National Institute for Health and Care Excellence

IP1524/1 – Processed nerve allograft to repair peripheral nerve discontinuities

IPAC date: Thursday, 14 September 2017

Com. no.	Consultee name and organisation	Sec. no.	Comments	Response Please respond to all comments
1	Consultee 1 NHS Professional		"The clinical evidence demonstrates that this product appears safe to use in small gap (<2 cm) sensory nerves; however there is no critical evidence that allograft has superior functional outcomes compared to autograft. This piece of research needs to be done. The other consideration is the cost to the NHS weighed against the donor site morbidity of autograft."	Thank you for your comment. The Committee has encouraged further research into processed nerve allografts to repair peripheral nerve discontinuities including information on the type of nerve repaired, the anatomical site, the size of the defect, patient reported outcome measures, functional outcomes, time to recovery and long-term outcomes (12–18 months). The IP programme does not assess comparative techniques or does assess its cost-effectiveness.
2	Consultee 2 NHS Professional	**1.2**	“Dear sirs, Please acknowledge receipt of my comments in response to the NICE consultation document on use of allograft in PNI. I raised the NICE guidance request.	Thank you for your comments. The consultee disagrees with point 1.2 of the guidance and suggests that the use of processed nerve allograft in pure sensory peripheral nerves in the limbs and tongue should be covered by point 1.1 of the

			I have just discovered from a colleague that provisional guidance has been issued by NICE and is subject to a period of consultation ending 20th July 2017. I have had had no update from NICE despite several emails requesting information and assuring me that someone will be contacting me with an update. I have contacted [redacted] directly for information in advance of the published 20th July deadline and am informed that they are on leave until the 24th July. I am requesting that you extend the deadline to give me sufficient opportunity to respond in full to the consultation document as despite contacting NICE on several occasions I have only been provided with notice of the consultation today. [redacted] is aware of my requests for information and had responded to my repeated requests by assuring me that I would be receiving an update, however it appears that the designated person is away until after the consultation closes. In brief my comments are below: I am a full time hand and nerve surgeon in the UK and have the largest series of nerve allograft to date in the NHS. For the purposes of my comments I will use the following terminology:	guidance. The consultee emphasizes the need for robust measures for data collection. The committee has decided not to change its recommendations as the majority of the evidence is for digital nerve repair. The consultee highlights the relevance of data collection into a registry and identifies current gaps in the literature. The Committee has encouraged further research into processed nerve allografts to repair peripheral nerve discontinuities including information on the type of nerve repaired, the anatomical site, the size of the defect, patient reported outcome measures, functional outcomes, time to recovery and long-term outcomes (12–18 months). A recommendation was also made regarding patient selection and consideration of site, type of nerve (motor, sensory, mixed) and the size of the defect. The consultee suggests that there should be a note about the management of painful neuromas in sensory nerves. This was discussed by the committee and a recommendation was made

			Complex nerve reconstruction procedures include proximal nerve gap repair in major nerve trunks including the brachial plexus and in patients with end neuroma after transaction or with neuroma in continuity after injury. Simple nerve gap reconstruction includes pure sensory nerve gaps in the hand or elsewhere in the peripheral nervous system. Simple cases can be treated with bridging of the gap with a conduit (small gap in a border-digit digital nerve) with gaps of 12mm or less and the evidence base supports this as satisfactory. Long gaps >12mm require a reconstruction using autologous graft (sensory) harvested from the same limb or the leg (sural). Dual limb surgery requires longer stays and general anaesthesia and there are higher risks of complications although typically this rate is low in the patient population typically treated. Allograft in the hand has evidence that is close to equivalence for gaps typically too long for a conduit, however the favourable results of any type of intervention drop when the gap is large (5cm) probably as a result of the wider zone of injury, potentially inadequate debridement and the problems with sustaining nerve regeneration for longer intervals over longer distances. Allograft can allow single limb operating under Regional Anaesthesia rather than the GA in the guidance and this is a benefit in terms of the patient journey and risk.	regarding the need for careful patient selection by clinicians. The committee felt that defining specific subgroups in which the procedure should be done is beyond the remit.

			My personal view is that all nerve gap reconstruction should be subject to surveillance and rigorous audit as part of standard clinical care, but use of allograft as a new intervention should have more robust measures in place to confirm that wider use by generalist hand surgeons is comparable to the published evidence to date from expert centres enlisted in the RANGER study. This will ensure that indications and contra indications are defined and clear protocols will exist for use and follow up. The format of this data collection could be in the form of a registry. In my practice I have a robust audit in place with outcomes measures and follow up pathways defined and I am happy to share my experience if needed. In addition I am in the process of REC / IRAS approvals for registration of our UK centre to the RANGER registry study in the UK as there is no current provision of a UK registry for nerve repair. The wider issue of sensory nerve repair outside the hand is an important one as most pure sensory nerves are peripheral in the limbs or in Max Fax the lingual nerve is typically injured within a zone where favourable regeneration is to be anticipated. I believe that for sensory nerve reconstruction allograft has advantages over sacrifice of another normal sensory nerve and the guidance could be widened to include this group of simple reconstruction cases subject to the same evaluation parameters as detailed for the digital nerve group above. Specifically I believe that there should be note about the management of a painful neuroma in a sensory nerve	

			where neuropathic pain drivers create a CNS sensitisation rendering them prone to donor autograft harvest sites sensitivity and symptomatic neuroma formation. This group in my practice are the prime indication in my opinion at this stage of evaluation. I would term this a complex nerve reconstruction as the process of evaluation and decision making regarding optimal treatment modalities is complex and the outcome may be hampered by pre-existing mapped neuropathic pain both peripherally and centrally in the nervous system. In terms of the other complex groups, mixed motor and sensory nerve (main nerve trunk) the challenge for the surgeon is the combination of multiple nerve fibre subtypes resulting in incomplete reinnervation, proximal injuries resulting in poorly sustained regeneration and a time-distance challenge to try and get motor axons back to end motor organs before the 9 month cut off when the success of this type of surgery falls off dramatically. Wider use should be subject to reporting of outcomes in order to properly evaluate the allograft. However it should be noted that direct comparison between patients is not easy as the nature of the injury, the timing of intervention, the site of injury, the surgical bed and the technique of repair will all have an impact on final outcome. I agree that robust audit is essential but would recommend research to continue in this area in the specific areas that I have outlined in the last paragraph below. In terms of brachial plexus injuries and proximal lower limb nerve injuries there is a strong argument for allograft as a primary procedure as the outcome is	

			generally poor and the trend towards targeted peripheral reconstruction with nerve transfers renders the proximal reconstruction a pain management strategy aimed at some functional and sensory recovery which is typically augmented with specialist peripheral nerve transfer surgery. I will not provide comment on obstetric brachial plexus palsy (OBPI) as this is not a main part of my practice other than to comment that the use of allograft will prevent the need for harvest of both lower limb sural nerves in babies which is disfiguring in 2 further limbs in a child already suffering from a single limb paralysing injury and the thought of additional limb surgery is frequently distressing for parents. In OBPI patients the potential for regeneration is greater and the reinnervation distances shorter and I believe that there should be favourable outcomes in this group and the reduction of donor site morbidity and reduced surgery duration is a distinct advantage. In terms of research what remains to be proven is that the use of allograft allows more adequate tailored debridement and a bespoke off the shelf reconstructive option to prevent tension following debridement. This can be tested in a digital nerve model and in a main forearm mixed nerve model. I am working up protocols to address these issues and to allow delivery in a multicentre UK based trial. Please acknowledge receipt of this outline response. Had I been informed of the consultation at the time of my requests for updates I would have been able to provide UK data from our current series. In addition I	

			would have welcomed the opportunity to provide a more comprehensive response.” [redacted]	
3	Consultee 2 NHS Professional	**1.2**	I am a UK based NHS hand and nerve surgeon and have the largest series of processed allograft used in the UK. I raised the consultation request for clarification of the issues as I believe there are key indications and some expanding indications for allograft use within my practice. However there are some important research questions that still need to be answered before widespread use of allograft for all nerve gaps achieves acceptability. "Simple cases can be treated with bridging of the gap with a conduit (small gap and in-border digit digital nerve) with gaps of 12mm or less and the evidence base supports this as satisfactory. Long gaps >12mm require a reconstruction using autologous graft (sensory) harvested from the same limb or the leg (sural). Dual limb surgery requires longer stays and general anaesthesia and there are higher risks of complications although typically this rate is low in the patient population typically treated. Allograft in the hand has evidence that is close to equivalence for gaps typically too long for a conduit, however the favourable results of any type of intervention drop when the gap is large (5cm) probably as a result of the wider zone of injury, potentially inadequate debridement and the problems with sustaining nerve regeneration for longer intervals over longer distances. Allograft can allow single limb operating under Regional Anaesthesia rather than the GA in the guidance and this is a benefit in terms of the patient journey and risk. "	Thank you for your comments. The consultee disagrees with point 1.2 of the guidance and suggests that the use of processed nerve allograft in pure sensory peripheral nerves in the limbs and tongue should be covered by point 1.1 of the guidance. The consultee emphasizes the need for robust measures for data collection. The committee has decided not to change its recommendations as the majority of the evidence is for digital nerve repair. The consultee highlights the relevance of data collection into a registry and identifies current gaps in the literature. The Committee has encouraged further research into processed nerve allografts to repair peripheral nerve discontinuities including information on the type of nerve repaired, the anatomical site, the size of the defect, patient reported outcome measures, functional outcomes, time to

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			reconstruction a pain management strategy aimed at some functional and sensory recovery augmented with specialist peripheral surgery. " I will not provide comment on obstetric brachial plexus palsy (OBPI) as this is not a main part of my practice other than to comment that the use of allograft will prevent the need for harvest of both lower limb sural nerves in babies which is disfiguring in 2 further limbsÂ in a child already suffering from a single limb injury and frequently distressing for parents. In OBPI patients the potential for regeneration is greater and the reinnervation distances shorter and I believe that there should be favourable outcomes in this group and the reduction of donor site morbidity and reduced surgery duration is a distinct advantage. "In terms of research what remains to be proven is that the use of allograft allows more adequate tailored debridement and a bespoke off the shelf reconstructive option to prevent tension following debridement. This can be tested in a digital nerve model and in a main forearm mixed nerve model. I am working up protocols to address these issues and to allow delivery in a multicentre UK based trial.Â " I would be happy to contribute my audit data on use and outcomes to date from the UK. I collect data in line with the RANGER Registry in the USA and I would be happy to advise on the relent datasets for prospective evaluation based on my experience as a peripheral nerve surgeon.	
4	Consultee 3 NHS Professional		In Parotid gland surgery, the facial nerve has to be removed and this can be extremely debilitating. This	Thank you for your comment.

			new material is a great addition to our ability to reconstitute the integrity of the facial nerve.	The Committee very much welcomes hearing from professionals with knowledge of the procedure. The committee has considered your experience and views in their deliberations.
5	Consultee 4 Company		On behalf of [redacted], I want to thank you for this opportunity to provide comments on the National Institute for Health and Care Excellence (NICE) draft guidance for processed nerve allografts to repair peripheral nerve discontinuities- Consultation Document. We've carefully reviewed the interventional procedural consultation document for processed nerve allografts to repair peripheral nerve discontinuities dated May 2017 and are providing comments to these draft recommendations. Attached is [redacted] comments for your consideration in addition to an Audit checklist template. Also, for your convenience we are providing literature references of the scientific literature presented in our response. Please note that sending these will likely require several emails which will be clearly serial numbered to ensure successful receipt. Please confirm receipt of all these materials. [redacted] [redacted]	Thank you for your comment. The consultee has presented a list of literature to be considered by the Committee. The papers by Berrocal 2013, Bibbo 2017, Henry 2015, Miloro 2015, Peled 2013, Salomon 2016, Turson 2016 were added to the update literature table. **The committee may wish to add them to Appendix A.** The papers by Brooks 2011, He 2013, Means 2016, Sousa 2016, Taras 2013 and Zuniga 2015 were already included in table 2 of the overview. Papers by Cho 2011, Ducic 2012, Guo 2013, Isaacs 2017, Karabekmez 2009, Rinker 2015, Shanti 2011 and Squintani 2013 were already included in appendix A of the overview. The papers by Flemmming 2014, Miloro 2017 were not relevant to the procedure; Zuniga 2017 was not yet published and does not report on new safety data.

understanding of how recommendations are developed. The comments are published as a record of the submissions that NICE has received, and are not endorsed by NICE, its officers or advisory committees."