Institution: University of Oxford

Unit of Assessment: 12 – Engineering

Title of case study: Normothermic Machine Perfusion for Increased Liver Graft Utilization and Improved Transplantation Outcomes

Period when the underpinning research was undertaken: 2004 - 2018

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:
Prof. Constantin Coussios	Director of the Institute of Biomedical Engineering	2004-present

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

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

1. Summary of the impact

Resulting from cross-disciplinary biomedical engineering research at the University of Oxford's Department of Engineering Science, the OrganOx *metra* is the world's first normothermic organ preservation device used for improved and prolonged preservation and functional testing of livers prior to transplantation. It enables the safe utilization of over 70% of livers which were until recently deemed unsuitable for transplant and makes it possible for hospitals to perform the majority of their transplants as a planned daytime procedure by more than doubling the total safe preservation time to well over 24 hours. Commercialisation of this device has resulted in over GBP7,000,000 of direct sales since product CE marking in 2016. Based on the evidence produced by a 220-patient randomized clinical trial (2016-17) published as a cover story in Nature (May 2018), normothermic machine perfusion was endorsed by the National Institute for Health and Care Excellence (NICE) in January 2019. The OrganOx *metra* is today deployed and routinely used in all seven UK liver transplant centres and has been used to perform over 850 liver transplants across 13 countries. Machine perfusion is currently used to preserve 12% of transplanted livers in the UK, with early-adopting individual UK transplant centres reporting a transformative 30% increase in their annual liver transplant numbers within current donation practice.

2. Underpinning research

The research underpinning the development of the world's first normothermic liver perfusion device took place as close cross-disciplinary collaboration between the Department of Engineering Science (led by Prof. Constantin Coussios *FREng*) and the Department of Surgical Sciences (led by Prof. Peter Friend *FMedSci*) between 2005 and 2019. Whilst there was overlap between the two departments in creating the *metra*, Prof. Coussios was responsible for its engineering, particularly haemolysis minimization, controller design and perfusion automation, and Prof. Friend led the surgical usability aspects of the metra, the *in vivo* work and the clinical trials. The device is the first to enable preservation of an organ in a functioning state outside the body for periods of up to 24 hours clinically [**R3**, **R5**] and up to 48 hours pre-clinically [**R4**], making it possible to (i) preserve organs for at least twice as long as conventional cold preservation techniques; (ii) assess the function of the graft during preservation before putting the recipient at risk; and (iii) safely use livers available within current donation practices that are currently perceived as being too risky for transplant, including fatty livers and organs from donors following circulatory death.

Coussios and Friend realized that improved preservation and organ utilization could only be achieved by replicating, in a robust, automated fashion, the physiological conditions encountered by the organ within the body, through perfusion of the organ at physiological temperature (37°C) with a red-cell suspension reconstituted from donor blood of the same blood type [**R2**]. The first key engineering challenge stems from fluid mechanics: both during rewarming from ice temperature and during normal operation, the liver will dramatically alter its vascular resistance to

flow, requiring a haemodynamic controller and fluidic circuit that allow the organ to regulate its own blood supply [**R2**], without ever forcing blood through the organ. This needs to be achieved whilst minimizing shear-stress-induced damage to red blood cells (haemolysis) by pumps, tubing and other blood-contacting components, to enable oxygen transfer to the organ over 24 hours without the need to change the perfusate. The second key challenge lies in understanding, predicting and implementing automated controllers to maintain oxygenation, mimicking the function of the lungs, and means of maintaining temperature, recirculating fluid lost by the organ during preservation, and quantifying bile production whilst in transport.

Following construction and testing of an early prototype, successful large animal trials of the prototype device between 2006-08 demonstrated that normothermic machine perfusion of the liver was able to produce equally good transplant outcomes using highly marginal grafts (from donors after circulatory death having undergone 40 minutes of warm ischaemia) compared to conventional grafts (donors after brain death with no warm ischaemia) [**R1**]. This evidenced the technology's potential for improved utilization of grafts that are currently not retrieved or retrieved and not transplanted.

Building on this finding, OrganOx Ltd was founded as a University spin-out in 2008 to design, build and test the *metra* device for a Phase I trial that demonstrated the safety and feasibility of normothermic liver preservation in a clinical setting. This was published as a cover article in the American Journal of Transplantation in 2016 [**R3**]. The OrganOx *metra* is arguably one of the most complex medical devices ever designed and built in the UK, as it must operate safely in operating theatres, during transport by road or in flight, and comprises almost every type of engineering sub-system, including hydraulic, pneumatic, haemodynamic, embedded and remote-access capabilities. A key achievement of the device is its complete automation and resilience following set-up, enabling the preservation of organs in a functioning haemodynamic, synthetic and metabolic state for up to 24 hours without supervision, twice as long as conventional cold storage. The data automatically sensed and collected during preservation, including bile production, maintenance of pH and arterial flow, can then be used to provide a functional assessment of the organ prior to transplantation.

A 220-patient randomized trial comparing warm to cold preservation across 7 European transplant centres was initiated in 2015, completed in 2017 and published in 2018 as a cover article in Nature [**R5**]. This first large randomized trial in liver preservation demonstrated that use of the normothermic device enables a 50% decrease in organ discard rate, a 50% increase in preservation time and yet results in a 50% decrease in post-transplant graft injury. Building on this success, Coussios and Friend received four further major NIHR awards [**G2a-d**], to assess the level of increased utilization that can be achieved nationwide using this novel technology, to explore the possibility of defattening steatotic livers prior to transplantation, to develop the first normothermic device to enable 24-hour preservation of discarded human kidneys [**R6**] and to perform a first-in-human trial of extended normothermic machine perfusion of donor kidneys prior to transplantation.

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

[**R1**] J. Brockmann, S. Reddy, C.-C. Coussios, D. Piggott, D. Guirriero, D. Hughes, R. Morovat, D. Roy, L. Winter and P.J. Friend, 'Normothermic Perfusion: a New Paradigm in Organ Preservation', *Annals of Surgery* 250:1-6 (2009). 10.1097/SLA.0b013e3181a63c10 (Journal article) {266 citations, Google Scholar, 05/01/21}

[**R2**] T. Vogel, J.G. Brockmann, C.-C. Coussios and P.J. Friend, "Normothermic Machine Perfusion of the Liver", in "Methods in Bioengineering: Organ Preservation and Reengineering", eds. Martin Yarmush and Robert Langer, Elsevier Special Series on Biotechnology pp1-20 (2011). (eISBN:9781608070145) (Book chapter, supplied on request)

[**R3**] R. Ravikumar, W. Jassem, H. Mergental, N. Heaton, D. Mirza, T. Perera, A. Quaglia, D. Holroyd, T. Vogel, C.-C Coussios and P.J. Friend, "Liver Transplantation After Ex Vivo Normothermic Machine Preservation: a Phase 1 (First-in-Man) Clinical Trial", *Am. J. Transplant*. 16(6):1779-87 (2016). 10.1111/ajt.13708 (Journal article) {297 citations, Google Scholar, 05/01/21}

[**R4**] T. Vogel, J.G. Brockmann, D. Pigott, D.A. Neil, A.S.R. Muthusamy, C.C. Coussios and P.J. Friend, "Successful Transplantation of Porcine Liver Grafts Following 48-hour Normothermic Preservation". *PLOS ONE* 12(11): e0188494 (2017). 10.1371/journal.pone.0188494 (Journal article) {27 citations, Google Scholar, 05/01/21}
[**R5**] D. Nasralla, C-.C. Coussios, *et al* , "A Randomized Trial of Normothermic Preservation in Liver Transplantation", *Nature* 557: 50–56 (2018). 10.1038/s41586-018-0047-9 (Journal article) {344 citations, Google Scholar, 05/01/21}
[**R6**] Weissenbacher, L. Lo Faro, O. Boubriak, M.F. Soares, I.S. Roberts, J.P. Hunter, D. Voyce, N. Mikov, A. Cook, R.J. Ploeg, C.C. Coussios and P.J. Friend. "Twenty-four-hour normothermic perfusion of discarded human kidneys with urine recirculation", *Am J Transplant*. 19 (1), 178-192 (2019). 10.1111/ajt.14932 (Journal article) {23 citations, Google Scholar, 05/01/21}

Grants:
[**G1**] To University of Oxford, EU 7th Framework programme grant (305934, R. Ploeg PI, Friend co-I) (http://www.cope-eu.com/)
[**G2a**] To University of Oxford, NIHR i4i award (NIHR201003, Friend PI, Coussios co-I) GBP1,029,499 [**G2b**] To University of Oxford, NIHR/MRC EME (NIHR131163, Friend PI, Coussios co-I) GBP1,173,123 [**G2c**] To University of Oxford, NIHR i4i award (II-ES-1010-10096, Friend PI, Coussios co-I) GBP845,381 [**G2d**] To University of Oxford, NIHR i4i award (NIHR200022, Friend PI, Coussios co-I) GBP908,482

4. Details of the impact

From trials to widespread adoption

The first patient was successfully transplanted in February 2013, and following successful completion of this Phase I study [**R3**], the OrganOx *metra* received its CE mark as a medical device in 2016. By December 2020, the OrganOx *metra* was being used routinely across all UK transplant centres and had been used to perform over 850 liver transplants in 4 continents and 13 countries (UK, Austria, Italy, Spain, Germany, Belgium, France, the Netherlands, India, UAE, Australia, Canada, USA) to maximize organ utilization [**S1**].

Patient Benefit – Make the Untransplantable Transplantable

Liver transplantation is a highly effective procedure that is heavily constrained by the limited pool of donor organs. Deaths from liver disease have soared by 25% in a decade and continue to rise, while the average age of death from liver disease (currently 50-59 years) continues to decrease. In the UK in the year to March 2018, there were 1,574 deceased donors, 1,149 liver retrievals and 975 liver transplants, indicating an underwhelming 62% overall liver utilization. The highest-risk donor organs, including from donors after circulatory death (DCDs) rather than donors after brain death (DBDs), were particularly poorly utilized (34%). As a result of this under-utilization, 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 [**S2**].

The OrganOx *metra* dramatically improves liver graft utilization, both amongst organs currently being considered for transplantation and amongst those currently discarded by every single transplant unit in the UK. The 220-patient randomized control trial comparing preservation by normothermic machine perfusion to static cold storage demonstrated that, even amongst organs currently deemed suitable for transplantation, the organ discard rate was halved, from 24% to 12% ($p=0.008$). Even though more organs (including more marginal organs) were utilized and were preserved for 50% longer, the post-transplant outcomes were still significantly better for normothermically preserved organs, as evidenced by a 49% reduction ($p<0.001$) in transaminase levels post-transplant (a validated surrogate marker for graft survival) [**R5**]. A second, independent study (VITTAL: Viability Testing and Transplantation of Marginal Livers, NCT02740608), led by the University of Birmingham and funded by the Wellcome Trust, investigated the impact of normothermic machine perfusion on utilization of liver grafts that had been discarded by all 7 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 utilization of over 70% of presently discarded grafts**.** [**S3**]

Based on this evidence, machine perfusion was endorsed by the National Institute for Health and Care Excellence (NICE) in January 2019 [**S4a**]. Machine perfusion is currently used to preserve 12% of transplanted livers in the UK. [**S2**]. 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*" [**S4b**].

The OrganOx *metra* is now deployed across all 7 liver transplant centres in the UK (Birmingham, Cambridge, King's, Leeds, Edinburgh, Royal Free and Newcastle) [**S1**]. The Professor of Transplantation at Addenbrooke's hospital, 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*." [**S5**]

Impacts on transplantation practice

The benefit of the OrganOx *metra* is not only due to the obvious healthcare benefit of increased organ utilization, but also on the positive impact of increased preservation times (from the conventional maximum of 12 hours to well over 30 hours) on transplantation logistics and the ability to plan transplants as day cases. A recently published UK health economic study conducted by the University of Southampton [**S6**] 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.

In Austria, the OrganOx *metra* has now been introduced for "[…]routine use in marginal organs, logistic challenges and complex recipients[…]", resulting in livers being "[…]successfully transplanted after preservation of up to 38 hours" 3 times longer than previously possible by conventional static cold storage. As a result, "night-time procedures and parallel transplantations were eventually omitted". In addition the use of the *metra* enabled a 36% (9/25) increase in transplant numbers [**S7**]. In a clinical trial, use of the *metra* device allowed 84% of transplants to take place during the day versus 65% with static cold storage [**S8**]. This may help transplant surgical teams avoid 'burn-out' of key personnel. There is good evidence that daytime operations have better outcomes; for example, Yang et al [**S9**] 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*".

Economic Impact

In the first three years since product CE marking in 2016, the OrganOx *metra* has seen over GBP7,000,000 of cumulative direct sales. As of Oct 2020, the company employs 29 staff (headcount: 29): 23 in the UK, 4 based 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 [**S1**]. 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 [**S1**].

Recognition

The engineering excellence of the OrganOx *metra* was recognised in the November 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 also shortlisted as one of 4 finalists for the 2019 50th anniversary MacRobert award which recognizes "engineering teams that demonstrate outstanding innovation, tangible societal benefit and proven commercial success within the UK engineering sector." Prof. Coussios further received the 2017 Silver Medal of the Royal Academy of Engineering for his role in the invention, development and clinical adoption of normothermic machine perfusion, and was elected a Fellow of the Royal Academy of Engineering in 2019. 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."* [**S10**]

5. Sources to corroborate the impact

[**S1**] Corroborator 1: CEO, OrganOx Ltd, may be contacted to confirm sales and use of the device worldwide, and employment data.

[**S2**] 2019-20 NHS Blood & Transfusion Report on Liver Transplantation corroborating statistics relating to liver disease and liver transplantation, and (pg21) on use of machine perfusion.

[**S3**] Mergental H, et al. Transplantation of discarded livers following viability testing with normothermic machine perfusion. *Nature communications*. 2020 Jun 16;11(1):1-2. doi: 10.1038/s41467-020-16251-3 (Journal article) Independent study results using the OrganOx *metra.*

[**S4**] **a**) Evidence of NICE approval (under special arrangements) of machine perfusion and **b)** NICE press release with testimonials from 16th January 2019: "More donor livers could be used for transplantation thanks to exciting new development, NICE says".

[**S5**] Letter from Professor of Transplantation, University of Cambridge, corroborating the benefits of the OrganOx *metra* and its adoption for routine procedures.

[**S6**] Javanbakht M, et al., "Cost-utility analysis of normothermic liver perfusion with the OrganOx *metra* compared to static cold storage in the United Kingdom." *Journal of Medical Economics*. 2020 Aug 26:1-9. doi: 10.1080/13696998.2020.1804391 (Journal article) Evidence of the cost-effectiveness of the device.

[**S7**] Cardini B, et al. Clinical Implementation of Prolonged Liver Preservation and Monitoring Through Normothermic Machine Perfusion in Liver Transplantation. *Transplantation*. 2020 Sep;104(9):1917-1928. doi: 10.1097/TP.0000000000003296. PMID: 32371845 (Journal article) Evidence of testimonials and international use of the *metra*.

[**S8**] Mariusz Bral, Khaled Dajani, Dayne Leon Izquierdo et al., "A Back-to-Base Experience of Human Normothermic Ex Situ Liver Perfusion: Does the Chill Kill?" *Liver Transpl* 2019 Jun 25(6):848-858. doi: 10.1002/lt.25464 (Journal article) Evidence corroborating the benefits of Normothermic Machine Perfusion.

[**S9**] 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 (Journal article) Evidence of the benefits of daytime surgery.

[**S10**] Portfolio of engineering awards for the OrganOx *metra* **a**) IET Innovation Emerging Technology Design Award 2013 Winner, **b**) OrganOx - Royal Academy of Engineering 2019, and **c**) Winners MedTech Insights Awards 2019, **d**) Professor Coussios RAEng Silver Medal.