Institution: University of Oxford

Unit of Assessment: 1 – Clinical Medicine

Title of case study: OrganOx: Organ preservation to improve liver transplantation

Period when the underpinning research was undertaken: 2000 – 2019

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:
Professor Peter J Friend	Professor of Transplantation	1999 – present
Professor Rutger Ploeg	Professor of Transplant Biology	2011 – present
Simon Knight	Senior Research Fellow, consultant	2016 – present
Susan Dutton	Lead statistician	2013 – present

Period when the claimed impact occurred: 1 August 2013 – 31 December 2020

Is this case study continued from a case study submitted in 2014? N

1. Summary of the impact

Research from the University of Oxford's Department of Surgical Sciences and Department of Engineering (UOA12) led to the development of the OrganOx metra – the world's first normothermic organ preservation device, used to improve and prolong preservation and function of livers prior to transplantation. The research was commercialised through the formation of the spin out company OrganOx and resulted in over GBP7,000,000 of direct sales since product CE marking in 2016. Based on the evidence produced by a 220-patient randomised clinical trial published as a cover story in Nature in 2018, normothermic machine perfusion was endorsed by NICE in January 2019. By 2020, the OrganOx metra was deployed and routinely used in all seven UK liver transplant centres and has been used to perform over 850 liver transplants across 13 countries. Improved organ preservation halves the number of discarded organs, and improves waiting times and clinical outcomes for patients.

2. Underpinning research

The research underpinning the development of the world's first normothermic liver perfusion device took place as a close cross-disciplinary collaboration at the University of Oxford between surgeon Professor Peter Friend and engineer Professor Constantin Coussios (University of Oxford, UOA12). The team improved preservation and organ utilisation by replicating, in a robust, automated fashion, the physiological conditions encountered by the organ within the body, through perfusion of the organ at a warm, normothermic, physiological temperature of 37°C with a red-cell suspension reconstituted from donor blood of the same blood type. Professor Friend led the surgical usability aspects of the device, the in vivo work and clinical trials. Professor Coussios led the engineering, specifically the haemolysis minimisation, controller design and perfusion automation.

The technology was developed using pig livers, the standard pre-clinical model for organ preservation studies. The team's initial perfusion studies confirmed that warm perfusion is superior to cold for the release of liver transaminase, bile production and protein synthesis after transplantation [1]. Having demonstrated warm perfusion was superior for liver function, they went on to confirm that minimising exposure to cooling was not just preferable but necessary for increased utilisation of donor livers [2].

The initial perfusion studies were translated into a pig liver transplant model [3], which further confirmed the advantages of warm perfusion, enabling successful liver transplantation under conditions of prolonged preservation of 20 hours. When the team combined this with clinically-relevant pre-preservation hypoxia it provided a model of organ retrieval following death confirmed by circulatory, rather than neurological, parameters. The team completed successful transplantation after very prolonged preservations of 48 hours. This evidenced the technology's potential for improved utilisation of livers that are currently not retrieved or retrieved and not transplanted [4].

Building on this proof of concept, OrganOx Ltd was founded as a University of Oxford spin-out in 2008 to design, build and test the device for a Phase I trial to demonstrate the safety and feasibility of warm liver preservation in a clinical setting. The first clinical use of warm liver preservation took place in February 2013 in a study involving 20 patients. The team demonstrated safety (100% graft and patient survival at 30 days) and a 50% reduction in an acute liver injury. This research [5] was published as a cover article in the American Journal of Transplantation and later judged as the journal's 'best clinical paper' of 2016.

A 220-patient randomised trial comparing warm to cold preservation across seven European transplant centres was initiated in 2015, completed in 2017 and published in 2018 as a cover article in Nature [6]. This first large randomised trial in liver preservation demonstrated that use of the normothermic device resulted in a 50% decrease in organ discard rate and a 50% increase in preservation time, whilst at the same time results in a 50% decrease in post-transplant graft injury. During the trial, clinicians began to use machine flow parameters and biochemistry to determine whether to transplant livers of marginal quality.

3. References to the research (University of Oxford UOA1 researchers in bold)

1. Butler AJ, Rees MA, Wight GD, Casey ND, Alexander G, White DJG, **Friend PJ** (2002) Successful extracorporeal porcine liver perfusion for 72 hr. *Transplantation* 73(8):1212-8. DOI: 10.1097/00007890-200204270-00005 (193 citations; Google Scholar 12/03/21)

2. Reddy SP, Bhattacharjya S, Maniakin N, Greenwood J, Guerreiro D, Hughes D, Imber CJ, Pigott DW, Fuggle S, Taylor R, **Friend PJ** (2004). Preservation of porcine non-heart-beating donor livers by sequential cold storage and warm perfusion. *Transplantation* 77(9):1328-32. DOI: 10.1097/01.tp.0000119206.63326.56 (124 citations; Google Scholar 12/03/21)

3. **Brockmann J**, Reddy S, Coussios C, Piggott D, Guirriero D, Hughes D, Morovat A, Roy D, Winter L, **Friend PJ** (2009). Normothermic Perfusion: a New Paradigm in Organ Preservation, *Annals of Surgery* 250:1-6. DOI: 10.1097/SLA.0b013e3181a63c10

4. Vogel T, Brockmann JG, Pigott D, Neil DAH, Muthusamy ASR, Coussios CC and **Friend PJ** (2017). Successful Transplantation of Porcine Liver Grafts Following 48-hour Normothermic Preservation. *PLOS ONE* 12(11): e0188494. DOI: 10.1371/journal.pone.0188494

5. Ravikumar R, Jassem W, Mergental H, Heaton N, Mirza D, Perera M, Quaglia A, Holroyd D, Vogel T, Coussios CC and **Friend PJ** (2016). Liver Transplantation After Ex Vivo Normothermic Machine Preservation: a Phase 1 (First-in-Man) Clinical Trial, *American Journal of Transplantation* 16(6):1779-87. DOI: 10.1111/ajt.13708

6. A Randomized Trial of Normothermic Preservation in Liver Transplantation (2018). 32 authors, of which four have University of Oxford affiliation, including: **Dutton S, Knight S, Ploeg R, Friend P**. *Nature* 557: 50–56. DOI: 10.1038/s41586-018-0047-9

Grants awarded to the University of Oxford that underpin this work:

Wellcome Trust project grant to Friend (PI) 'Liver transplant preservation by warm perfusion', GBP213,950 (reference 073394/Z/03/Z, 02-2005 to 01-2007).

EC FP7-HEALTH collaborative award coordinated by the University of Oxford, led by Ploeg (PI) and Friend (Co-I), for the Consortium for Organ Preservation in Europe (COPE). Oxford budget GBP1,618,468 (reference 305934, 01-2013 to 06-2018), total budget EUR7,847,753.

4. Details of the impact

Liver transplantation is a highly effective treatment for end-stage liver failure, but is heavily constrained by the limited pool of donor organs. In the UK in the year to March 2018, there were 1,574 deceased donors, 1,149 liver retrievals and 975 liver transplants, indicating 62% overall liver utilisation. The highest-risk donor organs, including from donors after circulatory death rather than donors after brain death, were particularly poorly utilised (34%). As a result of this under-utilisation, in 2018 some 30% of listed patients were still waiting for a transplant for six months after listing, and 12% of listed patients died whilst still on the waiting list within two years [A].

Regulatory approval, endorsement by NICE, and uptake of OrganOx metra

The research undertaken by Friend demonstrated the potential to increase the number of livers available for transplantation through increased utilisation of donor livers by warm perfusion, and the collaboration with Coussios made this technically possible through the development of the OrganOx metra. The first patient to benefit from this new approach was successfully transplanted in February 2013, and following successful completion of this Phase I study [5] the OrganOx metra received its CE mark as a medical device in 2016. Based on evidence from [6], machine perfusion was endorsed by NICE in January 2019 [B]. By December 2020, the OrganOx *metra* was being used routinely across all seven UK transplant centres in the UK (Birmingham, Cambridge, King's, Leeds, Edinburgh, Royal Free and Newcastle). It total it has been used to enable over 850 liver transplants in 4 continents and 13 countries (UK, Austria, Italy, Spain, Germany, Belgium, France, the Netherlands, India, UAE, Australia, Canada, and USA) [C].

Benefit to patients

The OrganOx metra has significant benefits for both liver transplant recipients and patients with end stage liver disease who are awaiting a liver transplant. Improved patient outcomes are due to a reduction in damage to the perfused liver after it has been removed from the donor, and the ability to assess the donated liver's function before it is transplanted, which result in more livers available for transplantation by using organs which would previously have been discarded. By increasing how long the liver can be stored before a transplant, clinicians can also choose to undertake a transplant at the optimal time point.

In the large randomised trial [6], the Oxford team halved the organ discard rate from 24% to 12%. Even though more organs (including more marginal organs) were utilised and were preserved for 50% longer, the post-transplant outcomes were still significantly better for normothermically preserved organs, as evidenced by a 50% decrease in post-transplant graft injury. The Professor of Transplantation at Addenbrooke's Hospital, Cambridge, the first UK centre to fully adopt the OrganOx metra for routine clinical use, confirmed in October 2020:

> "*Since its introduction into our routine clinical practice in February 2018 we have increasingly used the machine in three settings, to assess donor livers where doubt existed over viability, to enable us to tackle difficult recipient procedures without the pressure of accumulating cold ischaemia, and to overcome logistical issues such as where we accepted two livers simultaneously. By far the biggest use (70%) has been in the assessment of donor livers. Since we started using the normothermic liver perfusion our transplant activity has increased around 30%...As you would imagine this has had an impact on our waiting times and waiting list mortality, as well as enabling us to successfully use livers that would otherwise not have been used by any centre in the UK*." [D]

NICE issued a press release in January 2019 announcing their recommendation of the procedure and highlighting the benefits to patients:

> *"Every year hundreds of people with advanced liver disease die whilst waiting for a transplant. This new device offers real hope as it may improve transplant outcomes and allow livers that were previously thought to be unsuitable to be used and also increase the time that livers are able to be kept. It is an exciting development that has the potential to shorten waiting list times and reduce mortality rates from advanced liver disease. After transplant, the vast majority of people go on to lead full and healthy lives and it is truly amazing to see the transformation."* Director of Policy at the British Liver Trust [E].

Changes to clinical practice

In addition to increasing donated organ utilisation, the introduction of the OrganOx metra in to the seven UK transplant centres has had a significant impact on clinical practice in the field of liver transplantation. An independent study (VITTAL: Viability Testing and Transplantation of Marginal Livers, NCT02740608), led by the University of Birmingham between November 2016 – February 2018, investigated the impact of normothermic machine perfusion on utilisation of liver grafts that had been discarded by all seven liver transplant centres in the UK. Of the 31 liver grafts perfused on the OrganOx metra, 22 were subsequently transplanted with 100% 90-day survival, demonstrating that normothermic machine perfusion can enable safe utilisation of over 70% of presently discarded grafts [F]. Chief Investigator of the VITTAL study, transplant surgeon at University Hospital's Birmingham NHS Foundation Trust, said:

> "*In the 30 years I've been involved with transplantation, there have been three or four events which have been game changers and I'm absolutely certain we are looking at a game changer that will change the way we practice organ storage and transplantation. It is already changing practice at the centres that have been able to use this technology either within clinical trials or within an expansion of service evaluation*" [E].

The OrganOx metra has also had a significant impact on transplantation logistics. By increasing preservation times from the conventional maximum of 12 hours to well over 30 hours [G], clinicians have more flexibility about the timing of surgery and are able to plan more transplants as day cases, as noted in [6]. A study on the introduction of normothermic machine perfusion (NMP) at the Medical University of Innsbruck, Austria, found that *"NMP in a multidisciplinary approach enables a safe prolongation of liver preservation and overnight organ care. A first field test of NMP indicates safety and benefit of this approach"* [G]. This experience led to the omission of night-time procedures and parallel transplantations in Innsbruck [G]. In a separate study, use of the OrganOx metra device allowed 84% of transplants to take place during the day versus 65% with static cold storage [H]. This may help transplant surgical teams avoid 'burn-out' of key personnel. There is good evidence that daytime operations also have better outcomes for patients; for example, Yang et al [I] found that after-hours surgery was associated with significantly increased postoperative mortality and morbidity, and that: "*The timing of surgery plays a role in the outcome after the procedure and that both mortality and morbidities increase in surgeries performed outside of the regular working hours*".

A UK health economic study conducted by the University of Southampton in 2019 [J] concluded that, even though normothermic machine perfusion is more costly than static cold storage, it is also significantly more cost-effective by virtue of enabling additional transplants, with patients experiencing lower rates of early allograft dysfunction and adverse events: its incremental cost-effectiveness ratio was found to be GBP7,876 per Quality-Adjusted Life Year (QALY) gained.

Economic Impact

In the first three years since CE marking in 2016, the OrganOx metra has seen over GBP7,000,000 of cumulative direct sales since product CE marking in 2016. As of October 2020, the company employs 29 staff (headcount): 23 in the UK, 4 in the US, 1 based in France and 1 based in Germany. Revenue for the period 1st May 2019 – 30th April 2020 was GBP2,200,000 which represents a 30% increase in revenue from the previous year [C]. 40 devices are in use worldwide

across Europe, North America, Asia and Australia. In January 2020, the company received a GBP4,600,000 investment from BGF, a UK investment company, to enable expansion in the US, where a subsidiary has been incorporated [C].

Recognition

The OrganOx metra was recognised in the 2013 IET Innovation Awards, receiving 1st prize in 3 of 15 categories, including: 'Best Healthcare Technology', 'Best Intelligent System' and 'Best Emerging Technology Design'. The OrganOx metra was further shortlisted as one of 4 finalists for the 2019 50th anniversary MacRobert award of the Royal Academy of Engineering. In September 2019, OrganOx won the 'Best Proof-of-Value of an Innovation' category at the US Medtech Insight Awards in Boston, attracting the following citation:

> *"This is a major advancement in organ preservation. There is well-documented unmet medical need in this area, and it is a true achievement to have a method to help secure desperately needed organs for patients. The judges commented that OrganOx represents the true aspects of what it takes to be best value and best for patients. The need for better preservation for transported organs has been a true roadblock for patients desperately waiting for organ transplants. The perseverance of the team is obvious, and they overcame huge roadblocks to achieve success."* [K].

5. Sources to corroborate the impact

A. NHS Blood and Transplant Annual Report on Liver Transplantation (August 2019)

B. NICE guidance IPG636: Ex-situ machine perfusion for extracorporeal preservation of livers for transplantation. (16 January 2019). https://www.nice.org.uk/guidance/ipg636

C. Corroborator 1: CEO, OrganOx Ltd. May be contacted to confirm sales of the device worldwide, and employment data

D. Letter from Professor of Transplantation, University of Cambridge corroborating the benefits of the OrganOx metra and its adoption for routine procedures

E. NICE press release 16 January 2019 *More donor livers could be used for transplantation*

F. Journal article: Mergental H, et al (2020). Transplantation of discarded livers following viability testing with normothermic machine perfusion. *Nature Communications*. 11(1):1-2. DOI: 10.1038/s41467-020-16251-3

G. Journal article: Cardini B, et al (2020). Clinical Implementation of Prolonged Liver Preservation and Monitoring Through Normothermic Machine Perfusion in Liver Transplantation. *Transplantation*. 2020 104(9):1917-1928. DOI: 10.1097/TP.0000000000003296.

H. Journal article: Mariusz Bral , Khaled Dajani, Dayne Leon Izquierdo et al (2019), "A Back-to-Base Experience of Human Normothermic Ex Situ Liver Perfusion: Does the Chill Kill?" *Liver Transpl.* 848-858. DOI: 10.1002/lt.25464

I. Journal article: Nuo Yang, et al, Patient outcomes related to the daytime versus after-hours surgery: A meta-analysis*, Journal of Clinical Anesthesia***,** 2019 May, 54, 13-18. DOI: 10.1016/j.jclinane.2018.10.019

J. Journal article: Javanbakht M, et al (2020). Cost-utility analysis of normothermic liver perfusion with the OrganOx *metra* compared to static cold storage in the United Kingdom. *Journal of Medical Economics*. 26:1-9. DOI: 10.1080/13696998.2020.1804391.

K. Awards for the OrganOx metra a) IET Innovation Emerging Technology Design Award 2013 Winner http://www.ibme.ox.ac.uk/news-events/news/three-prestigious-awards-for-department-spin-out-organox, b) Royal Academy of Engineering 2019 https://bit.ly/2R78No5, c) MedTech Insights Awards 2019 https://pharmaintelligence.informa.com/events/awards/medtech-insight-awards-2019/winners-2019.