Appendix 1:

Supplementary Table 1: Summary of published literature on outcomes of Simple Limbal Epithelial Transplantation (SLET)

S. No.	Author	Country	Institute/Research group	Year	Type of article	Title	N	Indication	Anatomic Success (%)	Functional Success (%)	Mean Follow up (Years)
1	Sangwan *et al*[4]	India	LVPEI	2012	Clinical Study	Simple limbal epithelial transplantation (SLET): a novel surgical technique for the treatment of unilateral limbal stem cell deficiency.	6	Chemical injury	100	66.6	2.1
2	Bhaleka r *et al*[5]	India	LVPEI	2013	Case Report	Successful autologous simple limbal epithelial transplantation (SLET) in previously failed paediatric limbal transplantation for ocular surface burns.	1	Chemical injury	100	100	1
3	Vazirani *et al*[6]	India	LVPEI	2013	Case Report	Successful simple limbal epithelial transplantation (SLET) in lime injury-induced limbal stem cell deficiency with ocular surface granuloma.	1	Chemical injury	100	100	0.50
4	Amescua *et al*[7]	USA	Bascom Palmer Eye Institute	2014	Case Series	Modified simple limbal epithelial transplantation using cryopreserved amniotic membrane for unilateral limbal stem cell deficiency.	6	Chemical injury LSCD secondary to treatment for Melanoma	100	100	0.63
5	Das *et al*[8]	India	LVPEI	2015	Case Report	Molten metal ocular burn: long-term outcome using simple limbal epithelial transplantation.	1	Thermal Injury	100	100	2.3

6	Hernández-Bogantes *et al*[9]	Mexico	Instituto de Oftalmologia, Fundacion Conde de Valencia na, Bascom Palmer Eye Institute	2015	Clinical Study	Minor ipsilateral simple limbal epithelial transplantation (mini SLET) for pterygium treatment.	10	Primary pterygium	100	NA	0.67
7	Nair *et al*[10]	India	LVPEI	2015	Case Report	Outcome of cataract surgery following simple limbal epithelial transplantation for lime injury-induced limbal stem cell deficiency	1	Chemical Injury	100	100	0.42
8	Vazirani *et al*[11]	India	LVPEI	2015	Case Report	Customised simple limbal epithelial transplantation for recurrent limbal stem cell deficiency.	1	Chemical Injury	100	NA	0.42
09	Arya *et al*[12]	India	Government Medical College, Chandigarh	2016	Case Report	Simple Limbal Epithelial Transplantation in Acid Injury and Severe Dry Eye.	2	Chemical Injury, Severe Dry Eye due to Ocular surface Disease	100	50 (Case 2- cause of poor vision -Optic atrophy secondary to pre-existing glaucoma	0.50
10	Basu *et al*[13]	India	LVPEI	2016	Clinical Study	Simple Limbal Epithelial Transplantation: Long-Term Clinical Outcomes in 125 Cases of Unilateral Chronic Ocular Surface Burns.	125	Chemical Injury	76	75	1.5

11	Mittal *et al*[14]	India	Sanjivni Eye care, DrishtiCone Eye Care	2016	Case Series	Successful management of severe unilateral chemical burns in children using simple limbal epithelial transplantation (SLET).	4	Chemical Injury	100	75	5
12	Mittal *et al*[15]	India	Sanjivni Eye Care Hospital, Centre for Sight, Hyderabad	2016	Case Report	Primary Simple Limbal Epithelial Transplantation Along With Excisional Biopsy in the Management of Extensive Ocular Surface Squamous Neoplasia.	1	OSSN	100	NA	2
13	Queiroz *et al*[16]	Brazil	Universidade Federal de São Paulo	2016	Clinical Study	Assessment of surgical outcomes of limbal transplantation using simple limbal epithelial transplantation technique in patients with total unilateral limbal deficiency.	4	Chemical Injury	50	25	0.5
14	Vazirani *et al*[17]	India USA Mexico	LVPEI, SCEH, AIIMS, Sanjivni Eye Care Hospital, Disha Eye Hospitals, MEEI, Bascom Palmer Eye Institute, Instituto	2016	Clinical Study	Autologous simple limbal epithelial transplantation for unilateral limbal stem cell deficiency: multicentre results.	68	Chemical Injury	83.8	64.7	1

			de Oftalmologia, Fundacion Conde de Valencia na								
15	Arora *et al*[18]	India	Guru Nanak Eye Centre	2017	Clinical Study	Preliminary results from the comparison of simple limbal epithelial transplantation with conjunctival limbal autologous transplantation in severe unilateral chronic ocular burns.	10	Chemical Injury	100	100	0.5
16	Iyer *et al*[19]	India	Sankara Nethralaya	2017	Clinical Study	Outcome of allo simple limbal epithelial transplantation (alloSLET) in the early stage of ocular chemical injury.	18	Chemical Injury	94.1	72.2	0.86
17	Kaliki *et al*[20]	India	LVPEI	2016	Clinical Study	Concomitant Simple Limbal Epithelial Transplantation After Surgical Excision of Ocular Surface Squamous Neoplasia.	7	OSSN	100	NA	1
18	Singh *et al*[21]	India	AIIMS	2017	Clinical Study	Outcomes of deep anterior lamellar keratoplasty following autologous simple limbal epithelial transplant in pediatric unilateral severe chemical injury.	11	Chemical Injury	81.8	63.6	1.3
19	Basu *et al*[22]	India	LVPEI	2018	Clinical Study	Simple limbal epithelial transplantation (SLET) in failed cultivated limbal epithelial transplantation (CLET) for unilateral chronic ocular burns.	30	Failed CLET	80	NA	2.3
20	Gupta *et al*[23]	India	SCEH	2018	Clinical Study	Early Results of Penetrating Keratoplasty in Patients With Unilateral Chemical Injury After Simple Limbal Epithelial Transplantation.	7	Chemical Injury	100	57.1 (Reasons for poor vision in 3	1.3

										cases - glaucoma, amblyopia, graft failure)	
21	Gupta *et al*[24]	India	SCEH	2018	Clinical Study	Results of simple limbal epithelial transplantation in unilateral ocular surface burn.	30	Chemical Injury	70	50	1.1
22	Mednick Z *et al*[25]	Canada	University of Toronto	2018	Case Series	Simple limbal epithelial transplantation for recurrent pterygium: A case series	4	Recurrent Pterygium	100	75 (Case3 – cause of poor vision – epiretinal membrane)	0.67
23	Narang *et al*[26]	India	LJ Eye Institute, Centre for Sight Hyderabad, CMRI Hospital, Kolkata	2018	Clinical Study	Primary limbal stem cell transplantation in the surgical management of extensive ocular surface squamous neoplasia involving the limbus.	3	OSSN	100	NA	NA
24	Vasquez - Perez *et al*[27]	UK	Sussex Eye Hospital, Brighton	2018	case report	ModifiedAllogenic Simple Limbal Epithelial Transplantation Followed by Keratoplasty as Treatment for Total Limbal Stem Cell Deficiency.	1	Post Mitomycin treatment for Melanoma	100	100	0.92
25	Boutin *et al*[28]	Canada	University of Toronto	2018	case report	Simple limbal epithelial transplantation to treat recurring kissing pterygium.	1	Pterygium	100	100	0.67
26	Gupta *et*	India	SCEH	2019	Clinica	Scleral Ischemia in Acute Ocular Chemical Injury:	15	Chemical	53.3	NA	1.3

	al[29]				l Study	Long-Term Impact on Rehabilitation With Limbal Stem Cell Therapy.		Injury			
27	Hu XD *et al*[30]	China	Beijing Tongren Eye Center	2019	Clinical Study	Clinical observation of autologous simple limbal epithelial transplantation f or unilateral limbal stem cell deficiency	7	Chemical Injury	100	100	0.50
28	Sati *et al*[31]	India	Armed Forces Medical College	2019	Clinical Study	Mini-Simple Limbal Epithelial Transplantation Versus Conjunctival Autograft Fixation With Fibrin Glue After Pterygium Excision: A Randomized Controlled Trial.	40	Recurrent Pterygium	100	NA	0.50
29	Shah *et al*[32]	India	Drashti Nethralaya Eyelife Netra Mandir	2019	Clinical Study	Feasibility and outcome of simple limbal epithelial transplantation (SLET) in unilateral total limbal stem cell deficiency (LSCD) following chemical injury, in a semiurban location in Western India.	3	Chemical Injury	66.1	66.7	0.36
30	Reidl *et al*[33]	Germany	University Medical Center of the Johannes Gutenberg-University Mainz	2020	Clinical Study	Allogenic simple limbal epithelial transplantation (alloSLET) from cadaveric donor eyes in patients with persistent corneal epithelial defects	14	Persistent Epithelial defect	92.9	78.6	1

LVPEI- LV Prasad Eye Institute, Hyderabad, India; SCEH- Dr. Shroff's Charity Eye Hospital, New Delhi,India; AIIMS- All India Institute of Medical Sciences, New Delhi, India; MEE- Massachusetts Eye and Ear Infirmary, Boston, USA, OSSN – Ocular Surface Squamous Neoplasia

Appendix 2: Responses from the SLET survey questionnaire

In addition to surveying the published peer-reviewed literature we obtained institutional permission (Clinical, economic and social impact of Simple limbal epithelial transplantation [SLET] vs Cultivated limbal epithelial transplantation [CLET]- DrSayanBasu, DrVivek Singh- Ethics Ref No LEC BHR-P-04-20-414) to undertake questionnaires of surgeons concerning their use of SLET.The details of the questionnaire can be found in Appendix 1.The questionnaire was converted to an online format using Google form and the link was sent to The Ocular Surface group of ophthalmologists.

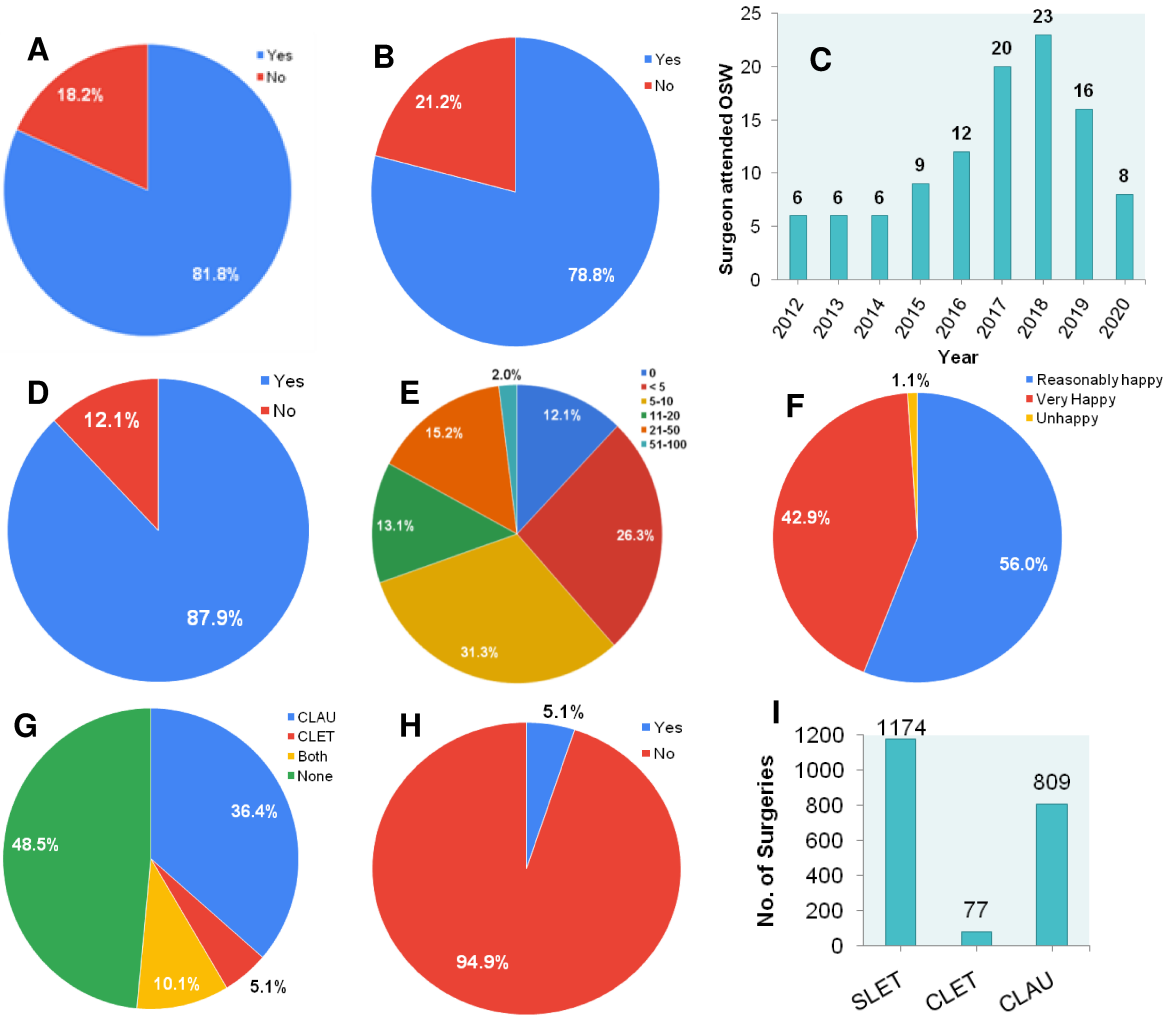
Out of the 294 members of The Ocular Surface group of ophthalmologists, 99members belonging to different institutes,hospitals andindividual clinics responded to this questionnaire. As SLET was conceptualized in India and most of the SLET workshops/ wet-lab/ training courses were conducted in India,themajority of the surgeons who participated in the survey were from India (91), however we also had participation of surgeons from USA (1), Mexico (3), Oman (1), Austria (1), Colombia (1), and Greece (1). Out of these 99 surgeons, 81% were happy to share their contact details**(Fig 1A).**

More than 78% of these surgeons had participated in SLET workshops/ Wet-lab/ Training Courses conducted by surgeons specialized in theSLET procedure (**Fig 1B)**. The number of participants in ocular surface workshops was constant in the initial years of SLET inception (2012 to 2014) with a slight increase seen thereafter till 2016 and peaking observed in 2018 **(Fig 1C)**.

Of these 87%surgeons had undertaken SLET surgery for treatment of 1174 LSCD patients**(Fig 1D)**. The responses were further categorized based on the number of surgeries. 29% of surgeons hadundertaken the surgery in less than 5 patients, 35% in 5 to 10 patients, 32% in11 to 50 patients and only 2% had experience of SLET in more than 50 patients **(Fig 1E)**.

In response to the clinical experience of SLET, 1%were unhappy, 56% reasonably happy and 42% were very happy with the SLET procedure **(Fig 1F)**.Surgeons comments regarding their experience with SLET were that the procedure is convenient, easy, cost effective, scientific, efficient, reliable and reproducible. Afew surgeons stated that there is a learning curve for SLET and there are issues of graft acceptance, vascularization from the edges post surgery and unusual responses in pediatric cases.

More than 50% of surgeons had undertaken other procedures such as CLAU and CLET for treatment of LSCD **(Fig 1G)**. CLAU was practiced by 36% of surgeons, both CLET and CLAU by 10% of the surgeons and CLET by only 5% of surgeons due to the fact that only 5%of surgeons had cell culture facilities for CLET **(Fig 1H)**. A total of 77 and 809 LSCD patients were treated using CLET and CLAU respectively **(Fig 1I)**. In response to if they were given a choice of SLET or CLET 100% of these surgeons responded that they would prefer SLET.



Supplementary figure 1. The quantitative analysis of responses to the questionnaire sent to surgeons who attended an Ocular Surface Workshop (OSW). (A) % of surgeons happy to share contact details (B) % of surgeons who participated in ocular surface workshop. (C)Participation of surgeons in ocular surface workshops. (D) % of surgeons who have undertaken SLET. (E) Number of SLET surgeries performed.. (F) Assessment of clinical experience of SLET procedures. (G) % of surgeons undertaken CLET and CLAU. (H) % of surgeons having cell culture facilities of CLET. (I) Number of surgeries performed using SLET, CLET and CLAU.

Appendix 3: Costs of SLET and CLET Pathways

Cost data from LVPEI, Hyderabad, India

The costs for India were estimated from the actual tariff costs of the different steps identified from the LVPEI costing database. Because of the mission of L V Prasad Eye Institute (LVPEI) to provide equitable and quality eye care to all sections of society (www.lvpei.org), around 50% of its services are provided free and fee-paying patients can choose between six categories of service as listed in the Table below.

There is no difference in the surgical procedures offered between these categories, but there is a difference in the provision of the associated non-surgical facilities such as the quality of hospital accommodation (please see the discussion for further details). For the base case deterministic analysis, we used the "Private" tariff but the least expensive the "Economy" and the most expensive the "Exclusive" were used to specify the lower and upper bounds for parametric distributions.

Supplementary table 2: Price schedule for fee-paying patients at LVPEI (in Indian Rupees)

Procedure name	Economy	Semi-Private	Private	Deluxe	Premium	Exclusive
Amniotic Membrane Graft Large	10300	17100	34800	53400	53400	86700
Limbal Biopsy	10300	17100	34800	53400	53400	86700
Limbal Transplantation	11700	19400	38900	58500	58500	98300
Stem Cell Transplant	18500	30700	63200	97400	97400	156000
Fibrin Glue	1800	2900	5900	8200	8200	14600
Simple Limbal Epithelial Transplant	19200	31900	67200	100200	100200	161700
General Anesthesia 1 - 15 Minutes	2400	3600	3600	3600	3600	9300
General Anesthesia 31 - 60 Minutes	4700	8200	8200	8200	8200	11600
Room Rent Per Day	1200	2000	3000	4000	4000	11000

Costs for patients receiving CLET

Stay in hospital

For adults receiving CLET, a local anaesthetic is used for the procedure and patients can leave hospital on the same day. As such, we assumed that there is no hospital stay for adults. For children, however, a general anaesthetic needs to be used which requires 1 to 3 days of overnight stay, at a cost of INR 3000 per day (range INR 1200 to INR 11000). Therefore, separate analyses were performed for adults and children.

First Surgery for CLET

At this first surgery, a small section of the limbus is taken for the laboratory expansion of cells. This is done under local anaesthetic for adults (included in surgery costs) and general

anaesthetic for children (mean INR 3600 with a range of INR 2400 to INR 9300). The procedure generally takes less than 30 minutes and the adult patients are discharged from hospital on the same day while the children need hospital stay (see above). The mean costs of this surgery are INR 34,800 with a range of INR 10,300 to INR 86,700. All patients are requested to return when the cells are ready for transplantation, typically two to three weeks later. They are also seen next for a follow up visit, if admitted or not.

Use of amniotic membrane

The amniotic membrane is used as a substrate on which to grow the cells from the limbal biopsy in the laboratory. This is sourced from a tissue bank run to international standards in LVPEI. While human tissue is donated for free clinical use, tissue banks charge a cost to cover the processing and storage of the tissues to help recoup the costs of running the bank. The processing costs associated with the tissue bank used by LVPEI is estimated as INR 2500.

Laboratory expansion of cells

In the case of CLET, cells are expanded on the amniotic membrane prior to transplantation to the eye. The time taken to expand a single biopsy ready for clinical use averages from two to three weeks. Using the daily costs associated with cell culturing of INR 25000 and assuming 17.5 days of cell culture (i.e. average of 2 to 3 weeks), the mean costs were estimated as INR 437,500 with a range of INR 350,000 (estimated assuming 2 weeks) and INR 525,000 (estimated assuming 3 weeks).

Second Surgery for CLET

At this second surgery, the cells that underwent laboratory expansion are transplanted back into the patient's eye after removal of the scar tissue. This is done under local anaesthetic for adults (included in the surgical cost) and general anaesthetic for children (mean INR 8200, range INR 4700 to 11600). The amniotic membrane is held in place with fibrin glue (mean INR 5900, range INR 1800 to INR 14600). A bandage contact lens is applied over the cultured cells at the end of procedure. The mean costs of this surgery are INR 34800 with a range of INR 10300 to INR 86700.

Stay in hospital

This is generally not required for adults where a local anaesthetic is used for the procedure. For children, however, a general anaesthetic needs to be used which is associated with overnight stays of 1 to 3 nights (at a cost of 3000 per day, range 1200 to 11000).

Costs for patients receiving SLET

Stay in hospital

This is not generally required for adults. For children, however, a general anaesthetic needs to be used which requires 1 to 3 days of overnight stays (at a cost of INR 3000 per day, range INR 1200 to INR 11000). As such, separate analyses were performed for adults and children.

Use of amniotic membrane

The amniotic membrane used is the same as for CLET, which is sourced from a tissue bank run to international standards, and the processing costs associated with the tissue bank used by LVPEI is estimated as INR 2500. When used in SLET the membrane provides a biodegradable substrate which is placed on the denuded eye held in place with fibrin glue.

SLET Surgery

At this surgery, the scar tissue from the affected eye is removed and a small piece of tissue from the healthy eye (1-2 mm) is taken and cut into approximately eight pieces. An amniotic

membrane is placed over the denuded eye and held in place with fibrin (as above) and then the pieces of corneal explant are placed on the membrane and held in place with a very small amount of fibrin glue and a bandage contact lens is placed over these. The costs of amniotic membrane and the fibrin glue are the same as for CLET.

This is done under local anaesthetic for adults (costs included in the surgery) and general anaesthetic for children (mean INR 8200, range 4700 to 11600). The procedure generally takes 30 minutes and the mean costs associated with the surgery are INR 34800, and a range of INR 10300 to INR 86700. Adult patients are discharged from hospital on the same day while the children need a hospital stay (see above).

Supplementary table 3: SLET cost data from Dr. Shroff's Charity Eye Hospital, New Delhi, India

Item	Most likely Value (in INR)	Lower estimate	Upper estimate
Costs associated with SLET			
Amniotic membrane	₹ 2,500	₹ 2,400	₹ 2,600
Single SLET Surgery	₹ 50,500	₹ 25,500	₹ 120,500
Fibrin Glue	₹ 10,000	₹ 9,900	₹ 10,100
Bandage contact lens	₹ 2,300	₹ 2,200	₹ 4,500
General anaesthesia*	₹ 5,000	₹ 4,900	₹ 5,100
Hospital stay (in days)*	2	1	3
Hospital costs per day*	₹ 3,000	₹ 1,500	₹ 6,000

*Only for children

Supplementary table 4: Cost data sourced from NICE assessment of Holoclar in England and Wales

Item	Most likely Value	Lower estimate	Upper estimate	Source
Costs associated with CLET				
First CLET Surgery (biopsy)	£864	£750	£950	Minor, Cornea or Sclera Procedure for Biopsy; Day case BZ65Z
General anaesthesia*	£220	£150	£334	Assumed to two thirds as much as private costs
Hospital stay (in days)*	2	1	3	Assumption
Hospital costs per day*	£340	£300	£380	Daily bed cost of excess stay with Very Complex, Cornea or Sclera Procedures with CC Score 0-1 BZ61B
Amniotic membrane	£220	£180	£250	Frozen Amniotic Membrane 2x2cm NHS Blood and

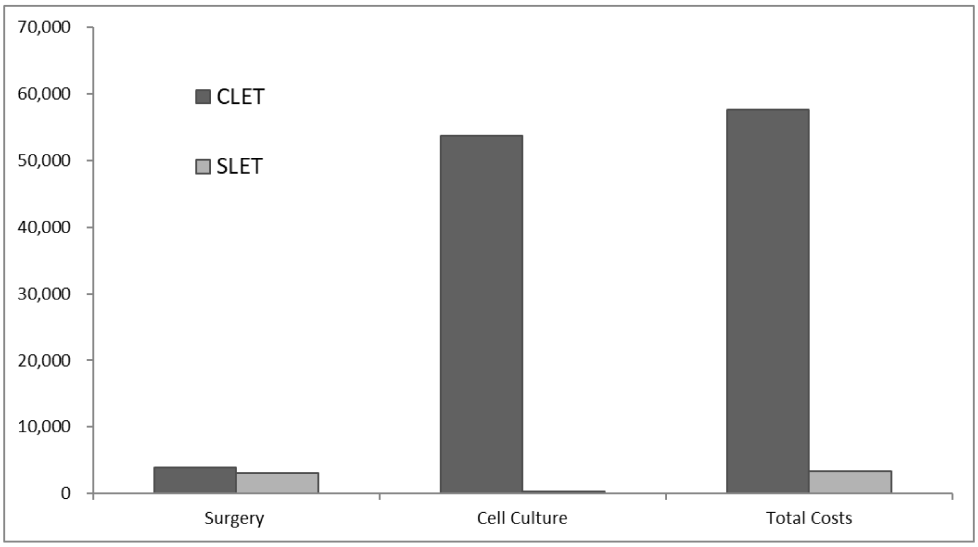
				Transplant
Cell culture	£50,000	£30,000	£80,000	Holoclar
Second CLET Surgery (transplantation)	£3,099	£2,600	£3,500	Very Complex, Cornea or Sclera Procedures with CC Score 0-1, Elective BZ60B
Fibrin Glue	£10	£8	£12	Assumption
Bandage contact lens	£4	£3	£5	Bandage contact lens applied by opthamologist
General anaesthesia*	£220	£150	£334	Assumed to two thirds as much as private costs
Hospital stay (in days)*	2	1	3	Assumption
Hospital costs per day*	£340	£300	£380	Daily bed cost of excess stay with Very Complex, Cornea or Sclera Procedures with CC Score 0-1 BZ61B
Costs associated with SLET				
Amniotic membrane	£220	£180	£250	Frozen Amniotic Membrane 2x2cm NHS Blood and Transplant
Single SLET Surgery	£3,099	£2,600	£3,500	Very Complex, Cornea or Sclera Procedures with CC Score 0-1, Elective BZ60B
Fibrin Glue	£10	£8	£12	Assumption
Bandage contact lens	£4	£3	£5	Bandage contact lens applied by opthamologist
General anaesthesia*	£220	£150	£334	Assumed to two thirds as much as private costs
Hospital stay (in days)*	2	1	3	Assumption
Hospital costs per day*	£340	£300	£380	Daily bed cost of excess stay with Very Complex, Cornea or Sclera Procedures with CC Score 0-1 BZ61B

*Only for children

Results of the economic analysis in UK

Supplementary table 5: Estimated costs of SLET and CLET in the UK

	CLET	SLET	Average Savings
Surgery	£3,921	£3,076	-845
Cell Culture	£53,432	£216	-53,216
Total Costs	£57,353	£3,292	-54,061



Supplementary figure 2: Estimated costs of SLET and CLET in the UK

Appendix 4: Social impact of SLET

The surgeons suggested that SLET negates the requirement for costly tissue engineering facilities which means it can be offered by more surgeons who do not have access to the specialist laboratories required for the cell-based technique. Hence, it is accessible to more patients who have been treated at clinics that would otherwise lack the expertise, facilities, and approval necessary for the cell culture treatment. Also, they highlighted that SLET requires only a single surgery and is quicker - whereas CLET demands a separate biopsy and transplantation, with surgeries that are separated by at least two weeks for the cells to be expanded in a laboratory. Furthermore, they suggested SLET avoids the risk of contamination associated with ex vivo tissue expansion, involving the use of bovine serum.

Less than 10% of surgeons made specific comments about the technique-the most common comment was that it was less expensive than the previous CLET technique and another comment shared by several was that it was comparatively easy to do .One surgeon made the point that they would like to see longer-term follow-up data before deciding, which is always a consideration with novel techniques (e.g. the same comment was made by NICE about the use of Holoclar) but as Table 1 shows there are now studies with up to 2 years follow-up for SLET. (https://www.nice.org.uk/guidance/ta467)