

Institution: University of Birmingham		
Unit of Assessment: UoA 1, Clinical Medicine		
Title of case study: Using suboptimal livers to save lives in transplant surgery		
Period when the underpinning research was undertaken: 2013–2020		
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:
Dr Simon Afford	Reader in Liver Immunology	1997–present
Mr Hynek Mergental	Honorary Senior Clinical Lecturer	2013–present
Professor Darius Mirza	Honorary Professor	1997–present
Period when the claimed impact occurred: 2014–December 2020		
Is this case study continued from a case study submitted in 2014? No		
1. Summary of the impact Summary of the impact The University of Birmingham has contributed to the development of machine perfusion to preserve donor livers and test their suitability ahead of transplant. This has enabled suboptimal-quality donor livers, previously rejected for transplantation, to be used safely. As a result we have: (i) Improved health and well-being of patients with liver disease, through 250 life-saving transplants carried out to date in the UK alone; (ii) Changed UK and US clinical guidelines on the use of liver machine perfusion in liver transplantation; (iii) Changed the practice of liver transplantation worldwide with up to 70% of suboptimal-quality livers now being transplanted; (iv) Improved liver transplant services in the UK contributing to an increase in transplants performed each year by 14% since 2014. (v) Raised public awareness of the new methods in liver transplantation.		
2. Underpinning research Liver disease is a major health problem worldwide. Incidence has increased 5-fold over the last 40 years. It is now the fifth commonest cause of premature death globally accounting for 8,500 deaths annually in the UK. Liver transplantation is a highly effective treatment for patients with end-stage liver disease and 5-year survival rates are 60–70%. However, access to life-saving transplantation is limited by a shortage of donor organs. 12% of patients registered on the transplant list in 2017–2018 died or became too sick for transplant within 12 months of being added to the list and a further 12% waited over 12 months to receive a liver. This shortage is a consequence of both greater demand, i.e. more patients needing transplantation, and the quality of donated organs decreasing over the last decade due to the increasing age, obesity and co-morbidities of many donors. Today, one third of donated livers are suboptimal quality and considered high-risk for transplant, and many are not used. In 2019, 15% of the retrieved donor livers were rejected and discarded compared to 10% in 2009. In 2013, Afford and Mergental at the University of Birmingham (UoB) established a research programme aimed at reducing the number of donor livers discarded by maximising the functional quality of sub-optimal organs. To do this they: • Developed methods to improve the preservation and recovery of function of suboptimal donated livers;		

- Established a set of 'viability criteria' that donated livers must meet to be transplanted.

Previously, donor livers were kept in cold storage until transplant in order to slow metabolism and reduce the effects of oxygen deprivation. Work by other groups in the UK and internationally had suggested that passing fluid through an organ's blood vessels ('perfusing') prior to transplant improves transplant efficiency. Friend (Oxford) proposed that to do this at body temperature (normothermic) might further enhance the quality of donor organs by preserving metabolic reactions important for liver function. If so, this could reduce the likelihood of organ damage during storage and transplantation, a particular problem when transplanting suboptimal livers. This led Afford's group to perform preclinical studies to assess whether donor livers could be preserved using machines that perfuse blood at body temperatures, so-called 'normothermic machine liver perfusion' (NMLP). At the same time, they developed a panel of tests that allowed assessment of the function of the preserved livers. In 2013/14, they used NMLP in the laboratory to preserve 12 livers that had been turned down by the transplant programme because they were considered too damaged to safely transplant. They found that the rejected livers could be divided into 2 groups according to whether or not they could clear lactate (a metabolite produced in response to oxygen deprivation). The ability to clear lactate was thus an indication of reduced tissue breakdown, better metabolic recovery and better liver function — all factors that would be expected to result in better transplant outcome. Lactate clearance and other functional tests were then incorporated into novel viability criteria capable of defining which suboptimal livers treated by NMLP are safe to transplant [R1].

In August 2014, the Liver transplant team at the Queen Elizabeth Hospital Birmingham carried out the first ever human transplant of a suboptimal donor liver reconditioned by NMLP and assessed using the novel viability criteria [R2]. By 2015, the team had completed the first pilot series of 5 suboptimal livers transplanted after NMLP. All livers functioned well and patients survived [R3]. The team published the protocol for the VITTAL (Viability Testing and Transplantation of mArginal donor Livers) clinical trial incorporating their viability criteria to assess the success of NMLP prior to transplantation [R4]. The trial commenced in 2017 and, in total, 31 suboptimal livers rejected for transplant by all UK transplant centres were enrolled and subjected to NMLP. 22 livers (71%) met the viability criteria and were successfully transplanted into recipients with 100% 12-month patient and organ survival [R5].

Key Findings (KF) from this research include:

KF1: Rejected, suboptimal donor livers are safe to transplant within 2–3 hours of warm perfusion (NMLP) if they fulfil viability criteria [R1].

KF2: Over 70% of suboptimal donor livers turned down for transplantation on standard criteria can be safely transplanted after NMLP [R5].

KF3: Suboptimal donor livers treated by NMLP that meet the viability criteria have excellent survival rates at 1-year when used for transplant [R2, R3, R5].

3. References to the research

- R1.** Development of Clinical Criteria for Functional Assessment to Predict Primary Nonfunction of High-Risk Livers Using Normothermic Machine Perfusion. **Mergental H**, Stephenson BTF, Laing RW, Kirkham AJ, Neil DAH, Wallace LL, Boteon YL, Widmer J, Bhogal RH, Perera MTPR, Smith A, Reynolds GM, Yap C, Hübscher SG, **Mirza DF**, **Afford SC**. *Liver Transpl.* 2018 Oct;24(10):1453-1469. doi: 10.1002/lt.25291. PMID: 30359490
- R2.** First human liver transplantation using a marginal allograft resuscitated by normothermic machine perfusion. Perera T, **Mergental H**, Stephenson B, Roll GR, Cilliers H, Liang R, Angelico R, Hübscher S, Neil DA, Reynolds G, Isaac J, Adams D, **Afford S**, **Mirza DF**, Muiesan P. *Liver Transpl.* 2016 Jan;22(1):120-4. doi: 10.1002/lt.24369. No abstract available. PMID: 26566737
- R3.** Transplantation of Declined Liver Allografts Following Normothermic Ex-Situ Evaluation. **Mergental H**, Perera MT, Laing RW, Muiesan P, Isaac JR, Smith A, Stephenson BT, Cilliers H, Neil DA, Hübscher SG, **Afford SC**, **Mirza DF**. *Am J Transplant.* 2016 Nov;16(11):3235-3245. doi: 10.1111/ajt.13875. Epub 2016 Jul 13. PMID: 27192971

R4. Viability testing and transplantation of marginal livers (VITTAL) using normothermic machine perfusion: study protocol for an open-label, non-randomised, prospective, single-arm trial. Laing RW, **Mergental H**, Yap C, Kirkham A, Whilku M, Barton D, Curbishley S, Boteon YL, Neil DA, Hübscher SG, Perera MTPR, Muiesan P, Isaac J, Roberts KJ, Cilliers H, **Afford SC**, **Mirza DF**. BMJ Open. 2017 Nov 28;7(11):e017733. doi: 10.1136/bmjopen-2017-017733. PMID: 29183928

R5. Transplantation after viability testing of discarded livers with normothermic machine perfusion: The VITTAL trial outcomes. **Mergental H**, Laing RW, Kirkham AJ, Yap C, Perera MPR, Boteon YL, Attard J, Barton D, Curbishley S, Wilku M, Neil DA, Hübscher SG, Muiesan P, Isaac JJ, Roberts KJ, Abradelo M, Cilliers H, Isaac J, Bion J, Murphy N, Morris C, Friend PJ, **Afford S**, **Mirza DF** Nature Communications 2020; 2020;11(1):2939. doi: 10.1038/s41467-020-16251-3

4. Details of the impact

(i) Improved the well-being of patients with liver disease requiring life-saving transplantation by increasing the number of transplantable donor organs

The lives of over 250 UK patients with end-stage liver disease have been saved as a result of the introduction of the UoB protocol for NMLP [R5; S1]. This includes 56 high-risk patients who were part of the NAPLES (Normothermic mACHine Perfusion of the Liver to Enable the high-risk recipientS) study. Previously, such patients would not have been considered candidates for suboptimal livers and 40% of them would have died waiting for a high-quality donor organ. 1-year patient survival was 93% after these most complex operations and there was no transplant-related mortality [S1]. As a result of these studies, NMLP is being adopted into routine practice allowing more patients to be successfully treated with a life-saving liver transplant.

Patients transplanted with suboptimal donor livers not only survive, the majority **have a near normal health-related quality of life and good life expectancy**. Patients' quality of life increases by 23% within 6 months of receiving a NMLP viability tested suboptimal liver [S2]. One of the first recipients of a rejected donor liver prepared for transplant using the Birmingham methods said "I couldn't be more happy. Without that machine I wouldn't have received this liver. I'm looking forward to a future. I think those two words right there, 'a future', says it all" [R2; S3i and ii].

(ii) US and UK clinical guidelines recommend the use of liver machine perfusion in liver transplant surgery

- In 2018, **The American Society of Transplant surgeons (ATS) Standards Committee** recommended liver machine perfusion as the best standard of care. In a white paper on Ex-Situ Liver Machine Perfusion, the Birmingham work [R3] is directly cited as the basis for this recommendation [S4].
- In 2019, the **UK National Institute for Health and Care Excellence (NICE)** drew on the evidence in [R3] to conclude that "ex-situ machine perfusion for extracorporeal preservation of livers for transplantation should be used under special arrangements" as more data is gathered as to its efficacy [S5i, Recommendation 1.1; S5ii]. The Birmingham studies were also highlighted in a headline news article by NICE [S5iii].

(iii) Worldwide change in clinical practice of liver transplant surgeons

In response to the Birmingham studies, transplant teams worldwide have **changed their practice and incorporated NMLP as part of their routine practice** [R3, R4; S6i]. In the UK, all 7 transplant centres now use NMLP and of these, 5 regularly use reperfusion by NMLP, with 4 of the 5 centres following our criteria to confirm functional viability of the liver. Testimonial statements from liver surgeons at leading liver transplant centres across Europe and the US confirm that adoption of Birmingham's methods has taken place globally [S6ii – iv]:

the benchmarks for assessing the functionality of the graft during machine perfusion, defined by the Birmingham group, have been adopted all over the world, as in our Liver Transplantation Unit. [Senior Lecturer in the Department of Surgical Science, University of Rome Tor Vergata, S6ii]

We use the criteria developed by Dr. Mergental on a daily basis and his work guides us in the field of ex-situ organ assessment. [Director, Liver Transplantation Cleveland Clinic, Ohio, S6iii].

[...] it cannot be overstated how important these criteria are [...] The Birmingham liver perfusion group has made an immense impact in the field of liver perfusion, and many feel this work will ultimately result in a paradigm shift in liver utilization and recipient outcomes. [Assistant Professor of Surgery in the Division of Transplant Surgery, University of California San Francisco, S6iv]

Other centres that have adopted the methodology include:

- **Europe:** Royal Free Hospital, Kings College Hospital, Leeds Teaching Hospital, Edinburgh, Innsbruck, Rome, Barcelona, Leuven, Hannover;
- **Australia:** Melbourne, Sydney, Perth;
- **North America and USA:** UPenn Philadelphia, Cleveland Clinic, St Louis, Ochsner New Orleans, Washington University, Duke University, Mayo Clinic Phoenix, University of Florida;
- **Canada:** Edmonton, Toronto;
- **China:** Guongdong Hospital, which has also evolved UoB's criteria to develop an ischaemia-free preservation method.

(iv) Improved Liver transplant services in the UK by minimising the proportion of retrieved livers rejected

Data from the Organ Donation and Transplantation reports published by NHS Blood and Transplant (NHSBT) show that **between 2014 and 2019 the number of transplants performed increased 14% (118 transplants), waiting list size decreased 21% (117), on-waiting-list patient mortality fell by 42% (34 patients) and the time patients wait on the list for transplant went down by 32% (46 days)** [S7]. Acknowledging that Birmingham's work contributed to these improved outcomes, the Medical Director of Organ and Tissue Donation and Transplantation, NHSBT stated: "The methods introduced by Birmingham to preserve and confirm the viability of donated livers prior to use in transplant has led to a greater proportion of the donated organs being actually transplanted into patients" [S8i]. The same view was echoed by the Chair of the NHSBT Liver Advisory Group, who stated that UoB's viability criteria have been "used safely to increase utilisation of donor livers and ensure that they are transplanted safely" [S8ii].

(v) Raised public awareness of the new methods in liver transplantation

The extensive coverage of UoB's research in medical and general media news articles globally has meant that **patients and the public have become aware of the innovations in liver transplantation** and the ability of surgeons to use more of the donor livers retrieved safely and with high efficacy, which gives hope and reassurance to potential recipients and encourages organ donation. For example, the BBC's ground-breaking documentary series 'Surgeons: At the Edge of Life', described the team's research and the story of a patient who participated in the first case series [R3; S3i and S9i]. The Altmetric attention score of 240 for R5 (as of 11/09/2020) placed it within the top 1% of research outputs with regard to the quality and quantity of online attention that it received, indicating the international interest and significance of the work to the public [S9ii].

5. Sources to corroborate the impact

- S1** Abstract reporting interim results from the NAPLES study.
- S2** Quality of life follow-up study from the VITTAL trial.
- S3i** Mv4 file of Episode 3 from the BBC documentary series 'Surgeons at the Edge of Life' (Jan 2018) featuring UoB's work on NMLP in liver transplantation surgery.
- S3ii** Testimonial from liver transplant patient receiving a suboptimal liver prepared by NMLP (Jan 2018).
- S4** The American Society of Transplant surgeons (ATS) Standard Committee White Paper on Ex-Situ Liver Machine Perfusion (May 2018).
- S5i** NICE guidance [IPG636] (2019) on Ex-situ machine perfusion for extracorporeal preservation of livers for transplantation.
- S5ii** Evidence for NICE Guidance [IPG636] (2019) on ex-situ machine perfusion for extracorporeal preservation of livers for transplantation.
- S5iii** NICE headline article accompanying NICE Guidance [IPG636].
- S6i** Liver Transplantation Review. Resch T, Cardini B, Oberhuber R, Weissenbacher A, Dumfarth J, Krapf C, Boesmueller C, Oefner D, Grimm M, Schneeberger S. Transplanting Marginal Organs in the Era of Modern Machine Perfusion and Advanced Organ Monitoring. Front Immunol. 2020 May 12;11:631. doi: 10.3389/fimmu.2020.00631.
- S6ii-iv** Testimonials from international surgeons in liver transplantation (July 2020).
- S7** Data report compiled from annual Organ Donation and Transplantation Reports by NHSBT between 2013/14 and 2018/19.
- S8i** Testimonial from the Medical Director of Organ and Tissue Donation and Transplantation, NHSBT (Oct 2020).
- S8ii** Testimonial from the Chair of the NHSBT Liver Advisory Group (Oct 2020).
- S9i** Headline TV and newspaper articles on UoB NMLP research.
- S9ii** Altmetric score page for [R5].