Institution: University of Sheffield		
Unit of Assessment: B-12 Engineering		
Title of case study: Making saving eyesight simple		
Period when the underpinning research was undertaken: 2003–2014		
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:**
MacNeil, S.	Professor of Tissue Engineering	1976–2018
Deshpande, P.	Postdoctoral Researcher	2009–2014
Period when the claimed impact occurred: August 2013–2020		
Is this case study continued from a case study submitted in 2014? N		

1. Summary of the impact (indicative maximum 100 words)

Sheffield's innovative research integrating tissue culture techniques with ocular surgery has led to a new treatment for blindness caused by ocular burns, called simple limbal epithelial transplant (SLET). To date 1,291 children and adults, across 14 countries in Asia, Europe, North and South America, have had their eyesight saved. SLET removes the need for dedicated clinical grade tissue culture facilities, results in improved patient outcomes and treatment accessibility, and a 90% reduction in treatment costs (INR400m saved in India). Furthermore, by providing new skills and treatment strategies to ophthalmologists, SLET has enabled them to treat more patients since August 2013 than with existing procedures over the past 20 years.

2. Underpinning research (indicative maximum 500 words)

Limbal stem cells ensure the avascularity and transparency of the cornea whilst preventing conjunctival epithelium cells (the white of the eye) from growing over the cornea. Limbal stem cell deficiency (LSCD) involves dysfunction or loss of these stem cells, ultimately resulting in blindness. Chemical and thermal burns are a primary cause of LSCD. In the EU, this only occurs in 30 people per million; in developing countries this domestic and workplace hazard is far more common and, for example, is estimated to have affected 1.5 million adults and children in India.

Since the 1990's, LSCD has been treated with conjunctival-limbal autograft (CLAU) which is a simple procedure but has a high risk (16%) of eyesight loss in both healthy and damaged eyes, and cultivated limbal epithelial transplantation (CLET) which is more complex and expensive procedure (a single European CLET treatment in costs £80,000 +VAT).

In 2003, research by Sheffield's Biomaterials and Tissue Engineering research group, led by Professor Sheila MacNeil, investigated the treatment of skin burns and non-healing wounds without the need to grow layers of epithelial cells. MacNeil showed that transferring sub-confluent populations of keratinocytes using an acrylic acid coated silicone carrier dressing worked as well as culturing cells into a continuous stratified layer **[R1]**. The dressing was successfully commercialised (MySkin) and proved to be a simpler and more robust method for delivering patient's own skin cells from the laboratory to patients in the clinic **[R2, R3]**.

Based on these insights and collaborating with India's leading ophthalmology hospital, LV Prasad Eye Institute (LVPEI), MacNeil and Deshpande conducted research with synthetic

alternatives to the human amniotic membrane used as a temporary dressing to deliver patient's cultured limbal stem cells to the cornea **[R4]**. During this time, MacNeil questioned the need to culture the limbal stem cells in a laboratory and hypothesised the possible transplantation of small pieces of tissue from the healthy eye directly into the affected eye of unilateral LSCD sufferers **[S3]**. MacNeil's prior experience of successfully translating the Sheffield skin repair research from the benchtop to the clinic now led to the development of a new approach to LSCD that essentially mitigated the risk of CLAU and the costs of CLET.

Working in close collaboration with LVPEI clinicians, MacNeil's novel approach SLET was developed into a new surgical procedure. A tiny 4 mm² strip of limbal tissue is harvested from a patient's healthy eye, subdivided into 8-10 stem cell explants, and evenly distributed over an amniotic membrane. When placed onto the damaged ocular surface the cells grow into a continuous epithelium. This technique eliminated the need for *ex vivo* expansion and a second surgery associated with CLET, and it was quickly translated, by LVPEI, into a first-in-human trial (6 patients). Sight was restored within 42 days, with visual acuity improving from worse than 20/200 (legally blind) in all affected eyes to 20/60 (near normal vision) or better in four eyes. These outcomes were comparable to CLET, but 2-3 weeks faster and using half the theatre time **[R5]**. Figure 1 shows clinical photographs of a recipient's eye before and after surgery.

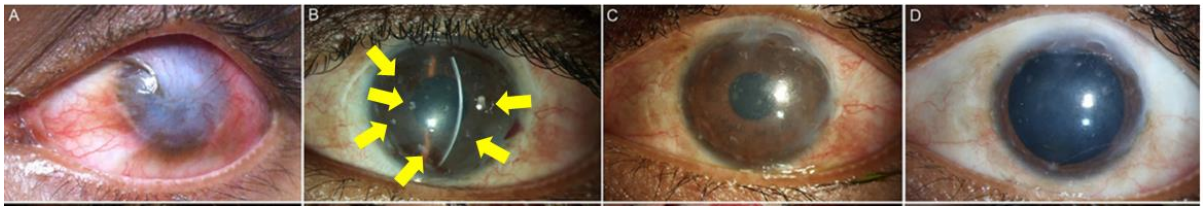

Figure 1. (A) Lime injury presented with a conjunctivalised corneal surface, (B) post repair at six weeks, arrows indicate positions of corneal explants (C) 3 months and (D) 6 months after SLET, the corneal clarity gradually improved. The visual acuity at 6 months after SLET was 20/20. Reproduced from **[R5]**.

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

Sheffield staff and students are in **bold** text.

R1. **MacNeil, S.** (2007). Progress and opportunities for tissue-engineered skin. *Nature, 445*(7130), 874–880. https://doi.org/10.1038/nature05664. Cited by 633.

R2. Hernon, C. A., **Dawson, R. A.,** Freedlander, E., **Short, R.,** Haddow, D. B., Brotherston, M., & **MacNeil, S**. (2006). Clinical experience using cultured epithelial autografts leads to an alternative methodology for transferring skin cells from the laboratory to the patient. *Regenerative Medicine, 1*(6), 809–821. https://doi.org/10.2217/17460751.1.6.809. Cited by 67.

R3. **Moustafa, M., Bullock, A. J.,** Creagh, F. M., Heller, S., Jeffcoate, W., Game, F., Amery, C., Tesfaye, S., Ince, Z., Haddow, D. B., & **MacNeil, S.** (2007). Randomized, controlled, single-blind study on use of autologous keratinocytes on a transfer dressing to treat nonhealing diabetic ulcers. *Regenerative Medicine, 2*(6), 887–902. https://doi.org/10.2217/17460751.2.6.887. Cited by 60.

R4. **Deshpande, P.,** Ramachandran, C., **Sefat, F.,** Mariappan, I., **Johnson, C.,** McKean, R., **Hannah, M.,** Sangwan, V. S., **Claeyssens, F., Ryan, A. J.,** & **MacNeil, S.** (2013). Simplifying corneal surface regeneration using a biodegradable synthetic membrane and

limbal tissue explants. *Biomaterials, 34*(21), 5088–5106. https://doi.org/10.1016/j.biomaterials.2013.03.064. Cited by 41.

R5. Sangwan, V. S., Basu, S., **MacNeil, S.,** & Balasubramanian, D. (2012). Simple limbal epithelial transplantation (SLET): a novel surgical technique for the treatment of unilateral limbal stem cell deficiency. *British Journal of Ophthalmology, 96*(7), 931–934. https://doi.org/10.1136/bjophthalmol-2011-301164. Cited by 152.

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

Sheffield's research enabled the clinical uptake of a pioneering new treatment for blindness. SLET surmounts major socio-economic and technical barriers associated with conventional techniques, increasing treatment accessibility for sufferers in developing countries. The World Health Organisation highlights that blindness causes removal from the workforce, deteriorating mental health, limited mobility, increased risk of accidents, and restricts child development. Restoring sight ameliorates these impacts for any individual and their dependants.

Chair of Regenerative Ophthalmology at the LVPEI in India stated *"This technique is now very much the standard of care in India. [...] The simplification of the technique has meant that it is more accessible to more centers and surgeons and hence more patients"* **[S1]**. The Director of the Ocular Surface Center at Bascom Palmer Eye Institute in the USA commented, *"it can be done anywhere in the world as a same-day surgery, you don't need fancy instruments or ex vivo expansion in a lab"* **[S2]**. The Director of Innovation at Dr Shroff's Charity Eye Hospital in New Delhi, India stated, *"there are less than 3 hospitals in India with established clean rooms suitable for CLET, whereas SLET is available to any hospital with trained surgeons"* **[S3]**.

Impact on the health and well-being of people

Based on the enhanced clinical outcomes from the initial clinical study **[R4]** and the costs associated with CLET that limited patient access **[S1**, **S3]**, the LVPEI decided in 2013 to perform SLET instead of CLET **[S1]**. A recent review verified the enhanced outcomes with statistically significant higher anatomical success rates with SLET (78%) than CLET (61%) **[S4]**.

The LVPEI sees approximately 100 new patients every year **[S5]**. Importantly, new patients can be treated promptly with SLET, whereas when the LVPEI used CLET, the number of patients was limited to the number that the cell culture laboratory could handle. To date, LVPEI has undertaken more than 750 SLET treatments and the Dr Shroff's Charity Eye Hospital has undertaken 70 SLET treatments **[S1, S3]**.

The international visibility of the success of SLET has led to its further uptake. SLET was voted the best limbal stem cell transplantation technique at the US ASCRS-ASOA symposium in 2016 **[S6]**. A review of published clinical studies during the REF period reported outcomes for 92 patients in 13 additional countries spanning Europe (the UK, Germany, Italy, France, Turkey, and Russia), North America (USA, Mexico, and Canada), South America (Brazil), and Asia (Thailand, China, and Japan) **[S7]**. In a 2020, blind survey of the Ocular Surface group of ophthalmologists and the Kera-net group, 135 different respondents from 17 countries reported a total of 1,291 SLET procedures, which was equivalent to the number of CLET and CLAU procedures combined (172 and 1,134 respectively) **[S8]**.

Economic impact

The research has enabled substantial cost savings for healthcare providers and patients. In India, cost is a major determinant of access to a treatment and costs are ultimately borne by the charity of the hospital **[S3]**. Table 1 summarises per patient total treatment costs of CLET and SLET at the LVPEI in 2020 **[S1]**.

	Total treatment cost		SLET cost saving per patient		
	CLET (INR)	SLET (INR)	(INR)	%	(GBP)
Adult	533,184	53,518	479,666	90%	4,931
Children	564,337	69,136	495,201	88%	5,091
Average	548,761	61,327	487,434	89%	5,011

Table 1. Total treatment costs and saved costs per patient at the LVPEI for CLET and SLET. (INR97=GBP1)

By adopting SLET over CLET, the LVPEI operating budget saves approximately INR49m annually, allowing more patients to receive treatment. Over the REF period, the application of Sheffield's research has allowed the LVPEI and Dr Shroff's Charity Eye Hospital to realise combined savings of INR400m for the 820 patients they have treated.

Impact on healthcare practitioners

LVPEI's active dissemination of the research via collaborative working, publications and presentations at meetings, and the provision of five annual international training workshops in India and Sweden (2015-2020) has led to the uptake of the SLET procedure and enhanced the knowledge, expertise, and skills of clinicians **[S9, S1, S3]**. According to the results of the aforementioned survey **[S8]**, over 95% of surgeons were confident using SLET and commented that it is convenient, cost effective, efficient, reliable, and reproducible; 93% of surgeons stated that they preferred SLET over the CLET. In addition, only 8% of the surgeons had access to the specialist facilities required for CLET. SLET has overtaken CLET as the preferred treatment for LSCD and helped more patients in the 7-year REF period than CLET has in the past 20 years.

Overall, the global adoption of SLET has led to the restoration of eyesight of over 1,291 adults and children, with better clinical outcomes than traditional techniques, and at a 90% cost saving, ensuring broader access to treatment. It has influenced the practice of healthcare practitioners in 14 countries worldwide.

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

S1. Confidential testimonial letter from the Chair of Regenerative Ophthalmology at LV Prasad Eye Institute, Hyderabad, India (2019 & 2020). Corroborates a) level of adoption in India, b) challenge of CLET in India, c) change in clinical practice, d) number of treatments undertaken, e) comparative cost of CLET and SLET & f) dissemination of knowledge.

S2. American Academy of Ophthalmology EyeNet Magazine Article on Simple Limbal Epithelial Transplant: Promising Results in the Right Patients (December 2016). Reports

uptake in the US. (Accessed 11th Dec 2020). https://www.aao.org/eyenet/article/simple-limbal-epithelial-transplant-promising-resu

S3. Confidential testimonial letter from the Director of Innovation at Dr Shroff's Charity Eye Hospital, New Delhi, India (2019 & 2020). Corroborates a) challenge of CLET in India, b) number of treatments undertaken, c) how treatments are funded in India & d) dissemination of knowledge.

S4. Shanbhag, S. S., Nikpoor, N., Rao Donthineni, P., Singh, V., Chodosh, J., & Basu, S. (2020). Autologous limbal stem cell transplantation: a systematic review of clinical outcomes with different surgical techniques. *British Journal of Ophthalmology, 104*(2), 247–253. https://doi.org/10.1136/bjophthalmol-2019-314081 reports anatomical success rates of CLET and SLET.

S5. Basu, S., Sureka, S. P., Shanbhag, S. S., Kethiri, A. R., Singh, V., & Sangwan, V. S. (2016). Simple Limbal Epithelial Transplantation: Long-Term Clinical Outcomes in 125 Cases of Unilateral Chronic Ocular Surface Burns. *Ophthalmology, 123*(5), 1000–1010. https://doi.org/10.1016/j.ophtha.2015.12.042. Confirms the number of cases seen by the LVPEI per year (penultimate paragraph in discussion section).

S6. Evidence of 2016 award at American Society of Ophthalmic Administrators symposium (end of article). (Accessed 4th Aug 2020). https://www.eyeworld.org/article-positive-outlook-for-new-technique-to-make-lscd-treatment-safer--cheaper--and-more-widespread

S7. Unpublished literature review of published clinical studies of SLET demonstrating uptake globally (carried out in-house, December 2020). 44 clinical studies across 14 countries to date, this shows a steady increase annually of the clinical use of SLET.

S8. Questions and results of the confidential LVPEI survey of surgeons sent to the Ocular Surface group of ophthalmologists and the Kera-net group concerning their use of SLET (2020). Ethics Ref No LEC BHR-P-04-20-414.

S9. Symposium paper summarising the benefits of SLET: Sangwan, V. S., Jain, R., Basu, S., Bagadi, A. B., Sureka, S., Mariappan, I., & **MacNeil, S**. (2014). Transforming ocular surface stem cell research into successful clinical practice. Indian Journal of *Ophthalmology, 62*(1), 29. https://doi.org/10.4103/0301-4738.126173. Review paper used to disseminate knowledge of SLET technique.