NICE National Institute for Health and Care Excellence

Professional Expert Questionnaire

Technology/Procedure name & indication: **IP1841 Regional Nerve Graft to restore Corneal Sensation**

Your information

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Nominated/ratified by (if applicable):	Click here to enter text.
Registration number (e.g. GMC, NMC, HCPC)	GMC 4589035

How NICE will use this information: the advice and views given in this questionnaire will form part of the information used by NICE and its advisory committees to develop guidance or a medtech innovation briefing on this procedure/technology. Information may be disclosed to third parties in accordance with the Freedom of Information Act 2000 and the Data Protection Act 2018, complying with data sharing guidance issued by the Information Commissioner's Office. Your advice and views represent your individual opinion and not that of your employer, professional society or a consensus view. Your name, job title, organisation and your responses, along with your declared interests will also be published online on the NICE website as part of the process of public consultation on the draft guidance, except in circumstances but not limited to, where comments are considered voluminous, or publication would be unlawful or inappropriate.

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☐ √ I give my consent for the information in this questionnaire to be used and may be published on the NICE website as outlined above. If consent is NOT given, please state reasons below:

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Please answer the following questions as fully as possible to provide further information about the procedure/technology and/or your experience.

Please note that questions 10 and 11 are applicable to the Medical Technologies Evaluation Programme (MTEP). We are requesting you to complete these sections as future guidance may also be produced under their work programme.

1	Please describe your level of experience with the procedure/technology, for example: Are you familiar with the procedure/technology?	Yes, I have introduced this procedure to the UK. Our unit performed the first procedure in the UK, and we have performed over 12 procedures.
	Have you used it or are you currently using it?	Yes, we are currently performing the procedure
	− Do you know how widely this procedure/technology is used in the NHS or what is the likely speed of uptake?	It is performed in a handful of centres due to the specialised nature, rarity of the conditions and need for a multidisciplinary team. We anticipate no more than 5-10 paediatric corneal neurotisations, and a similar number of adult procedures in the UK.
	− Is this procedure/technology performed/used by clinicians in specialities other than your own?	The procedure requires ophthalmic and plastic surgeons working together as the nerve grafts are obtained by plastic surgeons, and the nerve connection is established by ophthalmic surgeons
	− If your specialty is involved in patient selection or referral to another specialty for this	Such cases are referred by my specialty (ophthalmology) to specialist units that offer this procedure. We have received over 20 referrals from England, Wales and Ireland, and EU for this procedure. All referrals were from ophthalmologists.

	procedure/technology, please indicate your experience with it.	
2	– Please indicate your research experience relating to this procedure (please choose one or more if relevant):	I have done bibliographic research on this procedure. YES I have done research on this procedure in laboratory settings (e.g. device-related research). CADAVER DISSECTION IN LABORATORY I have done clinical research on this procedure involving patients or healthy volunteers. WE HAVE PUBLISHED CASE SERIES, AND CASE REPORTS ON THIS SUBJECT. I have published this research. YES I have had no involvement in research on this procedure. Other (please comment) I HAVE DELIVERED SEVERAL LECTURES ON THIS SUBJECT IN UK AND OVERSEAS MEETINGS
3	How innovative is this procedure/technology, compared to the current standard of care? Is it a minor variation or a novel approach/concept/design? Which of the following best describes the procedure (please choose one):	This is a novel approach, and unlike any previous technique. There are no previous procedures involving nerve transfer to the eye. It is particularly innovative in paediatric populations where the entire trigeminal territory is insensate, and the donor nerves must be sought from the cervical territory and the nerve graft has to be much longer, and adequate for bilateral procedures. Adult procedures usually involve unilateral cases with shorter nerve grafts and donor nerves from the forehead. Established practice and no longer new. A minor variation on an existing procedure, which is unlikely to alter the procedure's safety and efficacy. Definitely novel and of uncertain safety and efficacy. The first in a new class of procedure. √

4	Does this procedure/technology have the potential to replace current standard care or would it be used as an addition to existing standard care?	There is no current treatment for corneal anaesthesia. The only potential treatment is the use of neurotrophic growth factor which is not available in the UK and costs in excess of £10,000 per month.

Current management

5	Please describe the current standard of care that is used in the NHS.	Current treatment involves tarsorrhaphy to partially close the eyelids and reduce the exposed corneal surface, plugging/permanently closing the tear ducts, and frequent (1-2 hourly) use of ocular lubricants to minimise damage to the cornea. Inevitably, there is long term scarring despite the above. Recurrent ulcers may be treated with amniotic membrane grafts which are expensive and not curative, and need to be repeated.
6	Are you aware of any other competing or alternative procedure/technology available to the NHS which have a similar function/mode of action to this? If so, how do these differ from the procedure/technology described in the briefing?	The only alternative is use of neurotrophic growth factor which is not available in the UK, and costs >£10,000 per month. Importantly, it is not a permanent treatment while neurotisation has permanent benefits.

Potential patient benefits and impact on the health system

7	What do you consider to be the potential benefits to patients from using this procedure/technology?	The main benefit is prevention of further loss of vision, and potentially loss of the eye. Corneal graft surgery (penetrating keratoplasty) cannot be performed to treat corneal opacities in the absence of corneal sensation. Cases with corneal opacities with absent sensation are therefore untreatable without this technique. In children, this technique will prevent lifelong visual impairment, and avoid the need for multiple procedures to protect the ocular surface and corneal clarity. These patients develop recurrent corneal ulcerations which will damage corneal clarity, and infected or thinned cornea from recurrent or non healing ulcers can result in loss of the eye.
8	Are there any groups of patients who would particularly benefit from using this procedure/technology?	Children with trigeminal aplasia (isolated or part of syndromes such as Pontine cap aplasia, and Stuwe Weidemann syndrome), or who have lost trigeminal function from brain tumours. Adults with corneal anaesthesia from diabetes, trigeminal injury (surgical) and potentially herpetic eye disease
9	Does this procedure/technology have the potential to change the current pathway or clinical outcomes to benefit the healthcare system? Could it lead, for example, to improved outcomes, fewer hospital visits or less invasive treatment?	This treatment will radically alter the current pathway. Such patients require multiple hospital visits, hospitalisation and surgical procedures to repair and preserve the corneal surface, maintaining integrity of the eye and minimising visual impairment. The effect of the procedure is biphasic, with immediate improvement seen as the neurotrophic factors are released from the grafted nerve, lasting upto 2-3 months. The longer lasting effect is seen after 6 months, and is permanent. There is therefore a marked improvement in visual outcomes, with few to no episodes of corneal ulceration, and no further corneal scarring. The number of hospital visits will be reduced by upto 90%, with minimal followup required in the long term. Patients we have treated have upto 3 visits in the first year after surgery, and 1-2 further visits over the next 5 years. Many cases will avoid the need for corneal transplantation if treated in a timely fashion, and no need for amniotic membrane grafting, tarsorrhaphy, lifelong cost of ocular lubricants. Importantly, the need for registration as visually impaired will reduce considerably in children, avoiding need for special education, and enable return to work for adults.

10 - MTEP	Considering the care pathway as a whole, including initial capital and possible future costs avoided, is the procedure/technology likely to cost more or less than current standard care, or about the same? (in terms of staff, equipment, care setting etc)	The capital expenditure is minimal, as the surgical equipment is available in most units. We use electrophysiology (somatosensory evoked potentials) in children, to check for suitable donor sites as responses in young children can be difficult to interpret. This equipment is also available in large children's hospitals. The main cost is personnel (1 ophthalmic surgeon and 2 plastic surgeons, the theatre team) and theatre time, with one night stay in hospital. After care is minimal, with dressing removal at home. There is an average of 2 preop visits, 3 postop visits in the first year, and 1-2 in the next 5 years. This is considerably less expensive than the cost of repeated hospital visits, interventions in eye casualty and clinics, tarsorrhaphy and corneal ulcer treatment (medical and surgical), and lifelong cost of ocular lubricants.
11 - MTEP	What do you consider to be the resource impact from adopting this procedure/technology (is it likely to cost more or less than standard care, or about same-in terms of staff, equipment, and care setting)?	Please see answer to 10. The cost will be for theatre time, and staff time (typically, a bilateral procedure will take 6 hours operating time ie all day, and requires 1 ophthalmic surgeon and 2 plastic surgeons, while a unilateral case will take 3-4 hours). It will cost less than the current standard of care (repeated hospital visits, procedures including amniotic membrane grafting, visual loss and loss of productivity, lifelong use of lubricants) which is mainly supportive and reparative, rather than curative. The cost benefits will accrue rapidly.
12	What clinical facilities (or changes to existing facilities) are needed to do this procedure/technology safely?	The existing facilities in most hospitals should suffice. Having access to electrophysiology facilities will be useful in paediatric cases. In vivo confocal corneal microscopy (IVCM) is another method of looking for improvement in the sub-basal plexus in post-operative cases. This is possible in adults, and older children, but not younger children. The equipment costs in the region of £10000-15000.
13	Is any specific training needed in order to use the procedure/technology with respect to efficacy or safety?	There is a learning curve, and the team need to possess the knowledge of anatomy of the face, and rest of the body to adapt the procedure particularly in paediatric cases. Most ophthalmic and plastic surgeons possess the surgical skills. They need to develop familiarity with the technique which can be challenging outside of large referral cantres as the numbers are small.

Safety and efficacy of the procedure/technology

14	What are the potential harms of the procedure/technology? Please list any adverse events and potential risks (even if uncommon) and, if possible, estimate their incidence: Adverse events reported in the literature (if possible, please cite literature) Anecdotal adverse events (known from experience) Theoretical adverse events	Localised loss of sensation within the territory served by the donor nerve graft ie side of leg with sural nerve grafts, and medial surface of arm if medial anterior cutaneous branch of brachial nerve is used. Pain is a protective sensation, and loss of pain sensation can in theory result in injury, particularly on the foot. However this has not been reported. There are very few risks. Failure due to disconnection of anastomosis is a risk (<5%). There may be a hypertrophic scar on the site of graft harvesting (<5%). There is a risk of graft scarring/shortening (I have seen one case) if surgery is performed through an area of previous scarring (previous submandibular surgery in this case), or the grafted nerve is too short. This particularly applies to surgery performed for bilateral cases where cervical nerves are used. This might necessitate further surgery to use a longer graft and reroute the nerve behind the ear. References
15	Please list the key efficacy outcomes for this procedure/technology?	The key outcome of the procedure is improved health of the cornea. This can be measured by the reduction in incidence of corneal ulceration, improved speed of healing if it occurs, reduction in need for corneal lubrication, fewer corneal procedures to repair ulcers, improved corneal clarity, and ability to release the tarsorrhaphy. These are surrogate measures. It is possible to measure (quantify) the corneal sensation using Cochet- Bonnet aesthesiometry, or using a cotton tipped fibre to check sensation (patient will report sensation, or flinch). The former is not easy in younger children, and subjective assessment by parents (who report the child complains of eye drops hurting) and the surrogate measures reported above may have to be relied upon. (references below) In our experience, corneal sensation rarely returns in children with congenital corneal anaesthesia as they do not have a sub-basal neural plexus in contrast with cases of acquired corneal anaesthesia who have a well-developed plexus and regain sensation.

		In vivo confocal corneal microscopy (IVCM) is another method of looking for improvement in the sub-basal plexus in post-operative cases. This is possible in adults, and older children, but not younger children. There is insufficient literature on the status of the sub-basal plexus in congenital cases due to the young age at presentation, and inability to perform IVCM In summary, return of corneal sensation and improved corneal health are key outcomes in cases of acquired corneal anaesthesia. Surrogate measures mentioned above are the most reliable method of assessing efficacy in cases of congenital corneal anaesthesia. References Sepehripour S, Lloyd MS, Nishikawa H, Richard B, Parulekar M. Surrogate Outcome Measures for Corneal Neurotization in Infants and Children. J Craniofac Surg. 2017 Jul;28(5):1167-1170. Lambley RG, Pereyra-Muñoz N, Parulekar M, Mireskandari K, Ali A. Structural and functional outcomes of anaesthetic cornea in children. Br J Ophthalmol. 2015 Mar;99(3):418-24.
16	Please list any uncertainties or concerns about the efficacy and safety of this procedure/?	As it is a relatively new procedure, first reported from Toronto in 2014, the worldwide experience is limited to few centres with moderate number of cases. The collective experience shared among our peers, and reported in the published medical literature has not raised any concerns about the safety and efficacy of the procedure. From our experience of 13 cases, all our cases have been successful. One patient developed graft shortening as the grafted nerve passes through an area of previous surgery (submandibular) and needed further surgery to reroute the graft through the retro-auricular region).
17	Is there controversy, or important uncertainty, about any aspect of the procedure/technology?	The scientific rationale underlying the procedure is sound. The results are very encouraging, with few complications.
18	If it is safe and efficacious, in your opinion, will this procedure be carried out in (please choose one):	Most or all district general hospitals. A minority of hospitals, but at least 10 in the UK. **Fewer than 10 specialist centres in the UK**. √ Cannot predict at present.

Abstracts and ongoing studies

19	Please list any abstracts or conference proceedings that you are aware of that have been recently presented / published on this procedure/technology (this can include your own work). Please note that NICE will do a comprehensive literature search; we are only asking you for any very recent abstracts or conference proceedings which might not be found using standard literature searches. You do not need to supply a comprehensive reference list but it will help us if you list any that you think are particularly important.	There is recent work confirming that preserved (cadaveric, acellular) grafts do not give good results, and live autologous donor material is superior. https://journals.lww.com/prsgo/Fulltext/2020/09001/Corneal_Neurotization__A_Meta_analysis_of_Outcomes.40.aspx
20	Are there any major trials or registries of this procedure/technology currently in progress? If so, please list.	https://www.anzctr.org.au/Trial/Registration/TrialReview.aspx?id=336462

Other considerations

21	Approximately how many people each year would be eligible for an intervention with this procedure/technology, (give either as an estimated number, or a proportion of the target population)?	Upto 15-20/year
22	Are there any issues with the usability or practical aspects of the procedure/technology?	No
23	Are you aware of any issues which would prevent (or have prevented) this procedure/technology being adopted in your organisation or across the wider NHS?	The only limiting step would be funding for clinician time and availability of clinicians with the skills to provide the service
24	Is there any research that you feel would be needed to address uncertainties in the evidence base?	It would be helpful to introduce In vivo confocal microscopy as a routine objective measure in adults, and also children (although compliance might be an issue). It will also be useful to develop assays of neurotrophic growth factors generated by the transplanted nerves
25	Please suggest potential audit criteria for this procedure/technology. If known, please describe: − Beneficial outcome measures. These should include short- and long-term clinical outcomes, quality-of-life measures and patient-related outcomes. Please suggest the most appropriate method of measurement for each and the timescales over which these should be measured. − Adverse outcome measures. These should include early and late complications. Please state the post procedure timescales over which these should be measured:	Beneficial outcome measures: <u>Clinical outcome measures</u> Number of hospital visits in the 1 and 3 years preceding and following the procedure Number of surgical interventions in the 1 and 3 years preceding and following the procedure Visual acuity in the 1 and 3 years preceding and following the procedure Intensity of corneal staining using accepted scoring systems in the 1 and 3 years preceding and following the procedure In vivo confocal microscopy in adults prior to and 1 and 3 years following the procedure Cochet Bonnet aesthesiometry in adult patients prior to and 1 and 3 years following the procedure <u>QOL measures</u> Frequency of eye drops in the 1 and 3 years preceding and following the procedure

		Number of hospital visits in the 1 and 3 years preceding and following the procedure PROMs Number of working days lost by patient or parent (if the patient is a child) in the 1 and 3 years preceding and following the procedure Adverse outcome measures: Reoperation rate Surgical site infection rate following the procedure

Further comments

26	Please add any further comments on your particular experiences or knowledge of the procedure/technology,	

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Declarations of interests

Please state any potential conflicts of interest relevant to the procedure/technology (or competitor technologies) on which you are providing advice, or any involvements in disputes or complaints, in the previous **12 months** or likely to exist in the future. Please use the NICE policy on declaring and managing interests as a guide when declaring any interests. Further advice can be obtained from the NICE team.

Type of interest *	Description of interest	Relevant dates	
		Interest arose	Interest ceased
Non-financial personal			
Choose an item.	Nil		
Choose an item.	Nil		

☐ √I confirm that the information provided above is complete and correct. I acknowledge that any changes in these declarations during the course of my work with NICE, must be notified to NICE as soon as practicable and no later than 28 days after the interest arises. I am aware that if I do not make full, accurate and timely declarations then my advice may be excluded from being considered by the NICE committee.

Please note, all declarations of interest will be made publicly available on the NICE website.

Print name:	**Manoj V Parulekar**
Dated:	**02/12/2021**

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Professional Expert Questionnaire

Technology/Procedure name & indication: **IP1841 Regional Nerve Graft to restore Corneal Sensation**

Your information

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Professional organisation or society membership/affiliation:	Click here to enter text. Royal College of Ophthalmologists (RCOphth), British Ophthalmic Plastic Surgery Society (BOPSS), European Society of Ophthalmic Plastic and Reconstructive Surgery (ESOPRS), American Society of Ophthalmic Plastic and Reconstructive Surgery (ASOPRS).
Nominated/ratified by (if applicable):	Click here to enter text.
Registration number (e.g. GMC, NMC, HCPC)	Click here to enter text. GMC 4007898

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Please note that questions 10 and 11 are applicable to the Medical Technologies Evaluation Programme (MTEP). We are requesting you to complete these sections as future guidance may also be produced under their work programme.

1	Please describe your level of experience with the procedure/technology, for example: Are you familiar with the procedure/technology?	I am familiar with the technique of corneal neurotisation. I was one of the first surgeons in the UK to perform this procedure in the UK at the Queen Victoria Hospital NHS Foundation Trust, East Grinstead (I believe the first procedure in the UK was performed at the Birmingham Children's hospital in 2015). At QVH, we have performed 11 procedures between 2016-2018. No procedure has been performed since then at QVH, pending evaluation by NICE.
	Have you used it or are you currently using it? – Do you know how widely this procedure/technology is used in the NHS or what is the likely speed of uptake? – Is this procedure/technology performed/used by clinicians in specialities other than your own? – If your specialty is involved in patient selection or referral to another specialty for this	In 2018, I co-wrote a major review article on the technique and outcomes of corneal neurotisation. At the time, 35 patients had been reported to have undergone this procedure worldwide. A review article published in 2019 reported upon 54 procedures. In 2021, over 100 procedures have been reported in the literature, including our series of 11 cases with long-term outcomes. I understand that corneal neurotisation is regularly performed at The Birmingham Children's hospital. It has been sporadically performed in other Trusts UK-wide, including St George's Hospital, London. The speed of take up of this procedure is limited by the specialist teams that are available in a Trust. It requires an ophthalmologist with an interest in oculoplastic surgery and the ocular surface and plastic surgeon. Furthermore, to date, surgery has been reserved for individuals with total absence of corneal sensation that is not improving and are either not coping with the intense regime of lubricant and other drops required or are developing corneal epithelial defects despite current treatment. Worldwide, it is has been reported in approximately 20 cases for the treatment

	procedure/technology, please indicate your experience with it.	of neurotrophic keratopathy due to Herpes Simplex virus (HSV) keratitis, a commonly seen condition amongst ophthalmologists, that can result in loss of corneal nerve function (sensory and trophic healing). (Lin, Lai Ann Plast Surg 2019, Kim et al Ophth Plast Reconstr Surg 2021)
2	– Please indicate your research experience relating to this procedure (please choose one or more if relevant):	I have done bibliographic research on this procedure. Co-written a major review. I have published this research. I have performed this procedure with my colleagues at QVH on 11 patients and published retrospective data of outcomes and observations of this closely audited work.
3	How innovative is this procedure/technology, compared to the current standard of care? Is it a minor variation or a novel approach/concept/design? Which of the following best describes the procedure (please choose one):	**Worldwide, corneal neurotisation is now considered established practice and no longer new.** Publications continue to appear on variations in technique, as well the use of nerve allografts as an alternative to autologous sural nerve grafts or nerve transfer. Outcomes are consistent in all published series. That is to say, trophic nerve function of healing is restored in virtually all cases even where corneal sensation may not have been fully restored. Therefore, the consequences of neurotrophic keratopathy, ie corneal epithelial defects, corneal ulcers, scarring, perforation no longer occur following corneal neurotisation. Need for life-long drops is reduced, both in terms of duration and, also frequency.
4	Does this procedure/technology have the potential to replace current standard care or would it be used as an addition to existing standard care?	It would be used as an addition. Many patients with neurotrophic keratopathy can be managed and stabilised on lubricants and conservative measures.

Current management

5	Please describe the current standard of care that is used in the NHS.	Traditional standard of care comprises of continued/life-long treatment with the current conventional treatment of (preservative-free artificial tears, punctual occlusion, autologous serum eye drops and therapeutic contact lens) and possibly perform other surgical procedures such as tarsorraphy (closing the eyelids with sutures) and conjunctival flap (covering the cornea with a flap of conjunctiva). Based upon Mackey's classification of 3 stages: **Stage breakdown:** Stage 1 disease is treated with preservative- free artificial tear drops and ointments, punctal occlusion and treatment for blink lagophthalmos. Epithelial defects in stage 2 are treated to avoid progression to a corneal ulcer and to promote healing. Antibiotic drops are needed to prevent bacterial infections in addition to ocular surface lubrication. Options include corneal and scleral contact lenses, a lateral tarsorrhaphy, botulinum A toxin into the levator muscle or amniotic membrane transplantation to cover the non-healing epithelial defect. Lateral tarsorrhaphy renders a patient permanently uniocular. Botulinum toxin to the Levator muscle requires repeat injections and outpatient attendences. Amniotic membrane transplantation is expensive and provides a temporary membrane to promote corneal healing but does not restore corneal sensation. The ultimate visual restoring treatment is with corneal transplantation, but severely anaesthetic corneas have poor outcomes even after transplantation and therefore, corneal transplantation is not an option. • The conventional treatment methods therefore result in reduced quality of life and reduced vision –functional loss of one eye.

6	Are you aware of any other competing or alternative procedure/technology available to the NHS which have a similar function/mode of action to this? If so, how do these differ from the procedure/technology described in the briefing?	***Growth factor topical drops*** There has been increasing evidence in recent years on validating the value of newer biological agents. These include nerve growth factor (NGF), epidermal growth factor, vascular endothelial growth factor, semaphorins, neurotrophins 3 and 4 (NT-3, NT-4) and growth-associated protein-43. Other biological agents like IGF-1, substance P and matrix therapy agent (RGTA) (Cacicol20, OTR 3, Paris, France) have also demonstrated promising results in promoting corneal epithelial healing. Cenegermin, a recombinant form of human nerve growth factor, was recently approved in the European Union as an eye drop for the treatment of moderate or severe neurotrophic keratitis in adults. These different trophic factors showed positive results in the healing of neurotrophic corneas, but only few proved efficacious in restoring corneal sensitivity and nerve structure. Even with appropriate management, neurotrophic keratopathy may still progress to stage 3 disease as the underlying cause has not been treated. A Phase II randomized clinical trial of recombinant human nerve growth factor (rhNGF) showed improved epithelial healing, but not in corneal sensation in moderate to severe neurotrophic keratopathy (NK) after 8 weeks of therapy. The least-squares mean change in best-corrected visual acuity (BCVA) at 8 weeks improved in the 10 µg/ml group but failed to reach statistical significance in the 20 µg/ml group. The study authors suggest that final BCVA does not best reflect NK recovery due to possible induced optical aberrations following reepithelialization. The recurrence rate of epithelial defects in patients who healed after the initial 8-week rhNGF treatment was between 3.4% and 3.8% following 48 weeks of follow-up. (Bonini S, Lambiase A, Rama P, et al.; REPARO Study Group. Phase II randomized, double-masked, vehicle-controlled trial of re- combinant human nerve growth factor for neurotrophic keratitis. Ophthalmology 2018;125:1332–1343.) In contrast, the last major review of corneal neurotisation (Park et al 2020) showed a significant improvement in BCVA and central corneal sensation at a median time of 8 months with no reported recurrent epithelial defects. • Therefore, whilst this option delays the need for surgical procedures, research is still required for growth hormone treatment, there is limited published evidence currently available and it is not NICE approved. In the UK, this is not the preferred option due to the research status of growth hormone treatment. I am not aware of its cost, either.

Potential patient benefits and impact on the health system

7	What do you consider to be the potential benefits to patients from using this procedure/technology?	• High success rate • Few complications reported in reported literature
8	Are there any groups of patients who would particularly benefit from using this procedure/technology?	Neurotrophic keratopathy due to HSV keratitis (often end up with tarsorrhaphy closure of the eye) or due neurosurgery where a facial palsy has also occurred (therefore risk of corneal exposure-related complications is significantly greater-these patients would still require some degree of eyelid surgery to improve closure).
9	Does this procedure/technology have the potential to change the current pathway or clinical outcomes to benefit the healthcare system? Could it lead, for example, to improved outcomes, fewer hospital visits or less invasive treatment?	Yes. Improved outcomes for patients. Fewer hospital visits. Improved patient quality of life Reduced corneal-related complications and hospital attendances for this. Fewer procedures to prevent or manage corneal complications. Reduced medication costs (drops etc.) Improved visual acuity long-term. Corneal opacities improve in clarity following neurotisation. Furthermore, centres have published outcomes of penetrating keratoplasty (corneal grafting) in eyes that have undergone neurotisation with successful outcomes.
10 - MTEP	Considering the care pathway as a whole, including initial capital and possible future costs avoided, is the procedure/technology likely to cost more or less than current standard care, or about the same? (in terms of staff, equipment, care setting etc)	The costs outlined represent only one example of a clinical scenario. What is difficult to quantify is the need for intense ocular lubricants ie every hour or even 30 minutes, the restriction on activities that a neuropathic dry eye would entail ie limited activities in outdoor environments, inability to play sporting activities that require binocular vision or visual concentration, limitations on travel due to reliance on lubricants, medication and healthcare providers. This would not be temporary but in fact a long-term adjustment. A tarsorrhaphy is often required to prevent secondary ocular complications. This renders an individual effectively uniocular. Whilst this may reduce the likelihood of secondary ocular complications, it limits activities and is also cosmetically disfiguring. Given that patients are usually young, this disfigurement would have a negative impact on quality of life and perception of well-being over and above that of the medical consequences of a dry, neuropathic cornea.

		Conventional treatment costs: **Conventional Treatment** / **Total (£)** Lateral tarsorraphy (BZ45) **132** **Follow-up care** Follow-ups every 2-4 weeks @£66 for first two years **1980** ***Lifetime annual costs:*** Ciclosporin 0.1% preservative free eye drops (ikervis) once a day 864 Sodium hyaluronate 0.2% preservative free eye drops (Evolve HA) 144 Dexamethasone 0.1% preservative fee eye drops (minims) twice a day 218 Bandage contact lens (BZ65) changed each month per month @ £128 per procedure 1536 Xalin night eye ointment 30 Topical steroids 200 Autologous plasma treatment - upto 4 episodes per year 1552 **Total Annual Cost** **4544** **Additional Complications (per event, these may be multiple)** Corneal ulcers/scar or melt, epithelial defects - typical non-elective episode BZ60 3982 Corneal graft material - additional cost 1400 Botox injections into eyelid (BZ45) inc. botox 198
11 - MTEP	What do you consider to be the resource impact from adopting this procedure/technology (is it likely to cost more or less than standard care, or about same-in terms of staff, equipment, and care setting)?	What has been particularly impressive to see after corneal neurotisation is the reduced need for regular ocular lubricants. Patients often subsequently require drops perhaps 4 times a day. Their need for hospital visits and admissions is far less. They are effectively given greater freedom and less restricted due to this condition. Current national tariff of £5,886 - £8,971 on the basis of previous coding to an HRG of AA53 and depending on co-morbidities of patient.

		This reflects the cost of resource utilisation in terms of the following: - 4 hour theatre session involving ophthalmic/oculoplastic surgeon and plastic surgeon - Theatre consumables and drug costs - 1 night stay on ward post-op **a) Clinical and cost implications:** Follow-up costs may include two more follow-up visits in comparison to current management of these patients however, these patients are often regular attenders in the eye clinic due to neuropathic cornea-related complications.
12	What clinical facilities (or changes to existing facilities) are needed to do this procedure/technology safely?	No change in any theatre facility is required. Consumables are standard: suture material and standard operating instruments. Standard ophthalmic operating microscope.
13	Is any specific training needed in order to use the procedure/technology with respect to efficacy or safety?	No specific training required for a plastic surgeon experienced in harvesting a sural nerve graft. The technique for exposure of the supratrochlear nerve or supraorbital nerve is standard for a plastic or ophthalmic plastic surgeon. Nerve coaptation is also as per standard nerve graft surgery. Placement of the nerve fascicles to the ocular surface and cornea are based upon standard techniques. Videos on this procedure are readily available and shared amongst and by surgeons worldwide who are performing this technique for any surgeon interested in learning how to commence this procedure.

Safety and efficacy of the procedure/technology

14	What are the potential harms of the procedure/technology? Please list any adverse events and potential risks (even if uncommon) and, if possible, estimate their incidence: Adverse events reported in the literature (if possible, please cite literature)	In our series, no adverse events occurred. From personal communication with Dr Ilya Leyngold whose team have performed more cases than any other centre, worldwide: "*One of my patients (reported in literature) had persistent numbness and parasthesia in the SON distribution. Another had delayed presentation of maxillary molar abscess due to numbness in V2 (reported). The abscess was successfully treated and V2 numbness eventually improved. Also, one patient developed asymptomatic small bony excrescence at the site of supraorbital foramen(reported). One patient with intraop hematoma which was successfully evacuated during surgery. We have a summary of those in*

	Anecdotal adverse events (known from experience) Theoretical adverse events	*the recent article in Cornea (Rafailov L, Kim JS, Wisely CE, Espana EM, Soifer M, Leyngold IM. Clinical Outcomes and Patient Satisfaction After Corneal Neurotization. Cornea. 2021 Nov 1;40(11):1377-1386.) Other than that, nothing of significance to report. Please let me know if I can be of further assistance!"* Sural nerve donor sight morbidity has previously been studied where nerve grafts have been taken for other indications and include unsightly scarring, persistent pain, loss of protective sensation, and the need for revisional procedures. (IJpma FF, Nicolai JP, Meek MF. Sural nerve donor-site morbidity: thirty-four years of follow-up. *Ann Plast Surg* 2006;57:391–395.)
15	Please list the key efficacy outcomes for this procedure/technology?	Improved corneal trophic nerve function (including epithelial healing response, corneal staining) Improved central corneal sensation Fewer hospital visits. Reduced medication costs (drops etc.) Improved patient quality of life Reduced corneal-related complications and hospital attendances for this. Fewer procedures to prevent or manage corneal complications. Improved visual acuity long-term. Corneal opacities improve in clarity following neurotisation. Furthermore, centres have published outcomes of penetrating keratoplasty (corneal grafting) in eyes that have undergone neurotisation with successful outcomes. A neurotrophic cornea would otherwise be a contraindication for penetrating or lamella keratoplasty (corneal grafting) for opacity/scarring in order to improve vision.
16	Please list any uncertainties or concerns about the efficacy and safety of this procedure/?	Corneal nerve function may be considered in 2 aspects: trophic (healing) nerve function and sensory nerve function. It remains unclear why trophic nerve function appears to improve/fully recover whereas sensory nerve function variably recovers following corneal neurotisation surgery. However, recovery of trophic nerve function is, in many ways, the prime goal for corneal neurotisation surgery.

17	Is there controversy, or important uncertainty, about any aspect of the procedure/technology?	Studies are emerging on the use of nerve allografts as an alternative to sural nerve autografts of nerve transfers. Outcomes appear to be similar based upon small series. If this proves to be as successful then it would reduce theatre time and also donor autograft. In cases of herpetic neurotrophic keratopathy, risk of reactivation, and antiviral regimen of corneal neurotization remains uncertain.
18	If it is safe and efficacious, in your opinion, will this procedure be carried out in (please choose one):	~~Most or all district general hospitals.~~ ~~A minority of hospitals, but at least 10 in the UK.~~ **Fewer than 10 specialist centres in the UK.** ~~Cannot predict at present.~~

Abstracts and ongoing studies

19	Please list any abstracts or conference proceedings that you are aware of that have been recently presented / published on this procedure/technology (this can include your own work). Please note that NICE will do a comprehensive literature search; we are only asking you for any very recent abstracts or conference proceedings which might not be found using standard literature searches. You do not need to supply a comprehensive reference list but it will help us if you list any that you think are particularly important.	Rafailov L, Kim JS, Wisely CE, Espana EM, Soifer M, Leyngold IM. Clinical Outcomes and Patient Satisfaction After Corneal Neurotization. Cornea. 2021 Nov 1;40(11):1377-1386. doi: 10.1097/ICO.0000000000002759. PMID: 34633356. Giannaccare G, Bolognesi F, Pellegrini M, Spena R, Allevi F, Marchetti C, Scorcia V, Biglioli F. Corneal Neurotization: A Game-Changing Surgical Procedure for Neurotrophic Keratopathy. Cornea. 2021 Apr 14. doi: 10.1097/ICO.0000000000002746. Epub ahead of print. PMID: 33859084. Liu CY, Arteaga AC, Fung SE, Cortina MS, Leyngold IM, Aakalu VK. Corneal neurotization for neurotrophic keratopathy: Review of surgical techniques and outcomes. Ocul Surf. 2021 Apr;20:163-172. doi: 10.1016/j.jtos.2021.02.010. Epub 2021 Feb 26. PMID: 33647470; PMCID: PMC8113161. Elalfy M, Maqsood S, Hau S, Kannan RY, Nduka C, Hamada S, Malhotra R. Functional and Structural Changes Following Corneal Neurotisation in the Management of Neurotrophic Keratopathy: UK Single Centre Series. Clin Ophthalmol. 2021 May 24;15:2149-2160. doi: 10.2147/OPTH.S298941. PMID: 34079213; PMCID: PMC8163722.

		Malhotra R, Elalfy MS, Kannan R, Nduka C, Hamada S. Update on corneal neurotisation. Br J Ophthalmol. 2019 Jan;103(1):26-35. doi: 10.1136/bjophthalmol-2018-312104. Epub 2018 Sep 21. PMID: 30242061.
20	Are there any major trials or registries of this procedure/technology currently in progress? If so, please list.	Not to my knowledge

Other considerations

21	Approximately how many people each year would be eligible for an intervention with this procedure/technology, (give either as an estimated number, or a proportion of the target population)?	The incidence or prevalence of neurotrophic keratopathy (NK) in the population remains unknown. However, based upon a review of patients seen in a tertiary referral centre in Paris (Saad S, Abdelmassih Y, Saad R, Guindolet D, Khoury SE, Doan S, Cochereau I, Gabison EE. Neurotrophic keratitis: Frequency, etiologies, clinical management and outcomes. Ocul Surf. 2020 Apr;18(2):231-236. doi: 10.1016/j.jtos.2019.11.008. Epub 2019 Nov 20. PMID: 31759182.) reviewing all patients seen between 2009-2017, the authors estimated that of the 305,351 patients' seen, 335 (354 eyes) had NK. Therefore, 11/10,000 (0.11%) of patients attending a tertiary ophthalmic hospital. A third of these were Mackie stage 1 (mainly superficial punctate staining); a third were stage 2 (recurrent or persistent epithelial defects); and a third were stage 3 (corneal ulcer with stromal involvement, thinning, perforation etc). In general, anyone with Mackie stage 2 or worse would be considered an ideal, eligible candidate for corneal neurotisation, however even those with stage 1 may benefit if the compliance for lifelong intensive lubricants and other drops or need for improved vision are notable issues. It is noteworthy to highlight some of the observations in the above study. (Saad S, Abdelmassih Y, Saad R, Guindolet D, Khoury SE, Doan S, Cochereau I, Gabison EE. Neurotrophic keratitis: Frequency, etiologies, clinical management and outcomes. Ocul Surf. 2020 Apr;18(2):231-236. doi: 10.1016/j.jtos.2019.11.008. Epub 2019 Nov 20. PMID: 31759182.) During their follow-up, 5% of stage 1 cases rapidly progressed to stage 2, 10% of stage 2 cases rapidly progressed to stage 3 and 4% of stage 3 had perforated or were imminently perforating. Approximately 32% of NK cases were of herpes virus origin and 32% were iatrogenic, following interventions including surgery, radiotherapy or chemotherapy. 28% cases were due to CNS disorders. Overall, patients had a mean of 15 consultations over a mean of 21 months and 73

		patients required hospitalization, lasting a mean of 11.5 days. During follow-up, NK complications recurred in 70 eyes (over 20% of cases), for a mean of 1.5 recurrences per eye.
22	Are there any issues with the usability or practical aspects of the procedure/technology?	See above
23	Are you aware of any issues which would prevent (or have prevented) this procedure/technology being adopted in your organisation or across the wider NHS?	Reimbursement/tariffs
24	Is there any research that you feel would be needed to address uncertainties in the evidence base?	Adjunctive methods of improving speed of nerve function recovery, role of nerve allograft vs autograft
25	Please suggest potential audit criteria for this procedure/technology. If known, please describe: − Beneficial outcome measures. These should include short- and long-term clinical outcomes, quality-of-life measures and patient-related outcomes. Please suggest the most appropriate method of measurement for each and the timescales over which these should be measured. − Adverse outcome measures. These should include early and late complications. Please state the post procedure timescales over which these should be measured:	Beneficial outcome measures: Corneal sensation using Cochet–Bonnet aesthesiometry. Visual acuity Slit-lamp examination of corneal and conjunctival staining Tear production (Schirmer's 1 test) Tear film break-up time, tear film meniscus height, quality and osmolarity Central corneal thickness Structural outcomes: Changes in corneal nerve density and morphology with in-vivo confocal microscopy. Subjective outcomes: VFQ-25 QoL Questionnaire

		Adverse outcome measures: General ophthalmic complications: sight-threatening ocular infection/periorbital haemorrhage affecting vision, corneal perforation, new ocular symptoms eg pain, nerve dysesthesia Donor nerve site complications. These should all be evident within 6 months.

Further comments

26	Please add any further comments on your particular experiences or knowledge of the procedure/technology,	Based upon my experience and that of colleagues who perform this surgery, it is striking how effective this treatment appears to be. Corneal sensory nerve function returns within 8 months. Patients often report that by 3 months they can feel sensation in their brow-region (along the path of the nerve graft) whenever they instil drops into the neurotrophic eye when previously they felt nothing. This correlates with the return of trophic healing function.

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Declarations of interests

Please state any potential conflicts of interest relevant to the procedure/technology (or competitor technologies) on which you are providing advice, or any involvements in disputes or complaints, in the previous **12 months** or likely to exist in the future. Please use the NICE policy on declaring and managing interests as a guide when declaring any interests. Further advice can be obtained from the NICE team.

Type of interest *	Description of interest	Relevant dates	
		Interest arose	Interest ceased
Non-financial personal	I have co-authored 2 research papers on the subject of corneal neurotisation which may be used as evidence publications by the NICE advisory committee. One of these is a major review article (1st author) and the other (senior author), a retrospective case series reporting outcomes of 11 cases of corneal neurotisation managed by my team. I have also lectured at national and international meetings on the subject of corneal neurotisation.	**2015**	**Current**
Choose an item.			
Choose an item.			

☑ I confirm that the information provided above is complete and correct. I acknowledge that any changes in these declarations during the course of my work with NICE, must be notified to NICE as soon as practicable and no later than 28 days after the interest arises. I am aware that if I do not make full, accurate and timely declarations then my advice may be excluded from being considered by the NICE committee.

Please note, all declarations of interest will be made publicly available on the NICE website.

Print name:	**Click here to enter text.Raman Malhotra**
Dated:	**Click here to enter text.25 Oct 2021**