly place rejected kidneys in centres willing to transplant them. Declined deceased donor kidneys meeting defined entry criteria for the KFTS are simultaneously offered to all participating transplant centres. Kidneys are allocated through existing algorithms, but with the added flexibility that the accepting centre can implant the kidneys into the recipients of their choosing. An initial outcomes study published in 2017 reported that 286 DBD kidneys (Nov 2012-Apr 2015) and 237 DCD kidneys were transplanted (Mar 2013-Apr 2015), with results as good as non-fast track kidneys (1 year graft survival >90%) [B]. As of November 2020, the scheme continues to run UK-wide.

Increased number of patients receiving organ transplants: By demonstrating the quality and suitability of kidneys donated after DCD, Cambridge University research has contributed to the 25% (n=191) increase in number of patients receiving a DCD renal transplant between 2013/2014 and 2018/2019, with 6053 patients receiving kidneys from DCD donors since 2013, and 970 in 2018/2019 alone. From the Medical Director of NHSBT “*Research at the University of Cambridge...has contributed to an increasing acceptance in UK transplant centres of DCD kidneys, observable in an overall upwards trend of DCD kidney transplants since 2014*” [A].

Decreased waiting times for transplantation: Cambridge University research demonstrating safety and quality of organs has resulted in Cambridge patients waiting less time for a kidney

transplant (2014-17 median waiting time 360 days vs UK median 603 days [A]). This has particularly benefitted elderly patients listed for a kidney transplant, who generally wait longer for transplantation: 60% of Cambridge patients listed when 65 years or older received a transplant by five years, compared with only 38% of the equivalent patient group nationally. Elsewhere a higher proportion either died or were delisted before receiving a transplant [C].

Patient education and empowerment: Cambridge University research has engaged potential kidney transplant recipients in more informed discussions around the transplantation of kidneys from high-risk donors by quantifying the risks. In recognition of the need to discuss risk with patients, Cambridge co-led, with the Directorate for Organ and Tissue Donation and Transplantation NHS Blood and Transplant and key stakeholders, the development in 2015 of the first UK guidelines for consent for transplantation [D]. Consequently, common practices are now shared across UK NHS trusts, meaning that patients should be equally well informed when making decisions and receive parity of care wherever they are treated.

Impact on commerce and the economy

Healthcare savings by increasing the number of transplants: ATTOM confirmed that kidney transplantation is cheaper than dialysis, saving GBP15,000 per transplant in the first 6 years [E]. Cambridge University research has contributed to an additional 191 DCD kidney transplants in the UK between 2013/14 and 2018/19. A conservative estimate of healthcare savings to the NHS arising from these additional transplants is therefore at least GBP2,850,000. This is likely to continue to increase given the upward trajectory of use of DCD donor organs and other previously declined organs for transplantation.

Healthcare savings by increasing the success of transplants: The utilisation of biopsy information and functional assessment of kidneys by normothermic perfusion, together with the identification of the shorter tolerance of DCD kidneys to cold storage, all reduce the chance of unsuccessful transplants which are associated with prolonged inpatient stay and increased resource utilisation. The use of *in situ* normothermic perfusion and EVNP of livers has had a similar impact on liver transplantation locally, and this is likely to be translated nationally.

Impact on practitioners and the delivery of professional services

Improving international practice in organ selection and quality: Research into the risks of transmission of donor diseases has been incorporated into national and international guidance:

- Cambridge University researchers have co-authored guidance from the UK Advisory Committee on the Safety of Blood, Tissues and Organs (SaBTO). From the Chair of SaBTO: *“By removing uncertainty, and providing some estimation of risk, this body of work has made a major contribution not only to an increased acceptance and uptake of organs for transplantation but also provides both patients and health care professionals the best available evidence on which to make decisions about the use of scarce, life-saving organs.”* [F].
- Professor Watson formed part of the working group that developed the 7th Edition of the *Guide to the quality and safety of organs for transplantation* by the European Directorate for the Quality of Medicines & HealthCare of the Council of Europe (EDQM). In October 2020 the Council of Europe issued a recommendation that the governments of member States ensure that quality and safety standards for organ donation and transplantation are set in place in accordance with these guidelines. The guidelines are used not only by the UK and member states of Europe but have been accessed over 1000 times by non-EU countries [F].

Pioneering technology to improve uptake of organs:

Cambridge University researchers have pioneered the introduction of normothermic organ perfusion into clinical practice. In January 2019, NICE issued guidance (from evidence which cited [10]) recommending *ex situ* machine perfusion (EVNP) for extracorporeal preservation of livers for transplantation, under special arrangements as more data is gathered into its efficacy [G]. EVNP technology is now used clinically in at least three kidney transplant centres in the UK and the Cambridge perfusion protocol has been adapted for clinical use in The Netherlands and the USA [H]. Early work has shown a more rapid resumption of kidney function in DCD kidneys

than those not undergoing normothermic perfusion, reducing the need for post-operative dialysis and reducing inpatient stay [I].

The UK National Protocol for direct procurement of cardiothoracic organs and *in situ* normothermic regional perfusion (NRP) of the abdominal organs, co-written by Professor Watson, was published in May 2019 [J]. Cambridge research on *in situ* NRP was used by NHSBT to apply for funding to commission a national service for NRP in all DCD donors. In 2020 Professor Watson was invited by NHSBT to lead a committee implementing roll out of NRP in the UK [A]. Funding for the service has been granted in Scotland and Wales in 2019/20. Calculations on the cost benefit of this technology to the NHS show a substantial economic benefit: GBP2,380,000 cost of 100 retrievals using NRP vs GBP3,550,000 for 100 retrievals without NRP [A]. These cost savings are due to lower rates of post-transplant complications and higher rates of graft survival. In Cambridge alone between 2013 and 2020 the use of *in situ* NRP has led to the transplantation of 78 livers of which two-thirds would have otherwise been discarded, while maintaining high survival rates (April 2015 - March 2019 risk-adjusted 1 year survival rates for Cambridge liver transplants was 96.8% (CI 94.4 - 98.2)) [A].

5. Sources to corroborate the impact (indicative maximum of 10 references)

- [A] NHS Blood and Transplant: (i) Testimonial from Medical Director of NHSBT, November 2020 (ii) Annual Reports (containing data 2010-2020) :Kidney Transplantation Report for 2019/2020 p 38; Liver Transplantation Report for 2019/2020 (iii) Testimonial from *Senior Commissioning Manager*, NHS Blood and Transplant - Leeds
- [B] Callaghan CJ, Mumford L, Pankhurst L, Baker RJ, Bradley JA, Watson CJE. Early Outcomes of the New UK Deceased Donor Kidney Fast-Track Offering Scheme. *Transplantation*. 2017;101(12):2888-97.
- [C] Mirshekar-Syahkal B, Summers D, Bradbury LL, (...), Bradley JA, Pettigrew GJ. Local Expansion of Donation After Circulatory Death Kidney Transplant Activity Improves Waitlisted Outcomes and Addresses Inequities of Access to Transplantation. *Am J Transplant*: 2017;17(2):390-40
- [D] Guidelines for consent for solid organ transplantation in adults, NHSBT 2015
- [E] Li B, Cairns JA, Fotheringham J, Tomson CR, Forsythe JL, Watson C, et al. Understanding cost of care for patients on renal replacement therapy: looking beyond fixed tariffs. *Nephrol Dial Transplant*. 2015;30(10):1726-34.
- [F] Impact on international guidance: (i) Testimonial from Chair of SaBTO (ii) SaBTO guidance on Transplantation of organs from donors with a history of cancer and Transplantation of organs from donors with primary brain tumours (cites [6], page 7) pub April 2014, revised Nov 2020 (iii) Council of Europe guide to the quality and safety of organs for transplantation, 2018 (pages 225, 495) (iv) Council of Europe legislation recommendation (vi) Council of Europe Guidance access data
- [G] (i) NICE guidance Ex-situ machine perfusion for extracorporeal preservation of livers for transplantation 16 January 2019 (ii) NICE Interventional procedures programme (Evidence review), 2019 pg 35, 47.
- [H] Rollout of EVNP: (i) UK: Chandak P, *et al.* Dissemination of a novel organ perfusion technique: ex vivo normothermic perfusion of deceased donor kidneys. *Artif Organs*. 2019 Nov;43(11):E308-E319. (ii) Rijkse, E., IJzermans, J. N., & Minnee, R. C. (2020). Machine perfusion in abdominal organ transplantation: Current use in the Netherlands. *World journal of transplantation*, 10(1), 15–28. (iii) Kabagambe SK, Palma IP, Smolin Y, Boyer T, Palma I, Sageshima J, Troppmann C, Santhanakrishnan C, McVicar JP, Jen KY, Nuño M, Perez RV. Combined Ex Vivo Hypothermic and Normothermic Perfusion for Assessment of High-risk Deceased Donor Human Kidneys for Transplantation. *Transplantation*. 2019 Feb;103(2):392-400. doi: 10.1097/TP.0000000000002299.
- [I] Hosgood SA, Nicholson ML. The first clinical case of intermediate ex vivo normothermic perfusion in renal transplantation. *Am J Transplant*. 2014 Jul;14(7):1690-2.
- [J] UK National Protocol for direct procurement of cardiothoracic organs and *in situ* normothermic regional perfusion (NRP) of the abdominal organs, May 2019