

# National Institute for Health and Clinical Excellence

## 350 – Tissue-cultured limbal stem cell allograft transplantation for corneal regrowth

### Comments table

IPAC date: Thursday 15 February 2007

Consultee name and organisation	Section no.	Comment no.	Comments	Response Please respond to all comments
Individual respondent – clinician	1	1	<p>1) To harmonize terminology internationally and encompass a number of techniques (i.e. growing on Plastic and growing on amniotic membrane) , it would probably make sense to entitle the process :                      ""Ex-vivo cultured limbal stem cell allograft transplantation"". 2)Point 1.1. is questionable for several reasons: a) this guidance is based only on 3 papers. There are more papers published than the three listed and some with larger numbers. b) The alternative to ex-vivo stem allografts is either a keratolimbal allograft which has a very survival beyond two years or living related conjunctival limbal allograft which requires a tissue matched donor and a procedure on two individuals, the donor and recipient. Both alternatives require high dose immunosuppression and very close monitoring to improve survival. Considering the alternatives, ex-vivo stem cell allograft transplantation is less invasive, has better survival and requires lower dose and shorter duration of immunosuppression (this is based on our protocol and we now perform 2 about 2 cases a month). 1.3 - please review the literature again - a number of publications have been missed.</p>	<p>Title of procedure amended to 'tissue-cultured limbal stem cell allograft transplantation for corneal regrowth'</p> <p>No studies were identified in update searches.</p> <p>No comparative data are available</p> <p>Consultee was asked for references. These relate to animal studies or autograft transplantation.</p>

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Individual respondent - Ocular Tissue Advisory Group (OTAG)	1	2	Corneal and ocular tissue transplantation in the UK that takes place via the CTS eyebanks and some non-CTS eyebanks is registered with the United Kingdom transplant Service (UKT). Such registration provides traceability, collection of outcome/follow-up data and implementation of a protocol for serious adverse events and reactions as required by the European Directive. I would therefore, recommend that centres/surgeons undertaking "tissue -cultured limbal stem cell allograft transplantation" have such a system in place prior to undertaking this procedure	Thank you for your comment, however such recommendations are outside the remit of the NICE Interventional Procedures Programme.
Individual respondent – clinician	2.1	3	2.1.1 Undifferentiated cells in the deep limbal layers differentiate to produce corneal epithelial cells only. Conjunctival cells are felt to have stem cells that are found elsewhere (fornix)	The Committee agreed to remove the phrase 'conjunctival and' from section 2.1.1.
Individual respondent - Ocular Tissue Advisory Group (OTAG)	2.1	4	2.1.1 Second sentence incorrect. "Undifferentiated epithelial cells....to become corneal cells" delete "conjunctival". 2.1.2 Inaccurate sentences. I would suggest that: Some recovery of the ouclar surface may occur with local adjuvant treaments and removal of the noxious stimulus. Failure to recover may require surgical intervention, such as limbal tissue auto or allograft.	The Committee agreed to remove the phrase 'conjunctival and' from section 2.1.1.  The Committee amended section 2.1.2 to include: 'More serious cases may require surgical procedures such as conjunctival and keratolimb al allografts, possibly followed by corneal grafts. In cases of unilateral disease, the use of limbal stem cells from the fellow eye may be enhanced by tissue culture prior to grafting.'

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Individual respondent - Ocular Tissue Transplantation Standards Group, Sub-committee of the Professional Standards Committee, The Royal College of Ophthalmologists	2.1	5	<p>Sub-section 2.1.1 - It is factually incorrect that limbal stem cells (LSCs) give rise to both corneal and conjunctival cells. In addition, limbal stem cells rather than their production are affected or damaged by disease processes causing LSCD.</p> <p>Sub-section 2.1.2 - Lubricants can help to restore the ocular surface of the eye but are not the sole treatment of LSCD and other more costly co-adjuvant conservative treatment options exist such as autologous serum, bandage contact lenses, Punctum plugs, etc.</p>	<p>The Committee agreed to remove the phrase 'conjunctival and' from section 2.1.1.</p> <p>The Committee amended section 2.1.2 to include: 'More serious cases may require surgical procedures such as conjunctival and keratolimbal allografts, possibly followed by corneal grafts. In cases of unilateral disease, the use of limbal stem cells from the fellow eye may be enhanced by tissue culture prior to grafting.'</p>
Individual respondent - Ocular Tissue Advisory Group (OTAG)	2.2	6	2.2.1 Topical treatments include antimicrobials and steroids.	The Committee amended section 2.1.2 to include: 'More serious cases may require surgical procedures such as conjunctival and keratolimbal allografts, possibly followed by corneal grafts. In cases of unilateral disease, the use of limbal stem cells from the fellow eye may be enhanced by tissue culture prior to grafting.'
Individual respondent – clinician	2.2	7	2.2.1 Factually incorrect, not all techniques involve growing cells on amniotic membrane as a carrier. Daya et al and De Luca and Pellegrini, grow cells on plastic. Daya used amnion as a bandage to retain the cells after they have been transplanted to the corneal surface and limbus	The Committee agreed to add the phrase 'in culture ...or on plastic' to section 2.2.1.

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Individual respondent - Ocular Tissue Transplantation Standards Group, Sub-committee of the Professional Standards Committee, The Royal College of Ophthalmologists	2.3	8	The evidence presented here is very scarce and should include all studies and reviews such as the ones outlined in "Ex vivo expansion of limbal epithelial stem cells: amniotic membrane serving as a stem cell niche" by Scheffer Tseng's group (Survey of Ophthalmology, 48:631-46, 2003). Sub-section 2.3.4 - The main outcome measure of the procedure is to restore the corneal epithelial surface with consequent improvement in ocular discomfort and pain. Visual improvement does not often happen therefore should not be the only criterion for success.	We have reviewed the data included, and all clinical studies for cultured allograft transplantation have been included.  2.3.4 This is the comment of an individual adviser. We have also included the epithelial re-growth and the composite LSCD resolution outcome (which includes pain) from the published data.
Individual respondent – clinician	2.3	9	As mentioned earlier - not enough studies have been analysed. Compare these outcomes to alternative techniques (KLAL and IrCLAL) and the panel will understand that the alternatives by comparison are more invasive with poorer outcomes.	Thank you for your comment, however this is not within the NICE IP Programme's standard methods.
Individual respondent - Ocular Tissue Advisory Group (OTAG)	2.3	10	2.3.1 Spelling mistakes. Should read: re-epithelialisation, conjunctivisation 2.3.4 Spelling mistake: procedure	Thank you for your comments. Amendments to be made to typos.

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Individual respondent – clinician	2.4	11	2.4.3 I do not understand the issue of failure of ""supply"" can this be clarified please ? It is worth considering the morbidity of not intervening in this group of patients: they typically have persistent or recurrent epithelial defects, ocular inflammation and pain and have similar if not worse morbidity with no intervention. Additionally the panel may wish to evaluate safety of alternative techniques. The issue of Safety needs to be evaluated in the context of this procedure and in comparison to alternative techniques as well as non-intervention.	This is the opinion of a specialist adviser on theoretical adverse events.  The Committee amended section 2.1.2 to include: ‘More serious cases may require surgical procedures such as conjunctival and keratolimbal allografts, possibly followed by corneal grafts. In cases of unilateral disease, the use of limbal stem cells from the fellow eye may be enhanced by tissue culture prior to grafting.’
Individual respondent - Ocular Tissue Advisory Group (OTAG)	2.4	12	2.4.2: Should state trabeculectomy not trabeculotomy? 2.4.3 Rejection of the allograft is a significant risk. There is also the potential risk of a serious adverse reaction risk such as transmission of malignancy although this would be expected to be extremely rare. I would agree with the potential failure in the donor.	2.4.2 ‘Trabeculotomy’ was the procedure stated in the original study report. 2.4.3 We currently state the risk of infection, and failure of the graft.
Individual respondent - Ocular Tissue Transplantation Standards Group, Sub-committee of the Professional Standards Committee, The Royal College of Ophthalmologists	2.4	13	This section again uses a limited reference series and should take all the case series into consideration. Corneal perforation for example was noted in 31% of cases reported (4/13) in one series (Shimazaki et al., Ophthalmology 109:1285-90, 2002) but is most likely not to have occurred at all in all the other case series. In addition, glaucoma also seems to be an unlikely direct complication of the procedure itself. Furthermore, there is no reported evidence that taking a small limbal biopsy from the donor eye results in LSCD although there may be a theoretical risk.	All safety outcomes / adverse events that are reported in the original studies are extracted in the overview for this procedure. The risk of LSCD is already described as a theoretical risk and is marked as a specialist adviser comment.

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Individual respondent - Ocular Tissue Transplantation Standards Group, Sub-committee of the Professional Standards Committee, The Royal College of Ophthalmologists	3	14	Audit remains an essential part of the implementation of all new procedures (see comments above on regulatory issues).	Thank you for your comment. Section 1.1 of the guidance states that the procedure should not be used without special arrangements for consent and for audit or research.
Individual respondent - Ocular Tissue Transplantation Standards Group, Sub-committee of the Professional Standards Committee, The Royal College of Ophthalmologists	N/A – General Comments	15	<ul style="list-style-type: none"> <li>• A major flaw in the proposal is the exclusion of autologous transplantation because that is the main benefit of ex vivo expansion rather than the ex vivo expansion of allogeneic tissue.</li> <li>• The exact impact of limbal stem cell deficiency (LSCD) on the patient's quality of life has to be elaborated upon, including the frequency of hospital visits, frequent use of topical treatment, etc.</li> <li>• The main failure of the allograft procedure has not been addressed - i.e. the questionable long-term survival of allogeneic cells, as shown by others, including Daya et al. (Daya et al., Ophthalmology 112:470-77, 2005).</li> </ul> <p>There is no evidence at the Royal College of Ophthalmologists that NICE has contacted the College directly regarding this consultation process as is claimed on your website.</p>	<p>The original notification was for allograft transplantation. This is of course the only option to harvest tissue for culture in cases of bilateral deficiency.</p> <p>The description of the indication provided is only intended to be a brief background, rather than a definitive description of the condition.</p> <p>Survival of transplanted cells was considered to be a surrogate outcome; clinical outcomes from this study are included in the guidance.</p> <p>Two Specialist Advisers have been nominated or ratified by the RCOphth, via the president.</p>

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Individual respondent - Ocular Tissue Transplantation Standards Group, Sub-committee of the Professional Standards Committee, The Royal College of Ophthalmologists	N/A – Regulatory Issues	16	<p>From 1 April 2007, the Human Tissue Authority (HTA) will need to authorize every procedure involving the transplantation of tissue that has not been supplied from an HTA licensed tissue bank. This applies to tissue retrieved in the UK and used locally (e.g., whole eyes for limbal stem cell allograft transplantation). The need for HTA authorization is due to these activities falling under the requirements of the EU Tissues and Cells Directive (EUTCD), for all matters concerning the removal, storage, use and disposal of human tissue for schedule purpose. This includes responsibility for living donor transplantation.</p> <p>EU Tissues and Cells Directive (2004/23/EC) also requires that all serious adverse reactions and events associated with the therapeutic use of human tissue for transplantation be reported to a Tissue Establishment (e.g., eye bank) and the Human Tissue Authority (Competent Authority). UK Transplant, a division of the NHS BT is setting up a system for the reporting of any “Serious Adverse Reaction or Event” related to corneal and tissue transplantation, including limbal stem cell. The reporting protocol will be available very soon.</p> <p>Any doctor considering use in the NHS of a new interventional procedure such as tissue-culture limbal stem cell transplantation, which they have not used in the NHS before, should seek the prior approval of their NHS Trust’s Clinical Governance Committee. They should state whether the procedure is the subject of National Institute for Clinical Excellence (NICE) guidance as listed on their website, (<a href="http://www.nice.org.uk/ip">www.nice.org.uk/ip</a>). They must demonstrate that they have met standards of training; they must also describe the procedure for obtaining informed consent, and define how they will subject the procedure to clinical audit of outcomes.</p>	Thank you for your comment, however such recommendations are outside the remit of the NICE Interventional Procedures Programme.

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Individual respondent - Ocular Tissue Transplantation Standards Group, Sub-committee of the Professional Standards Committee, The Royal College of Ophthalmologists	N/A – Final Comments	17	<p>At present the source for the limbal transplant is either from the other healthy eye (unilateral diseases) or in cases of bilateral diseases, the graft could be obtained from a healthy living related or a cadaveric donor. However, allografts are limited by tissue availability and the recipient always requires systemic immunosuppression with their significant inherent risks. Therefore, this consultation document should also discuss alternative new techniques (e.g., the use of autologous oral mucosal stem cell to reconstruct corneas with LSCD) that do not require systemic immunosuppression. See the following reported papers:</p> <p>Nishida et al., Corneal reconstruction with tissue-engineered cell sheets composed of autologous oral mucosal epithelium. N Engl J Med 351 (12): 1187-96, 2004.</p> <p>Inatomi et al., Ocular surface reconstruction with combination of cultivated autologous oral mucosal epithelial transplantation and penetrating keratoplasty. Am J Ophthalmol. 142(5): 757-64, 2006.</p> <p>Inatomi et al., Midterm Results on Ocular Surface Reconstruction Using Cultivated Autologous Oral Mucosal Epithelial Transplantation. Am J Ophthalmol. 141(2): 267-275, 2006.</p> <p>It is of enormous importance that the final document highlights the importance of the new regulations (HT Act and clinical governance on new procedures) involving tissue-cultured limbal stem cell transplantation.</p>	Thank you for your comments. The IP Programme is not aware of any separate evidence on autografts for this procedure.
Individual respondent - Insurer	General comment	18	BUPA has not looked at this; my hunch (based on a presentation at an Academy of Medical Sciences study day on stem cell usage about 15 months ago) is that we would come to the same conclusion as you have. (We do routinely fund amniotic membrane dressings for eg radiotherapy induced corneal ulceration.)	Thank you for your comment.



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Individual respondent - Insurer	General comment	19	Not sure if this would be a help, but have you come across Hesselbarth U et al Cell Tissue Bank 2004;5:57-65, which gives the German standards for preparing amniotic membrane transplants?	Thank you for the suggested study. This study relates to amniotic membrane preparation rather than allogeneic limbal stem cell culture.