NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

INTERVENTIONAL PROCEDURES PROGRAMME

Interventional procedure overview of processed nerve allografts to repair peripheral nerve discontinuities

Accidents or major surgery can damage nerves, causing pain, reduced sensation and lack of movement. If the ends of the damaged nerve are too far apart to be stitched together, the gap (discontinuity) needs bridging. In this procedure, a specially treated nerve (an allograft) taken from a human donor after death is used to bridge the gap. The aim is to restore function of the damaged nerve.

Introduction

The National Institute for Health and Care Excellence (NICE) has prepared this interventional procedure (IP) overview to help members of the interventional procedures advisory committee (IPAC) make recommendations about the safety and efficacy of an interventional procedure. It is based on a rapid review of the medical literature and specialist opinion. It should not be regarded as a definitive assessment of the procedure.

Date prepared

This IP overview was prepared in April 2017.

Procedure name

- Processed nerve allografts to repair peripheral nerve discontinuities

Specialist societies

- Royal College of Surgeons of England
- The British Society of Neurological Surgeons
- British Society for Surgery of the Hand
- British Orthopaedic Oncological Society.

Description

Indications and current treatment

Peripheral nerve damage can be caused by trauma or surgery, and can lead to reduced sensation and mobility of the affected limb or region. If direct repair is not possible because the section of nerve discontinuity is too long, grafts or artificial nerve conduits can be used.

Autologous nerve grafting (using another nerve from the same patient) is used most frequently (usually using the sural nerve from the leg). However, this can be associated with donor site morbidity. Untreated allografts (using a nerve from a donor) have been used but, after these, immunosuppressive treatment is needed.

What the procedure involves

Acellular processed nerve allografts are nerves from deceased human donors which have had their immunogenic components removed using tissue processing techniques. They are stored frozen until implantation and are available in different sizes. Immunosuppressive treatment is not needed.

The procedure is done under general anaesthesia. The injured nerve is exposed and the nerve ends are cleared of necrotic tissues and resected to allow for tension-free alignment with the graft. The graft is sutured to the exposed nerve ends. After grafting, limb splinting may be needed for several weeks to allow optimal nerve regeneration. The typical length of an allograft implant is 1–3 cm.

The aim of the procedure is to bridge the peripheral nerve discontinuity to allow axonal regeneration and growth through the allograft towards the distal nerve.

Outcome measures

Static 2-point discrimination scoring (2PD)

Measures the innervation density (number of nerves present in an area) by testing the ability to discern the difference between 1 and 2 static pressure points.

1 to 5 mm	Normal
6 to 10 mm	Fair
11 to 15 mm	Poor
One point perceived	Protective sensation only
No points perceived	Anaesthetic

Weber 2-point discrimination scale (mm)

	Moving 2PD		Static 2PD
Excellent	≤4	Or	≤6
Good	5 to 7	Or	7 to 15
Fair			
Poor	≥8	or	≥16

Moving 2-point discrimination scoring

According to Dellon after nerve injury, moving 2-point discrimination returns earlier than static 2-point discrimination. The test is used to determine progress in return of sensation.
Seven of 10 correct answers are needed for an accurate response. Two millimetres is considered a normal moving 2-point discrimination distance.

Interpretation of the Semmes–Weinstein monofilament test (SWMF) of pressure threshold

WES monofilament (N)	1	2	3	4	5
SW monofilament number	2.833	3.61	4.31	4.56	6.65
Force (g)	0.07	0.2	2	4	200
Interpretation of threshold	Normal sensation	Reduced tactile sensation	Reduced protective sensation	Loss of protective sensation	Residual sensation

Mackinnon–Dellon scale – Classification of sensory recovery

Grade	Recovery of sensation	S2PD (mm)	m2PD (mm)
S0	No recovery of sensation in the autonomous zone of the nerve		
S1	Recovery of deep cutaneous pain sensation within the autonomous zone of the nerve		
S1+	Recovery of superficial pain sensation		
S2	Recovery of superficial pain and some touch sensation		
S2+	As in S2, but with over-response		
S3	Recovery of pain and touch sensation with disappearance of over-response	>15	>7
S3+	As in S3, but localisation of the stimulus is good and there is imperfect recovery of 2 point discrimination (7-12mm)	7 to 15	4 to 7
S4	Complete recovery	2 to 6	2 to 3

British Medical Research Council muscular function grading system

M0	No contraction

M1	Flicker/trace contraction
M2	Active movement with gravity eliminated
M3	Active movement against gravity
M4-	Slight movement against resistance
M4	Moderate movement against resistance
M4+	Strong movement against resistance
M5	Normal/full power

Modification of the Mackinnon–Dellon scale for stratification of 2-point discrimination results

Classification	Mackinnon–Dellon scale	Weber s2PD (mm)	m2PD (mm)
Excellent	S4	≤6	≤3
Good	S3+	7-15	4-7
Poor	S3 and below	≥16	≥8

Ninhydrin test

This is used to evaluate the autonomic system and sympathetic nervous system function. It does not need a voluntary response from the patient. Ninhydrin spray is a clear agent that turns purple when it reacts with a small concentration of sweat. The patient's hand is cleaned and air dried for 5 minutes. The fingerprints are placed on bond paper for 15 seconds, traced and sprayed with the agent. Absence of sweat is related to complete nerve laceration.

Literature review

Rapid review of literature

The medical literature was searched to identify studies and reviews relevant to processed nerve allografts to repair peripheral nerve discontinuities. The following databases were searched, covering the period from their start to January 2017: MEDLINE, PREMEDLINE, EMBASE, Cochrane Library and other databases. Trial registries and the Internet were also searched. No language restriction was applied to the searches (see appendix C for details of search strategy). Relevant published studies identified during consultation or resolution that are published after this date may also be considered for inclusion.

The following selection criteria (table 1) were applied to the abstracts identified by the literature search. Where selection criteria could not be determined from the abstracts the full paper was retrieved.

Table 1 Inclusion criteria for identification of relevant studies

Characteristic	Criteria
Publication type	Clinical studies were included. Emphasis was placed on identifying good quality studies. Abstracts were excluded where no clinical outcomes were reported, or where the paper was a review, editorial, or a laboratory or animal study. Conference abstracts were also excluded because of the difficulty of appraising study methodology, unless they reported specific adverse events that were not available in the published literature.
Patient	Patients with peripheral nerve discontinuities.
Intervention/test	Processed nerve allografts to repair peripheral nerve discontinuities.
Outcome	Articles were retrieved if the abstract contained information relevant to the safety and/or efficacy.
Language	Non-English-language articles were excluded unless they were thought to add substantively to the English-language evidence base.

List of studies included in the IP overview

This IP overview is based on about 430 patients from 1 randomised control trial, 1 non-randomised comparative study and 6 case series.

Other studies that were considered to be relevant to the procedure but were not included in the main extraction table (table 2) have been listed in appendix A.

Table 2 Summary of key efficacy and safety findings on processed nerve allografts to repair peripheral nerve discontinuities

Study 1 Means RJ Jr (2016)

Details

Study type	**Randomised controlled trial (RCT; pilot study)**
Country	US
Recruitment period	Not reported
Study population and number	n=**23 patients with 31 nerve injuries** (14 patients needing 18 repairs were randomised to the allograft group, 9 patients needing 13 repairs were randomised to the bovine graft group [xenograft])
Age and sex	Mean 42±13 years (range 21 to 63) in the allograft group and 38±12 years (range 20 to 53) in the bovine graft group. Males 86% (12/14) in the allograft group and 67% (6/9) in the bovine graft.
Patient selection criteria	Selection criteria: patients with ages between 18 and 70 years who sustained injuries needing repair of at least 1 digital nerve needing a graft with 5 to 20 mm in size, after resection of the healthy nerve. Exclusion criteria: distance from the injury to the sensory target was more than 125 mm, injury to the nerve was a crush or avulsion, incomplete nerve transection, implantation of the injured digit was needed, contralateral injuries corresponding to the target digit, nerves injuries in limb present proximal to crease of the wrist, end to side nerve repair was needed, injuries with significant vascular damage that could impair adequate perfusion of the target limb, patients who were having treatment with chemotherapy, radiation therapy, or other treatment known to affect the growth of neural or vascular structures. History of neuropathy, uncontrolled diabetes or any other known neuropathy, secondary nerve repair more than 12 weeks following initial injury, patient currently enrolled in another investigational study, expected use of medications during the study that are known to cause peripheral neuropathy, or history of Raynaud's or other disorders known to compromise circulation or sensation in the upper extremity. The use of bovine collagen–based hollow nerve graft (NeuroGen, NeuroMatrix, or NeuroFlex) was restricted in a patient with known or suspected bovine sensitivity (xenograft).
Technique	Repair was done using processed allograft (AxoGen) or bovine graft (NeuroGen) by surgeons with hand or microsurgical fellowship training. The manufacturer's implantation instructions were followed by all surgeons. Sensory assessment was done using the s2PD, m2PD and SWMF test. Disability of the Arm, Shoulder and Hand (DASH) scores were done using thermal discretion via the application of hot and cold objects; and pain assessment used via a visual analogue scale (0=no pain, 10=extreme pain).
Follow-up	**12 months**
Conflict of interest/source of funding	Financial support for the study was provided by AxoGen, Alachua, Florida. The authors declared no other conflict of interest.

Analysis

Follow-up issues: Standard sensory and safety assessments were conducted at baseline, 1, 3, 6, 9, and 12 months after reconstruction. In the allograft group, 50% (7/14) of the patients completed follow-up at 6 months and 36% (5/14) at 12 months. In the bovine graft group, 100% (9/9) of patients were followed-up at 6 months and 78% (7/9) at 12 months post procedure.

Study design issues: Baseline assessment and follow-up assessments of functional recovery and adverse events were done by qualified personnel blinded to the treatment. Patients were blinded to treatment and randomised intraoperatively, in a 3:2 allograft or bovine graft distribution, based on a randomisation code enclosed in numbered envelopes. Contralateral digit was used as control for all patients.

Study population issues: Patient demographics and baseline characteristics were not statistically significantly different.

Mean nerve gap prior repair was 12±4 mm (range 5 to 20) in both groups.

Other issues: One patient in the allograft group had multiple repairs, 1 of which used a 23-mm graft, beyond the established inclusion criteria, but was allowed as an exception because the patient had other injuries that qualified and were enrolled. This patient was lost to follow-up 3 months post repair and thus was not included in the outcomes analysis.

Key efficacy and safety findings

Efficacy

n=23 patients (14 allograft, 9 bovine graft)

	Allograft	Bovine graft	p
12 months			
	n=5 (6 nerves)	n=7 (9 nerves)	
s2PD	5±1 mm*	8±5 mm*	<0.05
m2PD	5±1 mm	7±5 mm	>0.05
SWMF	3.6±0.7	4.4±1.4	<0.05
Protective sensation**	100% (6/6)	75% (7/9)	NR
DASH score[1] (baseline)	49±20.6	42±28.3	0.559
Dash score (12 months)	5±6.5	8±6.3	0.318
Thermal sensation (baseline)	7% (1/14)	33% (3/9)	NR
Thermal sensation (12 months)	100% (6/6)	100% (7/7)	NR
Pain (baseline)	4.7±3.4	4.4±2.1	0.99
Pain (12 months)	0.5±0.6	0.9±1.0	0.432
6 months			
	n=7 (8 nerves)	n=9 (12 nerves)	
MRCC (S3+ or greater)	100% (8/8)	75% (9/12)	>0.05

* Corresponding to 66±6% and 38±11% improvement from baseline for the allograft and bovine graft groups, respectively.

** SWMF score of 4.31 or better.

[1] DASH score, 0= no disability, 100=most severe disability.

[2]Pain

Safety

Allograft group

Severe skin infection at injury site needing hospitalisation and antibiotics (allograft group) in 7% (1/14) patients. ***

Bovine graft group

Persistent pain at the repair site in 1/9 patient.

Tube extrusion, osteomyelitis and fungal infection resolved with amputation of the digit in 1/14 patient.

*** Microbiology suggested infection was related to initial trauma.

Abbreviations used: DASH score, disability of the arm, shoulder and hand; MRCC, Medical Research Council classification; MN, meganewtons; m2PD, moving 2-point discrimination; NR, not reported; RCT, randomised controlled trial; SD, standard deviation; SWMF, Semmes–Weinstein monofilament test; s2PD, static 2-point discrimination.

Study 2 He B (2012)

Details

Study type	**Non-randomised comparative study**
Country	China
Recruitment period	Not reported
Study population and number	**n=153**, patients needing digital nerve repair Allograft group (intervention): 72 patients (100 nerves), 94% male Tension free suture repair (control): 81 patients (123 nerves), 90% male
Age and sex	Allograft group: mean 33.0±11.1 years (range 18 to 61) Control group: mean 36.9±13.4 years (range 15 to 75)
Patient selection criteria	Selection criteria: digital nerve injury, between the ages of 14 and 80, needed direct suturing or had a nerve defect that was 1–5cm in length and needed nerve transplantation, provided informed consent and duration of injury less than 6 months. Exclusion criteria: acute infection, severe wound contamination, unstable vital signs and inability to conduct a functional assessment of the nerve repair due to damage to the skin, neurological and other diseases such as diabetes that could potentially affect the nervous system, chronic diseases that could potentially affect the nervous system, chronic diseases including gout and collagen vascular diseases, alcoholism, liver impairment and renal dysfunction, inability to comply with treatment, post-operative rehabilitation and follow-up; a defect greater that 5 cm or smaller than 10 mm. Withdrawal criteria: patients diagnosed with neurological or autoimmune diseases during trial and patients who were included by error.
Technique	Fresh peripheral nerves were harvested from traumatically amputated upper limbs with consent from the donors. The donor nerve were screened for multiple pathogens and rejected if infected. The graft was then prepared using the Sondell method (Sondell et al, 1998) of scaffold preparation. Efficacy was assessed using an s2PD and SWMF testing. Safety was assessed by local wound response and laboratory testing. Patients were discharged after suture removal, usually 2 weeks after the procedure.
Follow-up	**6 months**
Conflict of interest/source of funding	None

Analysis
Follow-up issues: Patients were followed-up for 1, 3 and 6 months after discharge.
Study design issues: A minimum sample size of 70 patients (each group) was deemed necessary assuming a non-inferiority clinical standard of ±15% in comparison with the control group (90% satisfaction), power of 80%, statistical significance level of 5% and dropout rate of 5%. There are a number of discrepancies in the statistical analysis and description of the results. Sensory evaluation (SWMF and s2PD tests) were done by a third party, and physicians doing the assessment were blind to group allocation.
Study population issues: The difference in age between the arms of the study was statistically significantly different, p=0.0047.
The mean time from injury to repair was statistically significantly greater in the allograft group (23.7±52 days; range 0–200 days) than in the control group (1.5±10.4 days; range 0–91 days), p=0.0005.
Other issues: No patient had immunosuppressive therapy.

Key efficacy and safety findings

<table>
<tr><td>Efficacy</td><td>Safety</td></tr>
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n=153 (72 allograft group, 81 control group)

Comparison of s2PD combining excellent and good scores at6-month follow-up (patient level)

Analysis sets	Allograft group	Control group	p value
PPS	67% (48/72)	64% (52/81)	0.749

Results of SWMF and s2PD testing at nerve and patient level

		Allograft[1]	Control[1]
Patient level	**p value**	**n=72**	**n=81**
SWMF=1.120	**0.571**		
Satisfied		94% (68/72)	93% (75/81)
Unsatisfied		6% (4/72)	7% (6/81)
Satisfaction rate difference[2]	2.02% (−6.07 to 10.87)		
s2PD=11.6178	0.003		
Excellent*		18% (13/72)	2% (2/81)
Good*		49% (35/72)	62% (50/81)
Poor		33% (24/72)	36% (29/81)

Sensitivity analysis and preference scores of SWMF testing using last observation carried forward and worst observation carried forward principles for missing data transfer also showed that the non-inferiority conclusion was credible, no statistically significant difference between groups.

[1]Groups were compared using adjusted centre effect Cochran–Mantel–Haenszel chi-squared test.

[2]Allograft group minus control group satisfaction rate, 95% CI

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n=78 (patients)

8% (6/78) patients reported mild pain 2 weeks after the procedure.

3% (2/78) patients needed secondary tenolysis at 6-month follow-up.

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<tr><td colspan="2">Abbreviations used: PPS, per protocol set; SWMF, Semmes–Weinstein monofilament test; s2PD, static 2-point discrimination.</td></tr>
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Study 3 Brooks DN (2011)

Details

Study type	**Case series**
Country	US
Recruitment period	2007–10
Study population and number	**n=108** adults (132 nerves), patients needing sensory, mixed or motor nerve repair
Age and sex	Mean 38±16 years (range 18 to 86), 77% males
Patient selection criteria	Inclusion criteria: patients over the age of 18 years able to consent.
Technique	Patients were recruited from 12 centres. Repairs were done by experienced plastic or orthopaedic surgeons with a minimum completed fellowship in hand or hand and microsurgery. Patients treated with processed nerve allograft (Avance, Axogen) were included in the study and had retrospective chart review. Quantitative measures included s2PD, m2PD, SWMF, range of motion, strength testing and MRCC for sensory and motor function. Qualitative assessment measures included pain assessment and patient or physician subjective assessment of improvement in function.
Follow-up	**264±152 days (range 40 to 717)**
Conflict of interest/source of funding	This study is part of the RANGER research program: a registry study of Avance Nerve Graft evaluating outcomes in nerve repair. Patient selection, treatment decision and study evaluations were done at the discretion of the authors or the institution's staff. Data analysis was done by independent biostatisticians.

Analysis

Follow-up issues:

Follow-up status	Insufficient follow-up	Lost to follow-up	Sufficient follow-up	Total
Subjects	34 (31%)	15 (14%)	59 (55%)	108
Repairs	37 (28%)	19 (14%)	76 (58%)	132

Study design issues: Patients with sufficient follow-up were placed in the outcomes population (OP) group. Data from the insufficient follow-up, lost to follow-up and sufficient follow-up groups was used to extract safety outcomes. Post-hoc power calculation assumed 0.05 significance level and sample size of 76, resulting in a power of 0.999.

Study population issues: Mean preoperative interval is 163±331 days (range 0 to 2,461).
Mean graft length 27±14 mm (range 5 to 50). Two patients had a preoperative interval of 2,461 and 1,460 day, accounting for the wider degree of variability.

Nerve repaired	Utilisation Population (n=132)	Outcomes population (n=76)
Digital	55% (73)	63% (48)
Median	17% (22)	14% (11)
Ulnar	11% (15)	8% (6)
Radial	3% (4)	3% (2)
Peroneal	4% (5)	3% (2)
Musculocutaneous	1	1
Anterior interosseous	1	0
Facial	2% (3)	4% (3)
Tibial	2% (2)	0
Sciatic	1	0
Spinal accessory	2% (2)	1
Posterior interosseous	1	0
Axillary nerve	1	1
Ulnar nerve motor branch	1	1

12% of the subjects in outcomes population had health conditions that could be a contributing factor to the overall outcome: 6 had uncontrolled hypertension, 1 had peripheral neuropathy, 10 were smokers or had smoked in the past. Analysis of the demographics has shown that the outcomes population was representative of the utilisation population. Sixty four percent of patients had concomitant vascular, tendon or skeletal injuries.

Other issues: None.

Key efficacy and safety findings

Efficacy

n=76 (patients)

Outcomes group: summary and efficacy by type of nerve repaired

Nerve type	n	Preoperative interval (days)	Follow-up (days)	Gap (mm)	Response rate[1]	Meaningful recovery[2]
OP	76	172±283 (0 to 1460)	264±152 (40 to 717)	22±11 (5 to 50)	90%	87% (66/76)
Sensory	49	182±323	276±169	19±8	92%	89%
Mixed	18	170±234	205±115	29±12	83%	77%
Motor	9	160±164	341±72	29±13	89%	86%

No nerve recovery - 11% (8/76) of patients, 5% (4/76) due to the failure of the allograft [3].

Surgical revision (no response patients) - 5% (4/76)

No statistically significant difference in meaningful recovery rates was found when doing subgroup analysis for: type of nerve repaired, time to repair, age or mechanism of injury.

[1]Quantitative or qualitative data.

[2]Meaningful functional recovery was defined to be S3–S4 or M3–M5 on the MRCC scale.

[3]Across 5 different sites and 6 surgeons. Mean age 33±15 years (range 18 to 65), mean nerve gap was 26±12 mm (range 15 to 50) mean time to repair 383±514 days (range 0 to 1,460). Upper extremities injuries: 4 sensor, 3 mixed, 1 motor.

Safety

n=132 (nerves)

Neuroma: 1/132 nerves

Abbreviations used: FU, follow-up; m2PD, moving 2-point discrimination; MRCC, Medical Research Council classification; SWMF, Semmes–Weinstein monofilament test; s2PD, static 2-point discrimination; UP, utilisation population.

Study 4 Zhu S (2016)

Details

Study type	**Case series**
Country	China
Recruitment period	Not reported
Study population and number	**n=64 patients** (64 nerves) needing nerve repair in the upper extremity
Age and sex	Mean age 35±11 years (range 11 to 68), 80% males (51/68)
Patient selection criteria	Patients who had nerve allograft implantation in the upper extremity and who were estimated to had been followed-up during the same time window.
Technique	Patient information was collected retrospectively from 13 hospitals using chart review. All patients' nerves were repaired using human acellular nerve allografts (Guangzhou Zhongda Medical devices company, China). Motor function assessment included range of motion and strength testing. Sensory function was assed using the s2PD, m2PD and SWMF. For autonomic nerve assessment the ninhydrin test was done. Qualitative assessment included pain and physician's subjective impression of function improvement.
Follow-up	**Mean 355±158 days (range 35 to 819)**
Conflict of interest/source of funding	None.

Analysis

Follow-up issues: Follow-up time window was estimated based on the nerve regeneration distance and peripheral nerve regeneration rate (1 mm/day).

Study design issues: Data was analysed by an independent statistician.

Study population issues: Average nerve gap was 27±13 mm (range 10 to 60).

Nerve repaired	**%**
Digital	58% (37/64)
Ulnar (upper arm)	13%(8/64)
Deep branch of the radial nerve	9% (6/64)
Median	9%(6/64)
Radial	8% (5/64
Superficial branch of the radial nerve	3% (2/64)

Other issues: None.

Key efficacy and safety findings

Efficacy

n=64

Injured nerve	n	Delay (days)	Follow-up (days)	Gap (mm)	Meaningful recovery[1]
Median	6	342±421	340±106	24±4	100% (6/6)
Ulnar	8	382±443	311±136	41±14	37% (3/8)
Digital	37	102±122	354±157	21±9	84% (31/37)
Radial	5	105±113	509±209	50±9	40% (2/5)
Deep branch radial	6	63±70	297±73	30±9	67% (4/6)
Sup. Branch radial	2	65±55	375±172	20±0	100% (2/2)
Overall	64	–	–	27±13	75% (48/64)

Outcomes for subgroups

Subgroup analysis for age, time to repair, gender and follow-up time did not find any statistically significantly difference between comparators.

Factors	n	Delay (days)	FU (days)	Gap (mm)	Meaningful recovery[1]
Nerve type					
Sensory	39	100±120	355±158	21±8	85% (33/39)
Mixed	19	296±394	372±172	38±15	58% (11/19)
Motor	6	63±70	297±73	30±9	67% (4/6)
Site					
Low	43	112±151	352±155	22±8	86% (37/43)*
Intermediate or high	21	243±370	360±162	38±14	52% (11/21)
Gap length[2]					
≤30 mm	49	136±205	352±149	–	88% (42/49)*
30–50 mm	9	129±193	344±146	–	33% (3/9)
≥50 mm	6	406±501	458±218	–	33% (2/6)*

Univariate analysis demonstrated that low site of injuries have statistically significantly higher likelihood of recovery that intermediate and high sites, OR: 5.606; 95% CI 1.663 to 18.903, p<0.05.

Univariate analysis demonstrated that the group with gap length smaller than 30 mm had a statistically significantly greater likelihood of meaningful repair than the group with gaps greater than 50 mm: OR 14.333; 95% CI 2.143 to 95.848, p<0.05.

[1]Meaningful functional recovery was defined to be S3–S4 or M3–M5 on the MRCC scale.

*Statistically significantly different

Safety

There were no signs of infection, tissue rejection or extrusion among the subjects.

Abbreviations used: CI, confidence interval; FU, follow-up; MRCC, Medical Research Council classification; m2PD, moving 2-point discrimination; OR, odds ratio; SWMF, Semmes–Weinstein monofilament test; s2PD, static 2-point discrimination.

Study 5 Souza JM (2016)

Details

Study type	**Case series**
Country	US
Recruitment period	2010–15
Study population and number	**n= 26** patients needing nerve graft after resection of painful neuromas of the foot and ankle
Age and sex	Mean 46 years (range 18 to 75)
Patient selection criteria	Inclusion criteria: patients with point tenderness and localised lower extremity nerve pain. Exclusion criteria: extremity without documented pulsatile blood flow and patients who had no relieve from injection of 1ml of lidocaine proximal to the area of greater tenderness.
Technique	All repairs were done using Avance processed nerve allograft (Axogen). Dissection was done a few centimetres proximal and distal to the area of greater tenderness. A splint was used to immobilise the nerve graft in its soft tissue bed for 2 weeks. After 2 weeks patients could ambulate as tolerated. Pain assessment used and ordinal scale (0 no pain to 10 worse pain) and PROMIS (disease unspecific outcome tool)
Follow-up	**Mean 66±31 weeks**
Conflict of interest/source of funding	None

Analysis

Follow-up issues: Only 22 patients completed the minimum 6 months follow-up and were included in the analysis.

Study design issues: Database data was reviewed retrospectively.

Study population issues: Nerves repaired were sural (10), superficial peroneal (9), common digital nerve (5), deep peroneal (1), and lateral plantar nerve (1). There were 8 patients with end neuromas and 18 with neuromas in continuity.

Other issues: None.

Key efficacy and safety findings

Efficacy	Safety
n=22 <u>Ordinal pain score</u> Ordinal pain scores decreased by 2.6 points (range +2 to −8) from a mean baseline score of 7.5, p=0.016. <u>PROMIS[1]</u> Pain behaviour T-score decreased by 7.3 (range+2 to −22) from 63 at baseline, percentile decrease of 24%, p<0.003. Pain interference T-score decreased by 11.3 (range +2 to −27) from 68 at baseline, mean percentile change of 31%, p<0.003. Subgroup analysis found no statistically significantly differences related to type of nerve repaired, location of the neuroma, or previous neuroma treatments. [1]Reported as T-scores which have a population mean of 50 and a standard deviation of 10. The 2 measures assess the effect of pain on patient behaviour and interference with daily function.	No safety events reported.
Abbreviations used: PROMIS, patient reported outcomes measurement information system.	

Study 6 Zuniga JR (2015)

Details

Study type	**Case series**
Country	US
Recruitment period	2007–13
Study population and number	**n=26 patients** (28 nerve) with lingual nerve and inferior alveolar nerve discontinuities
Age and sex	Mean 36.5±18.3 years (range 9 to 82), 54% males (14/26)
Patient selection criteria	All patients had injuries classified as Sunderland degree IV (only the epineurium is intact) or V (complete resection) before reconstruction.
Technique	Axogen processed nerve allograft was used in all patients. Neurosensory testing including brushstroke directional sensation and s2PD (level A), contact detection SWMF (level B), and pressure pain tolerance (level C). Neuropathic pain was assessed pre and postoperatively.
Follow-up	**12 months**
Conflict of interest/source of funding	None.

Analysis

Follow-up issues: only 21 of the 26 recruited patients had sufficient follow-up data. Sensory assessments were done at 3, 6 and 12 months. Patients with at least 6 month follow-up were included in the outcomes analysis.

Study design issues:

Reported sensory level	Neurosensory testing
Levels A, B and C within normative limits	Normal
Level A abnormal, level B and C within normative limits	Mild
Levels A and B abnormal, level C within normative limits.	Moderate
Levels A and B abnormal, level C has elevated measures.	Severe
Levels A and B abnormal, level C absent.	Complete

Study population issues: There were 2 patients having bilateral reconstructions

Variable	Total population	Outcomes population
Aetiology		
Third molar	61% (17/26)	57% (13/21)
Implant	11% (3/26)	9% (2/21)
Oncology	21% (6/26)	26% (6/21)
BSSO	7% (2/26)	9% (2/21)
Nerve location		
Lingual	61% (17/26)	65% (15/21)
Inferior alveolar	39% (11/26)	35% (8/21)

Other issues: None.

Key efficacy and safety findings

<table>
<tr><th>Efficacy</th><th>Safety</th></tr>
<tr><td>n=21 (23 nerves)

At last follow-up NSI was normal 52% (12/23), mild 9% (2/23), moderate 26% (6/23) and severe 13% (3/23).

<table>
<tr><th>Gap length</th><th>Repairs</th><th>NSI</th></tr>
<tr><td>8 to 20 mm</td><td>14</td><td>86% (12/14)</td></tr>
<tr><td>30 to 70 mm</td><td>9</td><td>89% (8/9)</td></tr>
</table>

<u>Pain</u>
There were 8% (2/26) patients reporting neuropathic pain preoperatively. Pain scores were maintained after surgical repair.</td><td>None of the patients reported adverse events.
None of the patients reported de novo neuropathic pain after surgery.</td></tr>
<tr><td colspan="2">Abbreviations used: BSSO, bilateral sagittal split osteotomy; IAN, inferior alveolar nerve; LN lingual nerve; NSI, neurosensory improvement; SWMF, Semmes–Weinstein monofilament test; s2PD, static 2-point discrimination</td></tr>
</table>

Study 7 Li X (2015)

Details

Study type	**Case series**
Country	China
Recruitment period	Not reported
Study population and number	**n=15 patients** (18 digits) with acute digital nerve injuries
Age and sex	Mean 36 years (range 17 to 57), 73% (11/15) males
Patient selection criteria	Patients with digital injuries needing nerve repair, admitted to the emergency department. Exclusion criteria: Patients with more than 60 years of age, diabetic or with immune deficiencies.
Technique	All repairs were done shortly after admission to the emergency department using processed nerve allograft (Guangzhou Zhongda Medical Devices Company, China), within 6 hours after injury. Brachial plexus block was given and a tourniquet was applied to the upper arm. A splint was used to inhibit wrist flexion and interphalangeal joint extension for 4 to 6 weeks. Recovery of sensation was observed using a modified Mackinnon–Dellon s2PD and the SWMF.
Follow-up	**Mean 12 months (range 6 to 24)**
Conflict of interest/source of funding	No conflict of injury reported.

Analysis

Follow-up issues: None.

Study design issues: None.

Study population issues: The average defect length was 19 mm (5–50 mm). Of these, 4 had a gap greater than 30 mm, 9 involved fractures, 8 involved a tendon and blood vessel damage. There were 5 emergency class-I clean wounds and 10 cases of class-II mildly contaminated wounds**.** No immunosuppressant drugs were given to the patients.

Other issues: None.

Key efficacy and safety findings

<table>
<tr><th>Efficacy</th><th>Safety</th></tr>
<tr><td>

n=15 (18 digits)

Mackinnon-Dellon s2PD

Excellent	50% (9/18)
Good	38% (7/18)
Poor	11% (2/18)

Excellent or good s2PD results were present in 89% (16/18) of the patients.

SWMF

Normal light touch	38% (7/18)
Reduced light touch	38% (7/18)
Slight light touch	11% (2/18)
Poor light touch and unable to position	11% (2/18)

The SWMF demonstrated that good or excellent result were present in 78% (14/18) of patients.

</td><td>

Local infection occurred in 1/15 patients, this improved after anti-infection treatment. (not specified)

</td></tr>
<tr><td colspan="2">Abbreviations used: SWMF, Semmes–Weinstein monofilament test; s2PD, static 2-point discrimination</td></tr>
</table>

Study 8 Taras JS (2013)

Details

Study type	**Case series**
Country	US
Recruitment period	Not reported
Study population and number	**n=17** patients (21 repairs) with digital nerve lacerations in the hand. Outcomes data reported in 14 patients (18 digits), 71% (10/14) males
Age and sex	Mean 39 years (range 18 to 76)
Patient selection criteria	Patients older than 18 years with digital nerve lacerations needing nerve grafting.
Technique	Postoperative sensation was assessed using SWMF and s2PD, pain was assessed using a VAS through the recovery period. A DASH was recorded before and after surgery. All repairs used the Avance processed nerve allograft (Axogen).
Follow-up	**Mean 15 months (range 12 to 25)**
Conflict of interest/source of funding	The study received financial support from Axogen. The main author is a member of the speakers' bureau for Axogen.

Analysis

Follow-up issues: Three patients did not complete the 12-month minimum follow-up period.

Study design issues: The authors used a self-designed outcome scale to grade the effectiveness of the operation. The scale is not validated.

Study population issues: Average nerve gap was 11 mm (range 5 to 30). There were concomitant fractures in 7 patients. Average time to surgery was 29 days (range 2 to 262)

Other issues: None.

Key efficacy and safety findings

<table>
<tr><th>Efficacy</th><th>Safety</th></tr>
<tr><td>

n=14 (18 digits)

Recovery of sensation

<table>
<tr><th></th><th>s2PD</th></tr>
<tr><td>Excellent</td><td>39% (7/18)</td></tr>
<tr><td>Good</td><td>39% (7/18)</td></tr>
<tr><td>Poor</td><td>22% (4/18)</td></tr>
</table>

S2PD was excellent or good in 78% (14/18) of patients.

<table>
<tr><th></th><th>Result/Mean value</th></tr>
<tr><td>Initial pain[1]</td><td>5</td></tr>
<tr><td>Final pain</td><td>2</td></tr>
<tr><td>Initial DASH[2]</td><td>44.8</td></tr>
<tr><td>Final DASH</td><td>26.3</td></tr>
</table>

There were 17% (3/18) patients reporting the same pain score at baseline and final follow-up: 1/10, 3/10 and 4/10.

[1]VAS range 0 (no pain) to 10 (extreme pain)

[2]Range 0 (no disability) to 100 (most severe disability)

</td><td>

There were no signs of infection, extrusion or graft reaction.

One patient had a preoperative pain score of 5/10 and reported a final pain score of 8/10.

</td></tr>
<tr><td colspan="2">Abbreviations used: DASH, Quick disabilities of the arm, shoulder and Hand score; m2PD, moving 2-point discrimination SWMF, Semmes–Weinstein monofilament test; s2PD, static 2-point discrimination; VAS, visual analogue scale.</td></tr>
</table>

Efficacy

Neurosensory recovery

Two-point discrimination test

In a randomised control trial (RCT) of 23 patients needing digital nerves repair comparing processed nerve allograft (PNA) with treated bovine graft), at 12-month follow-up, static 2-point discrimination assessment (s2PD; which tests the ability to discern the difference between 1 and 2 static pressure points) was statistically significantly better in the PNA group (n=5) than the bovine graft group (n=7; 5±1 mm versus 8±5 mm, $p<0.05$). In the same study, moving 2-point discrimination assessment (m2PD) was not statistically significantly different between the PNA group and the bovine graft group (5±1 mm versus 7±5 mm, $p>0.05$) at 12-month follow-up.[1]

In a non-randomised comparative study of 153 patients needing digital nerve repair comparing PNA repair (n=72) with tension-free suture nerve repair (n=81), s2PD scores (excellent plus good, defined as the ability to distinguish 2 static pressure points at a maximum distance of 15 mm) were not statistically significantly different between the PNA group (67% [48/72]) and the tension-free suture group (64% [52/81]) at 6-month follow-up ($p=0.749$).[2]

In a case series of 15 patients with acute digital nerve injuries treated by PNA grafting, s2PD were excellent or good in in 89% (16/18) of the patients, at 12-month follow-up.[7]

In a case series of 14 patients with digital nerve injuries treated by PNA grafting, s2PD was excellent or good in 78% (14/18) of patients, at 15-month follow-up.[8]

Semmes–Weinstein monofilament pressure test (SWMF)

In the RCT of 23 patients, Semmes–Weinstein monofilament test (testing of pressure threshold using a monofilament; range: 2.833= normal sensation to 6.650= residual sensation) was statistically significantly better in the PNA group than the treated bovine graft group (3.6±0.7 versus 4.4±1.4, $p<0.05$) at 12-month follow-up.[1]

In the case series of 15 patients with acute digital nerve injuries treated by PNA grafting SWMF pressure assessment was excellent or good in 78% (14/18) of patients, at 12-month follow-up.[7]

Thermal sensation

In the RCT of 23 patients needing digital nerves repair, thermal sensation was totally improved from baseline measurements in the PNA group (100% [6/6] from 7% [1/14]) and in the conduit group (100% [7/7] from 33% [3/9]) at 12-month follow-up, $p=0.432$.[1]

Meaningful recovery

In a case series of 76 patients needing nerve repair treated by grafting with PNA, meaningful recovery (defined as S3 [recovery of pain and touch sensation with disappearance of over-response] or better or M3 [active movement against gravity] or better) was achieved in 87% (66/76) of patients at 264 days (range 40 to 717) follow-up.[3]

In a case series of 64 patients needing nerve repair in the upper extremity and treated by grafting using PNA, there was meaningful recovery in 75% (48/64) of all patients. Univariate analysis showed that distal site of injuries have a statistically significantly higher likelihood of recovery than proximal upper limb sites (odds ratio [OR] 5.606, 95% confidence interval [CI] 1.663 to 18.903; $p<0.05$). In the same study, discontinuities smaller than 30 mm had a statistically significantly greater likelihood of meaningful repair than those greater than 50 mm (OR 14.333, 95% CI 2.143 to 95.848; $p<0.05$).[4]

In a case series of 26 patients with lingual nerve and inferior alveolar nerve discontinuities treated by PNA grafting, meaningful sensory recovery was assessed using a neurosensory test improvement tool (ranging from normal=best, through mild, moderate and severe to complete=worse). At 12-month follow-up, neurosensory test improvement scores were normal in 52% (12/23), mild in 9% (2/23), moderate in 26% (6/23) and severe in 13% (3/23) of patients. In the same study, neurosensory improvement was reported in 86% (12/14) of patients with discontinuities 8–20 mm in length and 89% (8/9) of patients with discontinuities 30–70 mm in length.[6]

Disability of the arm, shoulder and hand score (DASH)

In the RCT of 23 patients needing digital nerves repair, DASH score (0= no disability, 100=most severe disability) was not statistically significantly different between the PNA group (5±6.5) and the bovine graft group (8±6.3) at 12-month follow-up ($p=0.318$).[1]

In the case series of 14 patients with digital nerve injuries treated by PNA grafting, DASH scores were improved from 44.8 at baseline to 26.3 at 15-month follow-up.[8]

Graft failure (no sensory recovery)

In a case series of 108 patients needing nerve repair, there was no sensory recovery because of graft failure in 5% (4/76) of patients at last follow-up and surgical revision was needed.[3]

Surgical revision

In the case series of 76 needing nerve repair, surgical revision due to graft failure was needed in 5% (4/76) of patients.[3]

Pain

In the RCT of 23 patients, at 12-month follow-up, pain measured using a visual analogue scale (VAS, 0=no pain, 10 =extreme pain) had improved from baseline in both groups (PNA group: from 4.7±3.4 to 0.5±0.6; treated bovine graft: from 4.4±2.1 to 0.9±1.0) but there was no statistically significant difference between the groups (p=0.432).[1]

In a case series of 26 patients needing PNA after resection of neuromas of the foot and ankle, mean ordinal pain score (0= no pain to 10= worse pain) statistically significantly reduced from 7.5 points at baseline to 4.9 points at a mean 66-week follow-up (difference 2.6, range +2.0 to −8.0; p=0.016). In the same study, patient reported outcomes measurement information system scores were used to assess the impact of pain on patients' behaviour and daily function (reported as T-scores with a population mean of 50 and a standard deviation of 10). Pain behaviour T-score decreased by 7.3 (range+2.0 to −22.0) from 63.0 at baseline (percentile decrease of 24%, p<0.003). Pain interference T-score decreased by 11.3 (range +2.0 to −27.0) from 68.0 at baseline (mean percentile change of 31%, p<0.003).[5]

In the case series of 26 patients treated by PNA grafting, neuropathic pain was reported preoperatively in 8% (2/26) of patients, which was not improved at 12-month follow-up.[5]

In the case series of 14 patients with digital nerve injuries treated by PNA grafting, pain was assessed with a visual analogue scale (0= no pain to 10= extreme pain). Mean pain scores improved from 5 at baseline to 2 at 15-month follow-up. In the same study there were 17% (3/18) of patients reporting the same pain score at baseline and final follow-up: 1/10, 3/10 and 4/10.[8]

In the non-randomised comparative study of 153 patients treated by grafting using PNA 8% (6/78) of patients reported mild pain 2 weeks after the procedure.[2]

In a case series of 17 patients with digital nerve injury treated by grafting with PNA, pain (measured using a VAS: 0= no pain, 10= extreme pain) worsened in 1 patient (VAS score increased from 5 at baseline to 8 at 15-month follow).[8]

Patient satisfaction

In the non-randomised comparative study of 153 patients, difference in satisfaction rate was not statistically significantly different between the PNA group and the tension-free suture group (2.02%, 95% CI: −6.07 to 10.87), at 6-month follow-up.[2]

Safety

Repeated surgery

Tenolysis was needed in 3% (2/78) of patients at 6-month follow-up in a non-randomised comparative study of 153 patients needing digital nerve repair comparing processed nerve allograft (PNA) repair (n=72) with tension-free suture nerve repair (n=81).[2]

Neuroma

Neuroma was reported after 1 nerve repair of 132 nerves in a case series of 108 patients needing nerve repair.[3]

Infection

Local infection that improved after treatment (not specified) was reported in 1 patient in the case series of 15 patients treated by PNA grafting.[7]

Validity and generalisability of the studies

- There is considerable heterogeneity amongst the studies regarding the anatomic location of the repair, type of nerve, length of the gap and time to repair.
- Evidence on medium- and long-term follow-up is very limited with most papers in table 2 reporting outcomes after 12 to 15 months postoperatively.
- Most of the data comes from retrospective case series[3-8]. The only randomised study[1] has a small non-powered sample.
- There is some consistency in the tools used to measure neurosensory recovery with minor variations being adopted by some authors[2, 4, 8].

Existing assessments of this procedure

There were no published assessments from other organisations identified at the time of the literature search.

Related NICE guidance

Below is a list of NICE guidance related to this procedure. Appendix B gives details of the recommendations made in each piece of guidance listed.

Interventional procedures

- Phrenic nerve transfer in brachial plexus injury. NICE interventional procedure guidance 468. November 2013, Standard arrangements https://www.nice.org.uk/guidance/ipg468

Specialist advisers' opinions

Specialist advice was sought from consultants who have been nominated or ratified by their Specialist Society or Royal College. The advice received is their individual opinion and is not intended to represent the view of the society. The advice provided by Specialist Advisers, in the form of the completed questionnaires, is normally published in full on the NICE website during public consultation, except in circumstances but not limited to, where comments are considered voluminous, or publication would be unlawful or inappropriate. XXXX Specialist Advisor Questionnaires for processed nerve allografts to repair peripheral nerve discontinuities were submitted and can be found on the NICE website.

Patient commentators' opinions

Section to be inserted if there is patient commentary

NICE's Public Involvement Programme sent xxx questionnaires to xxx NHS trusts for distribution to patients who had the procedure (or their carers). NICE received xxx completed questionnaires.

Section to be inserted if there is no patient commentary at IPAC 1

NICE's Public Involvement Programme will send questionnaires to NHS trusts for distribution to patients who had the procedure (or their carers). When NICE has received the completed questionnaires, these will be discussed by the committee.

Section to be inserted if there is no patient commentary at IPAC 2

NICE's Public Involvement Programme was unable to gather patient commentary for this procedure.

Section to be inserted if patient commentators raised no new issues

The patient commentators' views on the procedure were consistent with the published evidence and the opinions of the specialist advisers.

Section to be inserted if patient commentators raised new issues

The patient commentators raised the following issues about the safety/efficacy of the procedure, which did not feature in the published evidence or the opinions of specialist advisers, and which the committee considered to be particularly relevant:

- [insert additional efficacy and safety issues raised by patient commentators and highlighted by IPAC, add extra rows as necessary].
- [Last item in list].

Company engagement

A structured information request was sent to 1 company who manufacture a potentially relevant device for use in this procedure. NICE received 1 completed submission. This was considered by the IP team and any relevant points have been taken into consideration when preparing this overview.

Issues for consideration by IPAC

- Papers 2 and 4 in table 2 were published by the same research centre and it is not clear if there is some sample overlap in the outcomes being reported.
- Ongoing trials:
  - NCT01809002 - Comparison of Processed Nerve Allograft and Collagen Nerve Cuffs for Peripheral Nerve Repair (RECON) – RCT, estimated recruitment, 150; start date, June 2015; estimated completion date, December 2019. Recruiting.
  - NCT00948025 - A Comparative Post-marketing Study of Commercially Available Peripheral Nerve Gap Repair Options (CHANGE),RCT, US; expected enrolment,32; start date, June 2009; expected completion date, December 2014. Completed, not yet published.

- **Registries**
- NCT01526681 - Registry of Avance Nerve Graft Evaluating Utilization and Outcomes for the Reconstruction of Peripheral Nerve Discontinuities (RANGER), multicentre US, estimated enrolment, 500; start date, November 2008; expected completion date, December 2020. Recruiting.

References

1. Means KR, Rinker BD, Higgins JP et al. (2016) A Multicenter, Prospective, Randomized, Pilot Study of Outcomes for Digital Nerve Repair in the Hand Using Hollow Conduit Compared With Processed Allograft Nerve. Hand 11(2), 144-51.
2. He B, Zhu Q, Chai Y, et al. (2015) Safety and efficacy evaluation of a human acellular nerve graft as a digital nerve scaffold: a prospective, multicentre controlled clinical trial. Journal of Tissue Engineering & Regenerative Medicine 9(3), 286-95.
3. Brooks DN, Weber RV, Chao JD et al. (2011) Processed nerve allografts for peripheral nerve reconstruction: a multicenter study of utilization and outcomes in sensory, mixed, and motor nerve reconstructions. Microsurgery 32(1), 1-14.
4. Zhu S, Liu J, Zheng C, Gu L et al. (2016) Analysis of human acellular nerve allograft reconstruction of 64 injured nerves in the hand and upper extremity: A 3 year follow-up study. Journal of Tissue Engineering and Regenerative Medicine.
5. Zuniga JR (2015) Sensory outcomes after reconstruction of lingual and inferior alveolar nerve discontinuities using processed nerve allograft - A case series. Journal of Oral and Maxillofacial Surgery 73(4), 734-744.
6. Souza JM, Purnell CA, Cheesborough JE et al. (2016) Successful treatment of foot and ankle neuroma pain with processed nerve allografts. Foot and ankle international, 1-8.
7. Li XY, Hu HL, Fei JR eta l. (2015) One-stage human acellular nerve allograft reconstruction for digital nerve defects. Neural Regeneration Research 10(1), 95-8.
8. Taras JS, Amin N, Patel N et al. (2013) Allograft reconstruction for digital nerve loss. Journal of Hand Surgery - American Volume 38(10), 1965-71.

Appendix A: Additional papers on processed nerve allografts to repair peripheral nerve discontinuities

The following table outlines the studies that are considered potentially relevant to the IP overview but were not included in the main data extraction table (table 2). It is by no means an exhaustive list of potentially relevant studies.

Article	Number of patients/follow-up	Direction of conclusions	Reasons for non-inclusion in table 2
Cho MS, Rinker BD, Weber RV et al. (2012) Functional outcome following nerve repair in the upper extremity using processed nerve allograft. Journal of Hand Surgery - American Volume 37(11), 2340-9.	n=56 Case series	There were no reported implant complications, tissue rejections, or adverse experiences related to the use of the processed nerve allografts. Overall recovery, S3 or M4 and above, was achieved in 86% of the procedures. Subgroup analysis demonstrated meaningful levels of recovery in sensory, mixed, and motor nerve repairs with graft lengths between 5 and 50 mm. The study also found meaningful levels of recovery in 89% of digital nerve repairs, 75% of median nerve repairs, and 67% of ulnar nerve repairs. Our data suggest that processed nerve allografts offer a safe and effective method of reconstructing peripheral nerve gaps from 5 to 50 mm in length. These outcomes compare favorably with those reported in the literature for nerve autograft, and exceed those reported for tube conduits.	Overlap with paper 3 in Table 2. No new safety data.
Deslivia MF, Lee HJ, Adikrishna A et al. (2015) Decellularized Nerves for Upper Limb Nerve Reconstruction: A Systematic Review of Functional Outcomes. Journal of Reconstructive Microsurgery 31(9), 660-7.	Not applicable	Six level VIII studies and one level VI study were included (with a total of 131 reconstructions. The basic data ranges of the studies were as follows: patient age, 18 to 86 years; duration between initial injury and nerve reconstruction procedure, 8 hours to 4 years; and follow-up period, 40 days to 2 years. The maximum lengths of the nerve gap for chemically washed decellularized nerves and cryopreserved decellularized nerves were 50 and 100 mm, respectively. Quantitatively, the functional outcome ranges were as follows: static two-point discrimination, 3 to 5 mm; and moving two-point discrimination, 2 to 15 mm. For motor assessment, all patients had a > M3 Medical Research Council score. It is also important to notice that a large variability occurs in almost every factor in the reviewed studies. Our study is the first to summarise the clinical results of decellularized nerves. Decellularized nerves have been used to bridge nerve gaps ranging from 5 to 100mm with associated satisfactory outcomes in static and moving two-point discriminations.	Systematic review, no meta-analysis, no new safety data. Overlap with: Taras (2013), Zhu (2016), And Brooks (2012) included in table 2. Systematic review would add 30 extra patients.
Ducic I, Rose , Iorio ML (2012) Innovative Treatment of Peripheral Nerve	n=48 (8 allografts)	To restore maximal target-organ function with minimal donor site morbidity, we have created an algorithm based on evidence for nerve reconstruction using allograft, conduit, and	Larger case series already

Injuries Combined Reconstructive Concepts. Ann Plastic Surgery 68: 180-187.	FU= 2.7 years	autologous donor nerve. Based on our clinical outcomes, despite small sample study, the adoption of the proposed algorithm may help provide uniform outcomes for a given technique, with minimal patient morbidity. Individualised reconstructive technique, based not only on nerve gap size but also on functional importance and the anatomical level of the nerve injury are important variables to consider for optimal outcome.	included in table 2. No new safety data.
Gunn S, Cosetti M, Roland JT et al. (2010) Processed allograft: novel use in facial nerve repair after resection of a rare facial nerve paraganglioma. Laryngoscope 120 Suppl 4, S206.	Case report n=1 Not reported	Traditional methods of facial nerve reconstruction, including autologous and cadaveric grafting, can lead to significant patient morbidity. Autologous nerve grafts are the "gold standard" for superior regenerative capability, but are limited by the length and potential neuroma formation at the donor site. Allogenic grafts from donors or cadavers have shown some efficacy, but can need immunosuppression. The Avance nerve graft is a cadaveric graft, processed and decellularized to maintain an extracellular matrix with laminin and intact endoneural tubes, thus providing support for the growing axon without generating an immune response. Initial studies of the Avance graft in animals and humans have examined repair of peripheral nerves, but this is the first reported case of human facial nerve reconstruction.	Larger case series already included in table 2. No new safety data.
Guo Y, Chen G, Tian G et al. (2013) Sensory recovery following decellularized nerve allograft transplantation for digital nerve repair. Journal of Plastic Surgery and Hand Surgery 47(6), 451-3.	n=5 Case series FU=12 months	No wound infections or signs of rejections were observed at wound site. All patients reported sensory improvement during the follow-up period after operation. It is believed that decellularised nerve allografts may provide a readily available option for repair of segmental nerve defect.	Larger case series already included in table 2. No new safety data.
Isaacs J, and Safa B (2017) A Preliminary Assessment of the Utility of Large-Caliber Processed Nerve Allografts for the Repair of Upper Extremity Nerve Injuries. Hand 12(1), 55-59.	Case series n=13 FU=13 months	Available quantitative data reported meaningful recovery of sensory and motor function in 67% and 85% of the repairs, respectively. Although based on a small subset of patients, PNAs of up to 5 mm in diameter appear capable of supporting successful nerve regeneration.	Overlap with study 3 in table 2. No new safety data.
Karabekmez FE, Duymaz, A and Moran SL (2009) Early Clinical Outcomes with the Use of Decellularized Nerve Allograft for Repair of Sensory Defects Within the	Case series n=7 FU=9 months	Decellularized nerve allografts were capable of returning adequate sensation in nerve defects ranging from 0.5 to 3 cm. There were no cases of infection or rejection. Decellularized nerve allograft may provide an option for segmental nerve gaps beyond 2 cm. Randomised comparative studies will be needed to determine efficacy in comparison to collagen conduits or nerve autograft.	Larger case series already included in table 2. No new safety data.

Hand. The Hand 4(3): 245-9.			
Rinker BD, Ingari JV, Greenberg JA et al. (2015) Outcomes of short-gap sensory nerve injuries reconstructed with processed nerve allografts from a multicenter registry study. Journal of Reconstructive Microsurgery 31(5), 384-90.	Case series n=24 FU= 1 to 2 years	Return to light touch was observed in 23 out of 32 repairs reporting Semmes–Weinstein monofilament outcomes (SWMF). There were no reported nerve adverse events. Sensory outcomes for processed nerve allografts were equivalent to historical controls for nerve autograft and exceed those of conduit. Processed nerve allografts provide an effective solution for short-gap digital nerve reconstructions.	Overlap with study 3 in table 2. No new safety data.
Shanti RM and Ziccardi VB (2011) Use of Decellularized Nerve Allograft for Inferior Alveolar Nerve Reconstruction: A Case Report. Journal of Oral and Maxillofacial Surgery 69(2):550-553.	Case report n=1 FU= 5 months	We believe that decellularized nerve allografts should be considered a valid alternative for peripheral trigeminal nerve reconstruction in the presence of large nerve gaps to avoid untoward tension and ischaemia, resulting in poor nerve regeneration and fibrosis.	Larger case series already included in table 2. No new safety data.
Squintani G, Bonnetti B, Paolin A et al. (2013) Nerve regeneration across cryopreserved allografts from cadaveric donors: a novel approach for peripheral nerve reconstruction. Journal of neurosurgery 119: 907-913.	Case series n=10 FU= 1 to 2 years	Some variables may affect functional recovery after allograft surgery, and the outcome of peripheral nerve reconstruction is more favourable when patients are carefully evaluated and selected for the surgery. The authors demonstrated that using cryopreserved allografts from cadaveric donors is a valid surgical strategy to restore function of the damaged nerve without the need for any immunosuppressive treatments. This approach offers new perspectives on procedures for extensive reconstruction of brachial and lumbosacral plexuses	Larger case series already included in table 2. No new safety data.

Appendix B: Related NICE guidance for processed nerve allografts to repair peripheral nerve discontinuities

Guidance	Recommendations
Interventional procedures	**Phrenic nerve transfer in brachial plexus injury.** NICE interventional procedure guidance 468 (2013) 8.1 The limited quantity of evidence on the efficacy of phrenic nerve transfer in brachial plexus injury shows useful recovery of arm function in some patients, but there is very little information about long-term functional and quality-of-life outcomes, and evidence on safety shows some impairment of respiratory function. 8.2 However, patients with brachial plexus injuries are often very disabled and treatment options may be limited. Therefore, this procedure may be used with normal arrangements for clinical governance, consent and audit. 8.3 During the consent process patients should be informed, in particular, that the procedure may not restore useful function in the arm and that it may compromise respiratory function. 8.4 Patient selection and treatment should only be carried out in units that specialise in the management of complex brachial plexus injuries and offer a full range of treatment options.

Appendix C: Literature search for processed nerve allografts to repair peripheral nerve discontinuities

Databases	Date searched	Version/files
Cochrane Database of Systematic Reviews – CDSR (Cochrane Library)	17/01/2017	Issue 1 of 12, January 2017
HTA database (Cochrane Library)	17/01/2017	Issue 1 of 12, January 2017
Cochrane Central Database of Controlled Trials – CENTRAL (Cochrane Library)	17/01/2017	Issue 1 of 12, January 2017
MEDLINE (Ovid)	17/01/2017	1946 to December Week 1 2016
MEDLINE In-Process (Ovid)	17/01/2017	January 13, 2017
EMBASE (Ovid)	17/01/2017	1974 to 2017 Week 03
PubMed	17/01/2017	-
BLIC	17/01/2017	-

Trial sources searched on 22/11/2016

- Clinicaltrials.gov
- ISRCTN
- WHO International Clinical Trials Registry

Websites searched on 22/01/2016

- National Institute for Health and Care Excellence (NICE)
- NHS England
- Food and Drug Administration (FDA) - MAUDE database
- Australian Safety and Efficacy Register of New Interventional Procedures – Surgical (ASERNIP – S)
- Australia and New Zealand Horizon Scanning Network (ANZHSN)
- EuroScan
- General internet search

The following search strategy was used to identify papers in MEDLINE. A similar strategy was used to identify papers in other databases.

1 Allografts/
2 Peripheral Nerves/su, tr
3 transplantation, homologous/ or transplantation, isogeneic/
4 Allograf*.tw.
5 ((Homologous* or isogeneic*) adj4 transplant*).tw.
6 Nerve Regeneration/
7 (nerve* adj4 (graft* or transplant* or repair* or regenerat* or reconstruct* or engineer* or surgery*)).tw.

8 ((Cadaver* or "off-the-shelf" or "off the shelf" or human* or donor* or decellulari*) adj4 nerve*).tw.
9 or/1-8
10 Sensation Disorders/
11 Sensory Receptor Cells/
12 ((Sensation* or sensor*) adj4 (disorder* or defect* or damage*)).tw.
13 Peripheral Nerve Injuries/
14 (nerve* adj4 (injur* or lesion* or trauma* or disorder* or discontinuit* or damage* or cancer*)).tw.
15 or/10-14
16 hand/ or fingers/ or thumb/ or metacarpus/ or wrist/
17 (Hand* or finger* or thumb* or metacarp* or digi* or wrist*).tw.
18 Upper Extremity/
19 Upper extremity*.tw.
20 or/16-19
21 15 and 20
22 9 and 21
23 Avance nerve graft.tw.
24 22 or 23
25 Animals/ not Humans/
26 24 not 25
27 (2006* or 2007* or 2008* or 2009* or 2010* or 2011* or 2012* or 2013* or 2014* or 2015* or 2016* or 2017*).ed.
28 26 and 27