Interventional procedure overview of targeted muscle reinnervation for managing limb amputation pain

Contents

Table 1 Abbreviations

Abbreviation	Definition
ASA	American Society of Anesthesiologists
BPI-PI	Brief Pain Inventory–Pain Interference
BPI-PS	Brief Pain Inventory–Pain Severity
CI	Confidence interval
IQR	Interquartile range
NRS	Numerical rating scale
Neuro-QoL	Quality of Life in Neurological Disorders
OPUS	Orthotics Prosthetics Users Survey
PCS	Pain Catastrophizing Scale
PLP	Phantom limb pain
PROMIS	Patient-Reported Outcomes Measurement Information System
RLP	Residual limb pain
RPNI	Regenerative peripheral nerve interface
RR	Relative risk
SD	Standard deviation
TMR	Targeted muscle reinnervation
VAS	Visual analogue scale

Indications and current treatment

A limb may need to be amputated for a variety of reasons, including peripheral vascular disease, infection, trauma, and cancer. When the limb is amputated, nerves at the end of the residual limb are cut. This can cause 2 types of persisting pain: residual limb pain (often resulting from nerve endings forming painful neuromas), or phantom limb pain sensed in the removed part of the limb. Pain can persist for many years after the amputation. It can have a substantial effect on quality of life and its management can be challenging.

Medicines that may be used to help relieve persisting limb pain after amputation include non-steroidal anti-inflammatory drugs such as ibuprofen, antiepileptics such as pregabalin or gabapentin, antidepressants that are used to treat nerve

pain such as amitriptyline or nortriptyline, opioids such as codeine or morphine, corticosteroid or local anaesthetic injections.

Surgical options for treating a painful neuroma include removal of the damaged nervous tissue (neurolysis), transposition of the neuroma away from the exposed painful region into a suitable tissue, and repair and reconstruction of the damaged nerve to make the nerve fibres regenerate into the distal nerve end with the possibility to regain function.

Unmet need

Chronic pain after amputation is common and can be difficult to manage. It can be debilitating, with a negative impact on quality of life and preventing mobilisation on prosthetic limbs. Conventional surgical treatments for neuroma include excision and burying the nerve endings in muscle, but the neuroma can reoccur.

What the procedure involves

Targeted muscle reinnervation (TMR) is a procedure that redirects nerves severed by amputation to new muscle targets. The aim is to reduce phantom limb pain or pain that is felt in the residual limb. It also aims to reduce chronic pain that has not responded to conventional treatments (intractable pain), without the risk of neuroma recurrence. The procedure can be done at the time of initial amputation to prevent pain developing or secondarily to treat pain that has developed after amputation.

The procedure is done under general anaesthetic. There are 3 main steps: preparation of the donor nerve, identification of a motor branch to the targeted muscle, and finally, nerve coaptation. The major mixed motor and sensory nerves proximal to the amputation site are identified. A nerve stimulator is used to show the motor and sensory nerve branches within, and these are traced distally

towards the stump. Motor nerve branches to muscles that are not functional after the amputation are identified and divided, and the involved sensory nerves are then coapted to these motor branches using 8-0 or 9-0 nylon sutures under magnification. It has been hypothesised that the nerve endings stop causing pain once they have found an alternative muscle, because their physiology is restored.

Regenerative peripheral nerve interface (RPNI) is another technique that involves innervation of denervated muscle. The severed nerve is dissected longitudinally into its main fascicles, which are then implanted into free muscle grafts. It might be done instead of TMR if no suitable muscle target is available. It is sometimes done at the same time as TMR, if multiple nerves are involved.

Outcome measures

The main outcomes included residual limb pain, phantom limb pain, medication use, neuroma development, ambulation, and complications such as infection, paraesthesia, wound dehiscence, and haematoma. The measures used are detailed in the following paragraphs.

Numerical Rating Scale (NRS)

The NRS is a measure of pain intensity that is widely used in research and clinical practice. It uses an 11-, 21- or 101-point scale where the end points are the extremes of no pain and pain as bad as it could be, or worst pain.

The authors of Dumanian et al. (2019) noted that a change in NRS of 2 points on an 11-point scale has been shown to be clinically important and correlates to a need for additional pain medication.

Patient-Reported Outcomes Measurement Information System (PROMIS)

The PROMIS is a set of person-centred measures that evaluates and monitors physical, mental, and social health in adults and children. The measures are

generic rather than disease-specific and can be used with the general population and with individuals living with chronic conditions. Pain-related subdomains include items for pain intensity, interference, behaviour, and pain quality. PROMIS measures use a T-score metric in which 50 is the mean of a relevant reference population and 10 is the standard deviation (SD) of that population. Higher scores mean more of the concept being measured.

Brief Pain Inventory – Pain Severity

The Brief Pain Inventory–Pain Severity (BPI-PS) instrument uses a numerical rating scale (0 to 10) to assess the worst, best, average, and current pain levels from the previous week. The overall severity score represents the average of these 4 scores. Higher scores represent worse outcomes.

Brief Pain Inventory–Pain Interference

The Brief Pain Inventory–Pain Interference (BPI-PI) instrument uses a numerical rating scale (0 to 10) to assess the extent to which pain interferes with 7 key domains of daily function (general activity, mood, walking ability, normal work, relations with other persons, sleep, and enjoyment of life). Higher scores represent worse outcomes.

Pain Catastrophizing Scale

The Pain Catastrophizing Scale (PCS) uses a numerical rating scale (0 to 4) to assess the severity of 13 catastrophising thoughts or feelings experienced with pain. Higher scores represent worse outcomes.

Quality of Life in Neurological Disorders

Neuro-QoL is a set of self-report measures that assesses the health-related quality of life of adults and children with neurological disorders. There are 17 domains and sub-domains used for adults: anxiety, depression, fatigue, upper extremity function, lower extremity function, cognitive function, emotional and behavioural, positive affect and wellbeing, sleep disturbance, ability to participate

in social roles and activities, satisfaction with social roles and activities, stigma, communication, end of life concerns, bowel function, urinary or bladder function, and sexual function.

Orthotics Prosthetics Users Survey

The Orthotics Prosthetics Users Survey (OPUS) is a self-report questionnaire consisting of 5 modules (The Upper Extremity Functional Status Survey, The Lower Extremity Functional Status Survey, OPUS-Health Related Quality of Life Index, OPUS-Satisfaction with Devices and OPUS-Satisfaction with Services). Higher scores indicate better outcomes.

Evidence summary

Population and studies description

This interventional procedures overview is based on about 730 TMR procedures from 1 systematic review (Tham 2023), 1 randomised controlled trial (Dumanian 2019), 1 retrospective propensity score-matched study (Shammas 2022), 1 prospective case series (O'Brien 2022) and 6 retrospective case series or cohort studies (Kang 2022; Goodyear 2024; Chang 2021; Li 2024; Chang 2024 and Smith 2024). Of the 9 primary studies, 3 were also included in the systematic review (Dumanian 2019; O'Brien 2022 and Chang 2021). This is a rapid review of the literature, and a flow chart of the complete selection process is shown in figure 1. This overview presents 10 studies as the key evidence in table 2 and table 3, and lists 26 other relevant studies in appendix B, table 5.

Most of the studies were based in the US and there was some overlap in authorship. The systematic review by Tham et al. (2023) included 10 studies, with 1,099 upper and lower limbs and 448 TMR procedures. Of the 10 studies, 1 was a randomised controlled trial, 6 were cohort studies and 3 were case series. The randomised controlled trial was graded as high quality and observational

studies were moderate to very low quality. The TMR procedure was done either at the same time as the amputation or as a later, secondary procedure. The comparators were other interventions for chronic, postamputation pain, standard care, or no treatment. Most of the studies included amputations from any cause, but 1 only included people who had amputations because of cancer. The mean age of people who had TMR ranged from 35 to 59 years and the proportion of males ranged from 56 to 86%. The mean follow-up was 17.9 months (range 9.6 to 24.0).

The randomised controlled trial reported by Dumanian et al. (2019), which was also included in the systematic review, compared delayed TMR (n=15 limbs) with neuroma excision and muscle burying (n=15 limbs). Treatment allocation was single blinded for the first year, after which people in the standard care group could choose to have TMR. The trial was intended to recruit 200 patients, but it was stopped early with recruitment of 28 patients, without a formal stopping rule. Only 2 of 7 planned centres in the US had the necessary surgeon complement and institutional review board clearance in time to participate. In addition, many more amputees than expected had already had neuroma excision and burying, which excluded them from the trial. The authors also noted that patients were communicating with each other through the internet, and some refused to be randomised after hearing more about standard surgery. Most people in the trial had lower limb amputations and the main reason for amputation was trauma. The mean age was 39 years in the TMR group and 45 years in the control group and the proportion of males was 86% and 57%, respectively. The mean follow-up was 17.7 months in the TMR group and 19.3 months in the control group.

The matched sample in the propensity score-matched study by Shammas et al. (2022) included 96 people who had below-knee amputation with or without TMR. The main aim of the study was to assess the risk of postoperative complications when TMR is done at the time of below-knee amputation. The mean age was

58 years (range 31 to 90) and 65% were male. The main indications for amputation were infection (67%) and ischaemia (27%). Follow-up was 60 days.

The prospective case series by O'Brien et al. (2022), which was also in the systematic review by Tham et al. (2023), included 81 people with major upper (19%) or lower limb (81%) amputations with concurrent TMR. The mean age was 52 years (range 18 to 85) and 42% were male. The main reasons for amputation were cancer (52%), trauma (20%) and infection (14%). Follow-up ranged from 3 months to 4.6 years.

The retrospective case series by Kang et al. (2022) was based in the UK and included 36 people with upper (27.5%) or lower (72.5%) limb amputation and intractable neuroma pain or phantom limb pain. The reasons for amputation included trauma (64%), peripheral vascular disease (8%), infection (8%) and tumour (6%). The TMR was delayed and the mean duration from amputation was 11 years. The mean age at the time of TMR surgery was 49 years (range 23 to 75 years) and 75% of the study population was male. Mean follow-up was 9.5 months (range 3 to 24 months).

The 2 retrospective cohort studies by Goodyear et al. (2024) and Li et al. (2024) compared acute (primary) TMR with delayed (secondary) TMR. They included 103 and 32 people, respectively, with upper or lower limb amputations. The reasons for amputation were mixed and included cancer, infection, trauma, and ischaemia. In the study of 103 people, the proportion of males was 58%, the mean age at surgery was 53 years and the mean time from TMR to survey was 18 months for the acute group and 23 months for the delayed group (p=0.31). In the study of 32 people, the proportion of males was 81%, the median age was 39 years, and the median follow-up was 24 months for acute TMR and 21 months for delayed TMR.

The 2 retrospective cohort studies by Chang et al. (2021 and 2024) compared TMR with traction neurectomy and muscle implantation. The 2021 study was also included in the systematic review by Tham et al. (2023). It included 200 procedures (100 TMR) on below-knee amputations. The most common reason for amputation was infection and there were none because of cancer or trauma. The mean age was 59.7 years in the TMR group and 58.8 years in the control group, and 68.5% were male. The mean follow-up was 9.6 months in the TMR group and 18.5 months in the control group ($p<0.01$). The 2024 study by Chang et al. included 99 people with through- or above-knee amputations. The main reasons for amputation were infection and ischaemia. The mean age was 60 years in the TMR group and 65 years in the control group, and the proportion of males was 68% and 57%, respectively. The mean follow-up was 9.5 months in the TMR group and 14.3 months in the control group ($p=0.10$).

The retrospective study by Smith et al. (2024) compared the rate of revision surgery in people who had primary transtibial amputation with (n=29) or without (n=83) TMR. The mean age of the cohort was 47 years, 88% were male and the median follow-up was 1.2 years.

Table 2 presents study details.

Figure 1 Flow chart of study selection

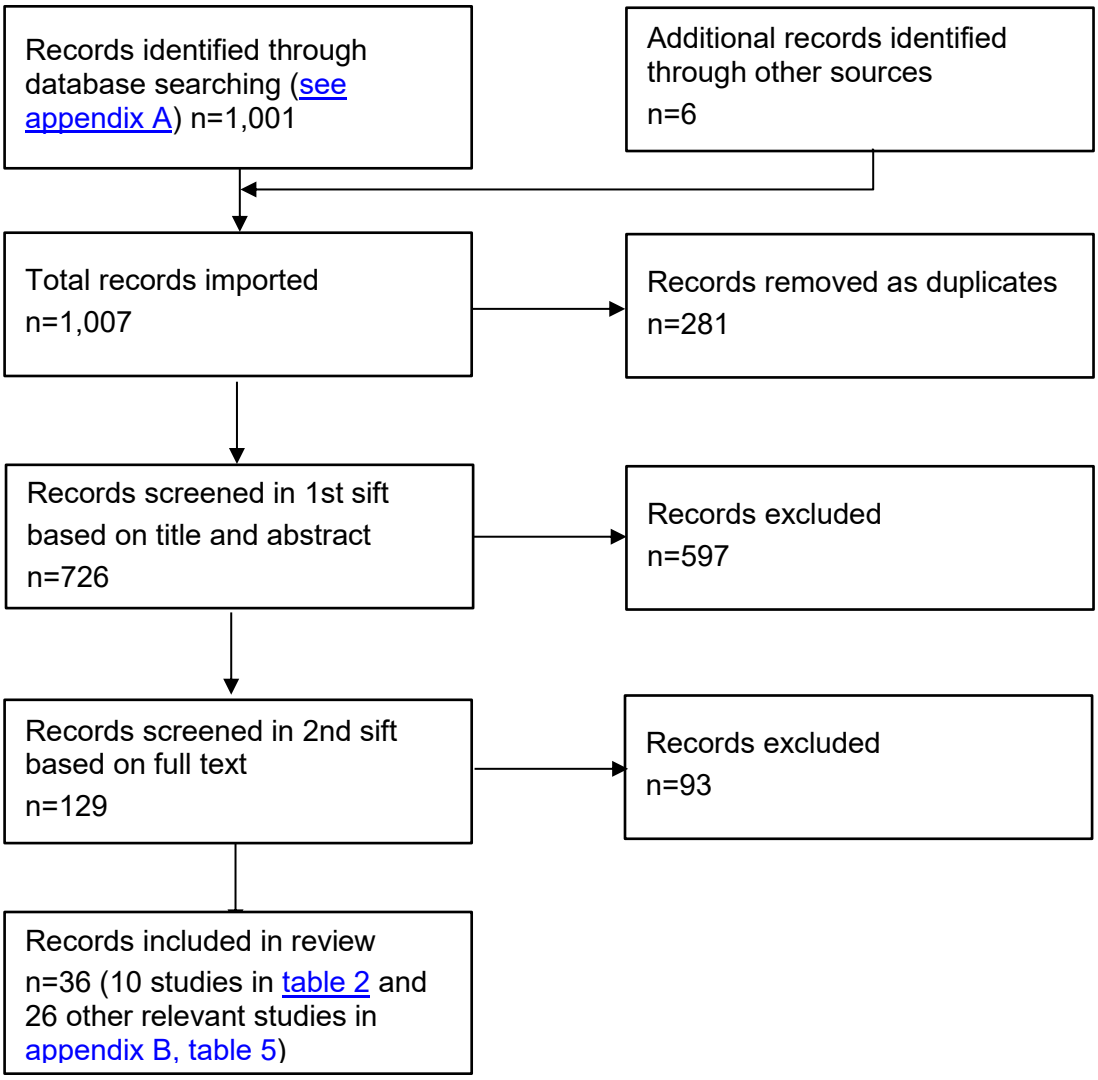

Table 2 Study details

Study no.	First author, date country	Characteristics of people in the study (as reported by the study)	Study design	Inclusion criteria	Intervention	Follow up
1	Tham JL (2023) Countries of included studies not reported.	10 studies (n=1,099 upper and lower limbs; 448 TMR procedures) The mean age of people who had TMR ranged from 35.0 to 59.6 years. The proportion of males in the studies ranged from 56 to 86%. The number of patients ranged from 13 to 100 in the TMR group, and 3 to 438 in the control group. Most studies included amputations from any cause, but 1 study only included	Systematic review and meta-analysis of 3 selected studies Search date: June 2022 Of the 10 included studies, 1 was a randomised controlled trial, 6 were cohort studies and 3 were case series.	Adults with neuropathic or chronic limb pain after amputation who had TMR. Studies were included if they reported quantitative outcome measures of pain or function at various time intervals, surgical complications, and medication usage.	• TMR • Comparator: other interventions for chronic postamputation pain, standard care, or no treatment (control) In 1 study, RPNI was done when the remnant nerve was too short or there was no suitable muscle target for TMR. The TMR was done either at the same time as the amputation or later, as a secondary procedure.	Mean 17.9 months (range 9.6 to 24.0).

Study no.	First author, date country	Characteristics of people in the study (as reported by the study)	Study design	Inclusion criteria	Intervention	Follow up
		people who had amputations because of cancer.				
2	Dumanian G, 2019 US Included in Tham et al. (2023)	n=28 (30 limbs) Mean age (years): • TMR=39.6 • Control=45.3 Male (%) • TMR=86% • Control=57% 71% in both groups were described as Caucasian. 26 lower limbs, 4 upper limbs Trauma was the reason for most (90%) amputations.	Randomised controlled trial (single blinded for 1 year). Treatment allocation was done in the operating room using sealed envelopes and a random number generator. Study enrolment: 2014 to 2017. At 1 year, people in the standard care group who still had symptoms could choose to have TMR.	People with chronic pain associated with major limb amputations above the wrist or ankle, older than 18 years old, and with no previous neuroma treatments for pain after their initial amputation.	• TMR (n=15 limbs) • Standard neuroma treatment of neuroma excision and muscle burying (n=15 limbs) TMR was delayed (most amputations were 5 or more years earlier) Selection of nerves to be treated for both groups was determined preoperatively by the location and distribution of pain found on physical examination.	Mean (months) • TMR=17.7 • Control=19.3

Study no.	First author, date country	Characteristics of people in the study (as reported by the study)	Study design	Inclusion criteria	Intervention	Follow up
3	Shammas R, 2022 US	**Matched sample** n=96 (31 TMR procedures) Mean age 58.5 years (range 31.6 to 90.9) Male 64.6% All amputations were below-knee. Ethnicity was described as White in 67.7% of people, and Black in 27.1% of people. 85% had diabetes and 77% were ambulatory. The main indications for amputation were infection (67%) and ischaemia (27%). The rate of peripheral vascular disease was lower in the TMR group	Retrospective propensity score-matched study. Procedures were done between January 2018 and June 2020.	Adults who had a below-knee amputation with or without TMR at either of 2 centres were included. People who were younger than 18 years old, were converted to an above-knee amputation, had an incomplete amputation, or had bilateral amputations were excluded from analysis.	Below-knee amputation with or without TMR at the same time. A small proportion of TMR procedures (19%) used a 2-incision approach. An incisional vacuum-assisted closure at the time of closure was commonly used after TMR.	60 days

Study no.	First author, date country	Characteristics of people in the study (as reported by the study)	Study design	Inclusion criteria	Intervention	Follow up
		(26% compared to 48%).				
4	O'Brien A, 2022 US Included in Tham et al. (2023)	n=81 (83 limbs) Mean age=52 years (range 18 to 85) Male=42% Ethnicity was described as White in 91% of people, African American or Black in 6% of people and other in 3% of people. Lower limb (including hip disarticulation)=81% (67/83) Upper limb (including shoulder disarticulation)=19% (16/83) Reason for amputation: • Cancer=52% • Infection=14% • Trauma=20%	Prospective single-centre case series Patients were surveyed at in-person follow-up appointments or telehealth appointments. Study period: October 2015 to December 2020	Adults (aged 18 or over) who had major limb amputation with TMR and without cognitive impairment. Patients were included if they had completed at least one survey. Patients were excluded if they were enrolled in concurrent trials for neuropathic pain or had metastatic or recurrent cancer or open wounds at the time of survey.	Major amputation (below-knee, above-knee, hip disarticulation, transradial, transhumeral, and shoulder disarticulation levels) and TMR at the same time. Common nerve transfers and targets were based on previously published studies.	Range 3 months to 4.6 years. Of the 81 enrolled people, 23 (28%) completed surveys at 18 months or later; the cohort completing surveys at 18 months or later had a mean follow-up time of 2.4 years (range 1.5 to 4.6 years).

Study no.	First author, date country	Characteristics of people in the study (as reported by the study)	Study design	Inclusion criteria	Intervention	Follow up
		• Ischaemia=1% • Other=14%.				
5	Kang N, 2022 UK	n=36 (40 TMR procedures) Mean age=49 years Male=75% (27/36) Lower limb=72.5% (29/40) Upper limb=27.5% (11/40) Reasons for amputation: • trauma (64%) • peripheral vascular disease (8%) • tumour (6%) • infection (8%) • unknown (14%). Mean ASA score=2.33	Retrospective single-centre case series Treatment period: 2013 to 2020	People with intractable neuroma pain or phantom limb pain after major amputation of an upper or lower limb.	TMR was delayed; the mean duration from amputation to TMR was 11 years.	Mean and median=38 weeks Range 3 to 24 months
6	Goodyear E, 2024 US	n=103 (105 limbs) Mean age at surgery=53 years	Retrospective cohort study	Patients were excluded if they were younger than 18 years, had a	Acute (n=73 procedures; 71 patients) or delayed (n=32) TMR. Acute	The mean time to survey was 18 months for the acute TMR cohort

Study no.	First author, date country	Characteristics of people in the study (as reported by the study)	Study design	Inclusion criteria	Intervention	Follow up
		Male=58% (61/105) Lower limb=82% (86/105) Upper limb=18% (19/105) Reason for amputation in acute TMR group: • Cancer=48% • Infection=12% • Trauma=22% • Ischaemia=3% • Other=15%. Reason for amputation in delayed TMR group: • Cancer=3% • Infection=31% • Trauma=41% • Ischaemia=9% • Other=16%.	Study period: October 2015 to December 2020	cognitive impairment, were enrolled in another neuropathic pain trial, or died within 6 months of TMR.	TMR was defined as TMR done within 14 days of major extremity amputation. Delayed TMR was defined as TMR done secondary to the development of a symptomatic neuroma.	and 22.9 months for the delayed TMR cohort.

Study no.	First author, date country	Characteristics of people in the study (as reported by the study)	Study design	Inclusion criteria	Intervention	Follow up
7	Li A, 2024 Australia	n=32 (38 major limb amputations) Median age=39 years (IQR 29 to 57) Male=81.3% Aetiology: • Trauma=75% • Ischaemia=13% • Complex regional pain syndrome=3% • Infection=6% • Malignancy=3% Upper limb only=22% Lower limb only=72% Upper and lower limbs=6%	Retrospective, single-centre cohort study TMR procedures were done between January 2018 and December 2021 Acute TMR was offered as the standard of care for all people for whom it was suitable, referred to the plastic surgery unit for major limb amputation.	People who had TMR for pain control following major limb amputation (at the level or proximal to the wrists and ankles) and completed at least 1 postoperative patient reported outcome measure questionnaire up to 30 June 2022. People were considered for the study if they had suitable nerves and targets, no proximal nerve injury, a clean wound with a good vascular supply, no anaesthetic contraindications to the extra operating time required for the procedure (up to 2 hours) and were expected to survive the injury or disease	Acute (n=16 patients, 22 limbs) or delayed (n=16 patients, 16 limbs) TMR. TMR was classified as acute if it was done during the same admission as the primary amputation and delayed if it was done during a later admission. The median time between initial amputation and TMR was 0.4 months for acute TMR and 61.9 months for delayed TMR ($p<0.001$).	Median length of follow-up was 24 months for acute TMR and 21 months for delayed TMR ($p=0.65$).

Study no.	First author, date country	Characteristics of people in the study (as reported by the study)	Study design	Inclusion criteria	Intervention	Follow up
				process leading to the amputation. Delayed TMR was offered to patients with significant peripheral nerve component to their chronic amputation pain.		
8	Chang B, 2021 US Included in Tham et al. (2023)	n=200 (100 TMR procedures) Mean age (years) • TMR=59.7 • Non-TMR=58.8 Male=68.5% All amputations were below knee. The most common reason for amputation was infection (76%). No amputations were done in the setting of acute trauma or cancer resection.	Retrospective, single-centre, cohort study TMR procedures were done between January 2018 and December 2019. The control group had amputations between January 2015 and December 2017.	The first 100 patients who had primary TMR at the time of below-knee amputation were included. The 100 patients who had below knee amputation immediately before the initiation of the TMR protocol were included as a cohort for comparison of outcomes.	• Below knee amputation with TMR (n=100) • Below knee amputation with traction neurectomy and muscle implantation of all identified nerves (n=100).	For the TMR group, mean follow-up was 9.6 months, compared to 18.5 months for the non-TMR group (p<0.01).

Study no.	First author, date country	Characteristics of people in the study (as reported by the study)	Study design	Inclusion criteria	Intervention	Follow up
		The mean Charlson Comorbidity Index was 5.3, and 57% of people had a Charlson Comorbidity Index greater than 5.				
9	Chang B, 2024 US	n=99 (41 TMR procedures) Mean age (years) • TMR=60.4 • Non-TMR=65.0 Male: • TMR=68.3% • Non-TMR=56.9% All amputations were through- or above-knee. Aetiology was infection in 46% of TMR group and 60% of non-TMR group, and dysvascular in 34% of TMR group and	Retrospective, single-centre, cohort study TMR procedures were done between January 2018 and December 2019.	Patients who had primary TMR at the time of through- or above-knee amputation were included. Patients who had a through- or above-knee amputation immediately before the initiation of the TMR protocol from January 2014 to December 2017 were included as a cohort for comparison of outcomes.	• Through- or above-knee amputation with TMR (n=41) • Through- or above-knee amputation with traction neurectomy and muscle implantation of all identified nerves (n=58)	For the TMR group, mean follow-up was 9.5 months, compared to 14.3 months for the non-TMR group (p=0.10).

Study no.	First author, date country	Characteristics of people in the study (as reported by the study)	Study design	Inclusion criteria	Intervention	Follow up
		31% in non-TMR group. The mean Charlson Comorbidity Index was 5.5 in the TMR group and 4.8 in the non-TMR group.				
10	Smith T, 2024 US	n=112 primary amputations (29 with TMR) and 51 revision amputations. Mean age at time of amputation was 47 years (range 24 to 81). Male=88% Indications for primary amputation included trauma, completion or revision traumatic amputations or failed limb salvage (n=72, 64%), osteomyelitis or infection (n=31, 28%), oncology	Retrospective, single-centre, cohort study. Amputations were done between January 2014 and April 2021.	People who had primary or revision transtibial amputation. Revision transtibial amputations that were done on primary amputations done outside of the study site were not included in analysis of revision rates for patients with and without TMR.	• Primary transtibial amputation with TMR (n=29) • Primary transtibial amputation without TMR (n=83) • Revision transtibial amputation (n=51) Primary TMR was defined by its occurrence at the time of initial amputation or in the setting of the same	Median=1.2 years (range 0 to 7.2 years).

Study no.	First author, date country	Characteristics of people in the study (as reported by the study)	Study design	Inclusion criteria	Intervention	Follow up
		(n=3, 3%), and other indications (n=6, 5%). Indications for revision included 11 (22%) for wound breakdown or dehiscence, 11 (22%) for infection, 9 (18%) for neuroma, 6 (12%) for scar revision or redundant tissue or debulking, 5 (10%) for heterotopic ossification or bony prominence, 4 (8%) for instability, 4 (8%) for myodesis or myoplasty failure, and 1 (2%) for seroma.			initial hospitalisation. Of the 51 revision amputations, 23 (21%) were in patients who had primary transtibial amputation at the study institution.	

Table 3 Study outcomes

First author, date	Efficacy outcomes	Safety outcomes
Tham, 2023	**Residual limb pain - NRS** Pooled mean difference for TMR compared with control was −2.68, 95% CI −3.21 to −2.14; p<0.0001; 4 studies [Mioton 2020, O'Brien 2021, O'Brien 2022, Valerio 2019]; I^2=0%) **Phantom limb pain - NRS** Pooled mean difference for TMR compared with control was −2.17, 95% CI −2.70 to −1.63; p<0.0001; 4 studies as above; I^2=51%) **Residual limb pain – PROMIS** ***Intensity*** Pooled mean difference for TMR compared with control was −13.39, 95% CI −14.59 to −12.19; p<0.0001; 3 studies [Mioton 2020, O'Brien 2021, Valerio 2019]; I^2=61%) ***Behavioural*** Pooled mean difference for TMR compared with control was −11.97, 95% CI −13.78 to −10.16; p<0.0001; 4 studies [Mioton 2020, O'Brien 2021, O'Brien 2022, Valerio 2019]; I^2=87%) ***Interference*** Pooled mean difference for TMR compared with control was −12.18, 95% CI −13.56 to −10.80; p<0.0001; 4 studies as above; I^2=70%) **Phantom limb pain – PROMIS** ***Intensity***	**Complications** Complication rates were reported in 4 studies and ranged from 0 to 16%. They predominantly included wound site or stump infections. **Hoyt et al. (2021)**: no TMR related complications were reported in the acute treatment group and there was 1 minor wound complication in the delayed TMR group (n=59). **Alexander et al. (2019)**: wound complications needing surgery=16% (5/31), including 1 person who needed a conversion from below knee amputation to above knee amputation because of a non-healing stump wound; 2 people had neuroma excisions and TMR of symptomatic neuromas that developed in pure sensory nerves that were not included in the initial nerve transfer. **Chang et al. (2021)** noted a statistically significantly lower rate of infections needing surgery in those who had TMR compared with those who had traditional traction neurectomy (16% TMR versus 30% control, p=0.02).

First author, date	Efficacy outcomes	Safety outcomes
	Pooled mean difference for TMR compared with control was −11.21, 95% CI −12.97 to −9.45; p<0.0001; 3 studies [Mioton 2020, O'Brien 2021, Valerio 2019]; I^2=61%) ***Behavioural*** Pooled mean difference for TMR compared with control was −10.45, 95% CI −12.39 to −8.52; p<0.0001; 4 studies [Mioton 2020, O'Brien 2021, O'Brien 2022, Valerio 2019]; I^2=76%) ***Interference*** Pooled mean difference for TMR compared with control was −11.48, 95% CI −12.82 to −10.13; p<0.0001; 4 studies as above; I^2=62%) **Functional outcomes** Mioton et al. used the Orthotics Prosthetics Users Survey (OPUS) for upper limb amputees who had TMR, which increased from 53.7 (SD 3.4) to 56.4 (SD 3.7), p<0.01 at 1 year postoperatively. Neuro-QoL was used for lower limb amputees who had TMR, which increased from 32.9 (SD 1.5) to 35.2 (SD 1.6), p<0.01 at 1 year postoperatively. Both the Neuro-QoL and OPUS showed higher functional scores in the TMR group, respectively. No studies reported the length of hospital stay or patient satisfaction.	**Dumanian et al. (2019)** reported no surgical complications (0%).
Dumanian G, 2019	**Worst pain score (NRS) in the last 24 hours (0 to 10), at baseline and 1 year (primary outcome); mean (SD)** ***Phantom limb pain*** • Baseline: TMR=5.8 (3.2), control=3.9 (2.7) • 1 year: TMR=2.6 (2.2), control=4.1 (3.0) • Change: TMR=3.2 (2.9), control=-0.2 (4.9)	There were no surgical complications.

First author, date	Efficacy outcomes	Safety outcomes
	• Mean (Adjusted 95% CI) difference of change scores=3.4 (-0.1 to 6.9) ***Residual limb pain*** • Baseline: TMR=6.6 (2.0), control=6.9 (2.5) • 1 year: TMR=3.7 (2.0), control=6.0 (2.8) • Change: TMR=2.9 (2.2), control=0.9 (3.3) • Mean (Adjusted 95% CI) difference of change scores=1.9 (-0.5 to 4.4) **Worst pain score (NRS) in the last 24 hours at last follow-up, intention to treat; mean (SD)** ***Phantom limb pain*** • Baseline: TMR=5.8 (3.2), control=3.9 (2.7) • Last follow-up: TMR=2.3 (2.3), control=4.4 (3.3) • Change: TMR=3.5 (3.1), control=-0.5 (5.3) • Mean (Adjusted 95% CI) difference of change scores=4.0 (0.8 to 7.2) ***Residual limb pain*** • Baseline: TMR=6.6 (2.0), control=6.9 (2.5) • Last follow-up: TMR=3.6 (2.1), control=5.7 (3.0) • Change: TMR=3.0 (2.1), control=1.2 (3.5)	

First author, date	Efficacy outcomes	Safety outcomes
	• Mean (Adjusted 95% CI) difference of change scores=1.8 (-0.3 to 4.0) Note: 3 people crossed over from standard care to TMR arm after 1 year **Proportion of people with no or mild phantom limb pain at longest follow-up** • TMR=72% • Control=40%, p value not stated **Proportion of people with no or mild residual limb pain at longest follow-up** • TMR=67% • Control=27%, p value not stated **PROMIS pain scales at 1 year, mean (SD)** ***Phantom limb pain - intensity*** • Baseline: TMR=52.4 (11.2), control=48.3 (9.5) • 1 year: TMR=38.0 (7.2), control=45.8 (10.9) • Change: TMR=13.7 (10.7), control=2.0 (17.9) Mean (Adjusted 95% CI) difference of change scores=11.7 (-0.3 to 23.7) ***Phantom limb pain – behaviour*** • Baseline: TMR=58.3 (11.8), control=58.5 (9.7) • 1 year: TMR=50.7 (9.9), control=52.0 (8.4)	

First author, date	Efficacy outcomes	Safety outcomes
	• Change: TMR=7.6 (9.7), control=6.5 (14.9) Mean (Adjusted 95% CI) difference of change scores=1.1 (-8.3 to 10.5) ***Phantom limb pain – interference*** • Baseline: TMR=60.2 (12.5), control=57.9 (11.0) • 1 year: TMR=50.4 (9.8), control=52.8 (8.9) • Change: TMR=9.8 (8.9), control=5.1 (16.0) Mean (Adjusted 95% CI) difference of change scores=4.7 (-5.0 to 14.3) ***Residual limb pain - intensity*** • Baseline: TMR=55.7 (7.6), control=55.0 (5.5) • 1 year: TMR=44.5 (8.2), control=49.5 (8.3) • Change: TMR=11.5 (8.3), control=5.7 (8.1) Mean (Adjusted 95% CI) difference of change scores=5.8 (-0.9 to 12.4) ***Residual limb pain – behaviour*** • Baseline: TMR=61.5 (3.7), control=61.9 (4.3) • 1 year: TMR=56.8 (7.0), control=56.6 (6.5) • Change: TMR=4.7 (7.1), control=5.3 (10.4) Mean (Adjusted 95% CI) difference of change scores=-0.5 (-7.2 to 6.1) ***Residual limb pain – interference*** • Baseline: TMR=64.4 (7.0), control=65.8 (5.1) • 1 year: TMR=56.8 (6.6), control=57.4 (8.6)	

First author, date	Efficacy outcomes	Safety outcomes
	• Change: TMR=7.6 (9.2), control=8.5 (11.0) Mean (Adjusted 95% CI) difference of change scores=-0.9 (-8.5 to 6.7) **Functional outcomes** Analysis of the lower extremity Neuro-QoL results (n=24) showed little difference between the groups at 1 year. When crossover data were included and at final follow-up, the mean NEURO-QOL t score increased from 39.9 to 45.2 in the TMR cohort showing functional improvement.	
Shammas, 2022	**Mean length of surgery, minutes** • TMR=188.5 (SD 63.6) • No TMR=88 (SD 28.2), p<0.001 **Mean estimated blood loss, ml** • TMR=154 (SD 143.3) • No TMR=136.3 (SD 118.9), p=0.04 **Mean length of hospital stay, days** • TMR=7.5 (SD 6.4) • No TMR=8.1 (SD 8.8), p=0.92	**Major complications within 60 days of amputation (primary outcome; defined as those that needed readmission, transfer to the intensive care unit, or reoperation, or a cause of death related to the amputation procedure)** • TMR=29.0% (9/31) • No TMR=24.6% (16/65), p=0.69 RR=1.20 (90% CI 0.57 to 2.55), p=0.35 **Readmission** • TMR=25.8% (8/31) • No TMR=18.5% (12/65), p=0.21 **Reoperation** • TMR=19.4% (6/31)

First author, date	Efficacy outcomes	Safety outcomes
		• No TMR=10.8% (7/65), p=0.13 **Admission to intensive care unit** • TMR=6.5% (2/31) • No TMR=10.8% (7/65), p=0.41 **Mortality (all cause)** • TMR=3.2% (1/31) • No TMR=9.2% (6/65), p=0.34 **Minor surgical complications** • TMR=25.8% (8/31) • No TMR=20.0% (13/65), p=0.65 RR=1.21 (90% CI 0.61 to 2.41), p=0.33 **Wound healing complication** • TMR=45.2% (14/31) • No TMR=33.8% (22/65), p=0.25 **Infection** • TMR=9.7% (3/31) • No TMR=6.2% (4/65), p<0.001
Kang, 2022	**Mean change in NRS at 12 months after TMR** ***Upper limb – neuroma pain (n=10)***	**Complications** There were 46 complications in 28 out of 40 TMR procedures (70%). Of the 36

First author, date	Efficacy outcomes	Safety outcomes
	Change=5.30 (SD 4.62), 95% CI 8.61 to 2.00, p=0.006 All pain had resolved at 12 months. ***Upper limb – phantom limb pain (n=10)*** Change=4.40 (SD 4.03), 95% CI 7.29 to 1.52, p=0.007 There was a slight increase at 3 months from 6.40 to 7.30 with a subsequent decrease to 3.50 at 6 months and stabilisation at 2.0 by 12 months. Of the 10 patients, 1 was pain free at 12 months and 5 had only mild pain (NRS between 1 and 3). ***Lower limb – neuroma pain (n=20)*** Change=4.35 (SD 4.53), 95% CI 6.47 to 2.23, p<0.0001 Of the 20 procedures, 10 resulted in complete resolution of neuroma pain and 2 patients had mild residual pain. ***Lower limb – phantom limb pain (n=20)*** Change=2.60 (SD 3.98), 95% CI 4.46 to 0.74, p=0.009 4 patients reported full resolution of pain at 12 months, and 3 noted marked decreases of pain to minimal levels (NRS between 1 and 3). **Medication use** Of the 18 patients who were taking pregabalin before the procedure, 9 had discontinued it after 1 year. There was a mean reduction of 352 mg in daily intake over the 12 months of follow-up (p<0.01). **Patient satisfaction** Data on satisfaction was reported for 22 patients (61%, 9 upper limb and 13 lower limb patients). 91% of these responses indicated overall satisfaction with the procedure at 12 months (9 upper limb	people, 13 had more than 1 complication. Complications occurred in 23 lower limb procedures (79%) and 5 upper limb procedures (45%). **Number of complications** ***Upper limbs*** • Infection, n=4 • Paraesthesia, n=1 • Wound dehiscence, n=1 • Haematoma, n=1 • Seroma, n=1 ***Lower limbs*** • Unmasking of neuromas, n=12 (symptoms of unmasking typically became apparent within a few weeks of surgery, and 4 patients needed an additional TMR procedure) • Infection, n=7 • Bursa, n=6 • Paraesthesia, n=4 • Wound dehiscence, n=3 • Haematoma, n=2 • Ulceration, n=2

First author, date	Efficacy outcomes	Safety outcomes
	and 11 lower limb patients). However, out of 22 patients, only 50% (6 upper limb, 5 lower limb patients) felt they would have agreed to a prophylactic (preventive) TMR procedure.	• Seroma, n=1 • Lymphatic discharge, n=1 The authors noted that they now recommend not to wear a prosthesis for at least 6 weeks after surgery in the lower limbs and longer if there is any delay to wound healing, to reduce the risk of complications.
O'Brien, 2022	**NRS at 3 months after TMR (worst pain in a 24-hour recall period), n=53** • PLP: mean=2.51 (SD 2.91), median=2 (IQR 0 to 5) • RLP: mean=2.08 (SD 2.94), median=1 (IQR 0 to 3) **NRS at 6 months after TMR, n=49** • PLP: mean=2.37 (SD 3.2), median=1 (IQR 0 to 3) • RLP: mean=1.86 (SD 2.8), median=0 (IQR 0 to 3) **NRS at 12 months after TMR, n=43** • PLP: mean=2.05 (SD 2.71), median=0 (IQR 0 to 4) • RLP: mean=1.79 (SD 2.9), median=0 (IQR 0 to 2) **NRS at 18 months or more after TMR, n=23** • PLP: mean=0.96 (SD 1.69), median=0 (IQR 0 to 2) • RLP: mean=1.04 (SD 2.03), median=0 (IQR 0 to 2) **PROMIS Interference score at 3 months after TMR, n=53** • PLP: mean=46.38 (SD 9.43), median=40.7 (IQR 40.7 to 52.3)	No safety outcomes were reported.

First author, date	Efficacy outcomes	Safety outcomes
	• RLP: mean=45.55 (SD 9.31), median=40.7 (IQR 40.7 to 47.9) **PROMIS Interference score at 6 months after TMR, n=49** • PLP: mean=45.29 (SD 8.6), median=40.7 (IQR 40.7 to 47.9) • RLP: mean=43.68 (SD 7.19), median=40.7 (IQR 40.7 to 40.7) **PROMIS Interference score at 12 months after TMR, n=43** • PLP: mean=45.23 (SD 9.2), median=40.7 (IQR 40.7 to 40.7) • RLP: mean=44.81 (SD 8.82), median=40.7 (IQR 40.7 to 40.7) **PROMIS Interference score at 18 months or more after TMR, n=23** • PLP: mean=42.4 (SD 4.93), median=40.7 (IQR 40.7 to 40.7) • RLP: mean=44.13 (SD 7.21), median=40.7 (IQR 40.7 to 40.7) **PROMIS Behaviour score at 3 months after TMR, n=53** • PLP: mean=47.83 (SD 8.73), median=50.1 (IQR 36.7 to 53) • RLP: mean=45.97 (SD 9.44), median=50.1 (IQR 36.7 to 51.1) **PROMIS Behaviour score at 6 months after TMR, n=49** • PLP: mean=46.7 (SD 9.45), median=50.1 (IQR 36.7 to 53.9) • RLP: mean=44.59 (SD 9.38), median=36.7 (IQR 36.7 to 51.1) **PROMIS Behaviour score at 12 months after TMR, n=43** • PLP: mean=46.62 (SD 9.64), median=50.1 (IQR 36.7 to 52.1) • RLP: mean=44.7 (SD 9.8), median=36.7 (IQR 36.7 to 53.9) **PROMIS Behaviour score at 18 months or more after TMR, n=23** • PLP: mean=45.61 (SD 9.06), median=50.1 (IQR 36.7 to 53.9)	

First author, date	Efficacy outcomes	Safety outcomes
	• RLP: mean=43.07 (SD 9.15), median=36.7 (IQR 36.7 to 53.9) Unadjusted pairwise analysis demonstrated a statistically significant difference in mean PLP NRS scores between 3 months and 18 months (mean difference −1.38, p=0.004), 6 months and 18 months (mean difference −1.14, p=0.02), and 12 months and 18 months or later (mean difference −1.02, p=0.04). There were no statistically significant differences in unadjusted pairwise comparisons for any time points (3 months onwards) regarding the NRS scores for RLP and the PROMIS pain interference or pain behaviour scores for PLP or RLP.	
Goodyear, 2024	**Subsequent neuroma development (in the same nerve distributions included in original TMR operation)** • Acute TMR=1.4% (1/73) • Delayed TMR=18.8% (6/32), p<0.05 **Neuroma development in a new distribution that was not previously included in TMR operation** • Acute TMR=5.5% (4/73) • Delayed TMR=9.4% (3/32), p=0.433 In multivariate analysis, those who had delayed TMR had 28.9 times greater odds of developing a subsequent neuroma compared with acute TMR, when controlling for age, sex, and extremity involved (95% CI 2.4 to 347.3; p=0.008).	**Complications** The rate of major complications was 11.0% (8/73) for acute TMR and 12.5% (4/32) for delayed TMR (p=0.136). The rate of minor complications was 17.8% (13/73) for acute TMR and 15.6% (5/32) for delayed TMR (p=0.559). **Major complications – acute TMR** • Infection=5.5% (4/73) • Haematoma=1.4% (1/73) • Dehiscence=4.1% (3/73) **Major complications – delayed TMR** • Abscess=6.3% (2/32)

First author, date	Efficacy outcomes	Safety outcomes
		• Haematoma=3.1% (1/32) • Dehiscence=3.1% (1/32) **Minor complications – acute TMR** • Superficial dehiscence=11.0% (8/73) • Cellulitis=5.5% (4/73) • Abscess=1.4% (1/73) **Minor complications – delayed TMR** • Superficial dehiscence=6.3% (2/32) • Cellulitis=3.1% (1/32) • Abscess=6.3% (2/32)
Li, 2024	***Comparison of PROMs between paired baseline and follow-up surveys for delayed TMR*** **Overall PLP score at 6 months, median (IQR)** • Baseline=5.5 (2.8 to 6.3) • Follow-up=3.4 (1.5 to 4.5), p=0.01 **Overall PLP score at 12 months, median (IQR)** • Baseline=5.5 (4.5 to 6.0) • Follow-up=3.5 (0.5 to 4.8), p=0.02 **Overall PLP score at 18 months, median (IQR)** • Baseline=5.8 (4.5 to 6.8) • Follow-up=3.0 (1.0 to 4.0), p=0.03 **Overall PLP score at 24 months, median (IQR)** • Baseline=5.5 (2.5 to 6.8)	There was no statistically significant difference in complication rate between acute and delayed TMR (p=1.00). In the acute TMR group, 1 person developed a haematoma needing surgical evacuation and debridement. In the delayed TMR group, 1 person had delayed wound healing, and another developed an infection, both needing surgical debridement. All complications were grade 3B according to the Clavien–Dindo classification.

First author, date	Efficacy outcomes	Safety outcomes
	• Follow-up=3.5 (2.3 to 3.8), p=0.15 **Overall RLP score at 6 months, median (IQR)** • Baseline=5.6 (4.8 to 6.5) • Follow-up=3.5 (2.8 to 4.8), p=0.02 **Overall RLP score at 12 months, median (IQR)** • Baseline=5.8 (5.3 to 6.0) • Follow-up=4.0 (2.8 to 5.3), p=0.07 **Overall RLP score at 18 months, median (IQR)** • Baseline=5.5 (4.5 to 6.0) • Follow-up=3.3 (0.0 to 4.5), p=0.01 **Overall RLP score at 24 months, median (IQR)** • Baseline=5.8 (4.5 to 6.5) • Follow-up=4.0 (2.0 to 5.8), p=0.13 **Worst PLP score at 6 months, median (IQR)** • Baseline=7.5 (4.0 to 9.0) • Follow-up=5.5 (2.0 to 8.0), p=0.06 **Worst PLP score at 12 months, median (IQR)** • Baseline=8.0 (4.0 to 9.0) • Follow-up=7.0 (0.0 to 8.0), p=0.19 **Worst PLP score at 18 months, median (IQR)** • Baseline=8.0 (4.0 to 9.0)	

First author, date	Efficacy outcomes	Safety outcomes
	• Follow-up=4.0 (2.0 to 7.0), p=0.14 **Worst PLP score at 24 months, median (IQR)** • Baseline=7.0 (3.0 to 9.0) • Follow-up=6.0 (3.0 to 7.0), p=0.32 **Worst RLP score at 6 months, median (IQR)** • Baseline=8.0 (7.0 to 10.0) • Follow-up=6.0 (4.0 to 7.0), p=0.02 **Worst RLP score at 12 months, median (IQR)** • Baseline=8.0 (7.0 to 9.0) • Follow-up=7.0 (3.0 to 7.0), p=0.15 **Worst RLP score at 18 months, median (IQR)** • Baseline=8.0 (7.0 to 8.0) • Follow-up=7.0 (0.0 to 8.0), p=0.13 **Worst RLP score at 24 months, median (IQR)** • Baseline=8.0 (7.0 to 9.0) • Follow-up=5.0 (2.0 to 8.0), p=0.06 **Pain interference score at 6 months, median (IQR)** • Baseline=7.7 (5.6 to 9.0) • Follow-up=4.4 (2.0 to 6.9), p=0.051 **Pain interference score at 12 months, median (IQR)** • Baseline=7.2 (5.8 to 9.5)	

First author, date	Efficacy outcomes	Safety outcomes
	• Follow-up=2.8 (0.0 to 7.1), p=0.12 **Pain interference score at 18 months, median (IQR)** • Baseline=7.7 (6.0 to 10.0) • Follow-up=6.0 (0.0 to 8.0), p=0.16 **Pain interference score at 24 months, median (IQR)** • Baseline=7.9 (6.0 to 10.0) • Follow-up=7.1 (4.9 to 8.6), p=0.52 **Pain catastrophisation score at 6 months, median (IQR)** • Baseline=34.0 (19.0 to 44.0) • Follow-up=10.5 (10.0 to 13.0), p=0.003 **Pain catastrophisation score at 12 months, median (IQR)** • Baseline=30.0 (19.5 to 42.5) • Follow-up=5.5 (0.0 to 24.5), p=0.04 **Pain catastrophisation score at 18 months, median (IQR)** • Baseline=33.0 (18.0 to 50.0) • Follow-up=1.0 (0.0 to 38.0), p=0.08 **Pain catastrophisation score at 24 months, median (IQR)** • Baseline=34.0 (18.0 to 50.0) • Follow-up=27.5 (13.0 to 36.0), p=0.42 ***Comparison of acute versus delayed TMR*** **Overall PLP score at 6 months, median (IQR)**	

First author, date	Efficacy outcomes	Safety outcomes
	• Acute TMR=0.0 (0.0 to 1.6) • Delayed TMR=3.4 (1.6 to 4.6), p<0.001 **Overall PLP score at 12 months, median (IQR)** • Acute TMR=0.0 (0.0 to 0.8) • Delayed TMR=3.5 (0.5 to 6.0), p=0.002 **Overall PLP score at 18 months, median (IQR)** • Acute TMR=0.0 (0.0 to 0.9) • Delayed TMR=3.0 (1.0 to 4.0), p=0.001 **Overall PLP score at 24 months, median (IQR)** • Acute TMR=0.0 (0.0 to 0.0) • Delayed TMR=3.4 (2.5 to 3.6), p<0.001 **Overall RLP score at 6 months, median (IQR)** • Acute TMR=0.5 (0.0 to 1.8) • Delayed TMR=3.5 (2.3 to 4.8), p<0.001 **Overall RLP score at 12 months, median (IQR)** • Acute TMR=0.0 (0.0 to 1.8) • Delayed TMR=4.0 (0.8 to 6.0), p=0.002 **Overall RLP score at 18 months, median (IQR)** • Acute TMR=0.0 (0.0 to 1.3) • Delayed TMR=3.3 (0.5 to 4.5), p=0.01 **Overall RLP score at 24 months, median (IQR)** • Acute TMR=0.0 (0.0 to 0.0)	

First author, date	Efficacy outcomes	Safety outcomes
	• Delayed TMR=3.8 (1.4 to 5.3), p<0.001 **Worst PLP score at 6 months, median (IQR)** • Acute TMR=0.0 (0.0 to 3.5) • Delayed TMR=5.5 (2.5 to 8.0), p=0.002 **Worst PLP score at 12 months, median (IQR)** • Acute TMR=0.0 (0.0 to 2.0) • Delayed TMR=7.0 (0.0 to 8.0), p=0.006 **Worst PLP score at 18 months, median (IQR)** • Acute TMR=0.0 (0.0 to 1.5) • Delayed TMR=4.0 (4.0 to 6.0), p=0.004 **Worst PLP score at 24 months, median (IQR)** • Acute TMR=0.0 (0.0 to 0.0) • Delayed TMR=6.0 (4.0 to 6.5), p<0.001 **Worst RLP score at 6 months, median (IQR)** • Acute TMR=1.0 (0.0 to 5.0) • Delayed TMR=6.0 (3.5 to 7.0), p=0.006 **Worst RLP score at 12 months, median (IQR)** • Acute TMR=0.0 (0.0 to 3.0) • Delayed TMR=7.0 (1.0 to 9.0), p=0.006 **Worst RLP score at 18 months, median (IQR)** • Acute TMR=0.0 (0.0 to 1.5)	

First author, date	Efficacy outcomes	Safety outcomes
	• Delayed TMR=7.0 (2.0 to 8.0), p=0.01 **Worst RLP score at 24 months, median (IQR)** • Acute TMR=0.0 (0.0 to 0.0) • Delayed TMR=5.0 (1.0 to 8.0), p=0.002 **Pain interference score at 6 months, median (IQR)** • Acute TMR=1.5 (0.0 to 2.9) • Delayed TMR=4.5 (2.0 to 6.4), p=0.04 **Pain interference score at 12 months, median (IQR)** • Acute TMR=0.0 (0.0 to 2.4) • Delayed TMR=4.7 (0.0 to 7.4), p=0.048 **Pain interference score at 18 months, median (IQR)** • Acute TMR=0.0 (0.0 to 1.5) • Delayed TMR=5.9 (2.0 to 6.6), p=0.03 **Pain interference score at 24 months, median (IQR)** • Acute TMR=0.0 (0.0 to 0.0) • Delayed TMR=6.4 (3.9 to 7.9), p<0.001 **Pain catastrophisation score at 6 months, median (IQR)** • Acute TMR=0.0 (0.0 to 6.0) • Delayed TMR=10.0 (3.0 to 13.0), p=0.006 **Pain catastrophisation score at 12 months, median (IQR)** • Acute TMR=0.0 (0.0 to 5.0)	

First author, date	Efficacy outcomes	Safety outcomes
	• Delayed TMR=11.0 (8.0 to 32.0), p=0.003 **Pain catastrophisation score at 18 months, median (IQR)** • Acute TMR=0.0 (0.0 to 0.0) • Delayed TMR=8.5 (0.0 to 33.0), p=0.03 **Pain catastrophisation score at 24 months, median (IQR)** • Acute TMR=0.0 (0.0 to 0.0) • Delayed TMR=18.5 (10.0 to 34.0), p<0.001 **Mixed-effect models for pain outcomes – regression coefficients for acute versus delayed TMR, (95% CI)** *Overall PLP scores=-2.18 (-3.4 to -0.93), p=0.001* *Overall RLP scores=-1.81 (-2.9 to -0.72), p=0.001* *Worst PLP scores=-3.02 (-4.8 to -1.2), p=0.001* *Worst RLP scores=-2.42 (-4.1 to -0.74), p=0.01* *Pain interference=-2.23 (-4.1 to -0.38), p=0.02* *Pain catastrophisation=-7.88 (-16.0 to 0.25), p=0.06*	
Chang, 2021	**Proportion of people who were pain free at follow-up** • TMR=71% • Non-TMR=36%, p<0.01 **Mean pain score for those people who had pain** • TMR=3.2 • Non-TMR=5.2, p<0.01 **Proportion of people with RLP** • TMR=14%	**Surgical complications** **Stump wounds or infections that needed operative debridement and revision** • TMR=16% • Non-TMR=30%, p=0.02

First author, date	Efficacy outcomes	Safety outcomes
	• Non-TMR=57%, p<0.01 **Proportion of people with PLP** • TMR=19% • Non-TMR=47%, p<0.01 **Proportion of people taking opioids within 1 month of last follow-up** • TMR=6% • Non-TMR=24%, p<0.01 **Mean dose in those taking opioids (morphine equivalent per day)** • TMR=47.6 • Non-TMR=37.4, p=0.66 **Proportion of people taking neuroleptic medication at last follow-up** • TMR=42% • Non-TMR=48%, p=0.20 **Proportion of people who were ambulatory** • TMR=90.9% (80/88); none were nonambulatory because of pain • Non-TMR=70.5% (55/78), p<0.01; 9 could not ambulate because of uncontrollable pain Two people in the TMR group developed symptomatic neuromas and PLP that needed a secondary TMR, 1 involving the sural nerve and 1 involving the saphenous nerve.	**Mean number of additional interventions when revision was needed** • TMR=2.3 • Non-TMR=2.0 **Mortality at 12 months** • TMR=4.9% • Non-TMR=6.0%, p=0.80

First author, date	Efficacy outcomes	Safety outcomes
Chang, 2024	**Proportion of people who reported any type of pain** • TMR=41.5% • Non-TMR=67.2%, p=0.01 **Proportion of people who reported RLP** • TMR=26.8% • Non-TMR=44.8%, p=0.04 **Proportion of people who reported PLP** • TMR=19.5% • Non-TMR=43.1%, p=0.01 **Overall pain severity in those who reported pain (range 0 to 10)** • TMR=4.9 • Non-TMR=5.5, p=0.64 **Proportion of people taking narcotics more than 1 month after amputation** • TMR=9.8% • Non-TMR=25.9%, p=0.05 **Proportion of people taking neuroleptic medication** • TMR=56.4% • Non-TMR=60.3%, p=0.70 **Proportion of people with a minimum 3-month follow-up who were ambulatory with a prosthetic** • TMR=41.9% • Non-TMR=22.7%, p=0.11	**Surgical complications** **Superficial wounds needing woundcare only** • TMR=22.0% • Non-TMR=19.0%, p=0.72 **Need for operative stump revision** • TMR=14.6% • Non-TMR=32.8%, p=0.22 2.4% of people who had TMR were offered a revision TMR procedure for a symptomatic stump neuroma and PLP. **Mortality at 3 months** • TMR=12.2% • Non-TMR=3.4% (p value not reported) **Mortality at 12 months** • TMR=26.5% • Non-TMR=15.5% (p value not reported)

First author, date	Efficacy outcomes	Safety outcomes
Smith, 2024	**Reoperation after primary amputation** • TMR=21.4% (6/28) • No TMR=22.7% (17/75), p=0.11 **Rate of revision for symptomatic neuroma** • TMR=3.6% (1/28) • No TMR=4.0% (3/75), p=0.97 **Mean VAS score for pain at 2 weeks** • TMR=3.26 (n=27) • No TMR=3.33 (n=64), p=0.91 **Mean VAS score for pain at 6 weeks** • TMR=2.21 (n=28) • No TMR=1.83 (n=64), p=0.43 **Mean decrease in VAS score between 2 and 6 weeks** • TMR=0.96, p=0.06 • No TMR=1.5, p=0.0002	**No safety outcomes were reported**

Procedure technique

The site of amputations varied and included upper and lower limbs, so the nerves involved in the TMR procedures varied within and between studies. The TMR was done as a delayed procedure only in 2 studies (Dumanian 2019 and Kang 2022). It was done at the same time as the amputation in 5 studies (Shammas 2022, O'Brien 2022, Chang 2021, Chang 2024 and Smith 2024). Two studies compared outcomes between acute and delayed TMR (Goodyear 2024, Li 2024). In the 10 studies included in the systematic review by Tham et al. (2023), the procedure was done either at the same time as the amputation or as a later secondary procedure.

Efficacy

Residual limb pain (RLP)

In the systematic review of 10 studies by Tham et al. (2023), the pooled mean difference in NRS for RLP for TMR compared with control was -2.68 (95% CI -3.21 to -2.14, p<0.0001; 4 studies, I^2=0%) The pooled mean difference for PROMIS intensity score was -13.4 (95% CI -14.6 to -12.2, p<0.0001; 3 studies, I^2=61%). The pooled mean difference for PROMIS behavioural score was -12.0 (95% CI -13.8 to -10.2, p<0.0001; 4 studies, I^2=87%) and the pooled mean difference for PROMIS interference score was -12.2 (95% CI -13.6 to -10.8, p<0.0001; 4 studies, I^2=70%).

In the randomised controlled trial of 28 people (4 upper and 26 lower limbs), the worst pain score (NRS) for RLP reduced from 6.6 at baseline to 3.7 at 1 year in the TMR group and from 6.9 to 6.0 in the control group. The mean difference of change scores was 1.9 (adjusted 95% CI -0.5 to 4.4). The proportion of people with no or mild RLP at last follow-up was 67% in the TMR group and 27% in the control group (p value not stated). The PROMIS intensity score for RLP reduced from 55.7 at baseline to 44.5 at 1 year in the TMR group and from 55.0 to 49.5 in

the control group. The mean difference of change scores was 5.8 (adjusted 95% CI -0.9 to 12.4). The PROMIS behaviour score for RLP reduced from 61.5 at baseline to 56.8 at 1 year in the TMR group and from 61.9 to 56.6 in the control group. The mean difference of change scores was -0.5 (adjusted 95% CI -7.2 to 6.1). The PROMIS interference score for RLP reduced from 64.4 at baseline to 56.8 at 1 year in the TMR group and from 65.8 to 57.4 in the control group. The mean difference of change scores was -0.9 (adjusted 95% CI -8.5 to 6.7; Dumanian 2019).

In the prospective case series of 81 people (83 upper or lower limbs), the mean worst pain score (NRS) for RLP was 2.08 at 3 months after TMR (n=53), 1.86 at 6 months (n=49), 1.79 at 12 months (n=43) and 1.04 at 18 months or more (n=23). The changes in scores from 3 months onwards were not statistically significant. The mean PROMIS interference score for RLP was 45.6 at 3 months after TMR and the mean PROMIS behaviour score was 46.0. The changes from 3 months onwards were not statistically significant (O'Brien 2022).

In the retrospective cohort study of 32 people (38 upper or lower limbs) who had acute or delayed TMR, the overall RLP score for delayed TMR was 3.5 at 6 months follow-up compared with 5.6 at baseline (p=0.02). The score was 4.0 at 12 months (p=0.07), 3.3 at 18 months (p=0.01) and 4.0 at 24 months (p=0.13). The median scores for acute TMR were statistically significantly lower than for delayed TMR for all timepoints. The worst RLP score for delayed TMR was 6.0 at 6 months follow-up compared with 8.0 at baseline (p=0.02). The score was 7.0 at 12 months (p=0.15), 7.0 at 18 months (p=0.13) and 5.0 at 24 months (p=0.06). Again, the median scores for acute TMR were statistically significantly lower than for delayed TMR for all timepoints (Li 2024).

In the retrospective cohort study of 200 people who had below-knee amputation with TMR or traction neurectomy and muscle implantation, 14% of those in the TMR group had RLP at follow-up compared with 57% of those in the control

group (p<0.01; Chang 2021). In the cohort study of 99 people who had through- or above-knee amputation with TMR or traction neurectomy and muscle implantation, 27% of those in the TMR group had RLP at follow-up compared with 45% of those in the control group (p=0.04; Chang 2024).

Phantom limb pain

In the systematic review of 10 studies by Tham et al. (2023), the pooled mean difference in NRS for PLP for TMR compared with control was -2.17 (95% CI -2.70 to -1.63, p<0.0001; 4 studies, I^2=51%) The pooled mean difference for PROMIS intensity score was -11.2 (95% CI -13.0 to -9.45, p<0.0001; 3 studies, I^2=61%). The pooled mean difference for PROMIS behavioural score was -10.4 (95% CI -12.4 to -8.52, p<0.0001; 4 studies, I^2=76%) and the pooled mean difference for PROMIS interference score was -11.5 (95% CI -12.8 to -10.1, p<0.0001; 4 studies, I^2=62%).

In the randomised controlled trial of 28 people (4 upper and 26 lower limbs), the worst pain score (NRS) for PLP reduced from 5.8 at baseline to 2.6 at 1 year in the TMR group and increased from 3.9 to 4.1 in the control group. The mean difference of change scores was 3.4 (adjusted 95% CI -0.1 to 6.9). The proportion of people with no or mild PLP at last follow-up was 72% in the TMR group and 40% in the control group (p value not stated). The PROMIS intensity score for PLP reduced from 52.4 at baseline to 38.0 at 1 year in the TMR group and from 48.3 to 45.8 in the control group. The mean difference of change scores was 11.7 (adjusted 95% CI -0.3 to 23.7). The PROMIS behaviour score for PLP reduced from 58.3 at baseline to 50.7 at 1 year in the TMR group and from 58.5 to 52.0 in the control group. The mean difference of change scores was 1.1 (adjusted 95% CI -8.3 to 10.5). The PROMIS interference score for PLP reduced from 60.2 at baseline to 50.4 at 1 year in the TMR group and from 57.9 to 52.8 in the control group. The mean difference of change scores was 4.7 (adjusted 95% CI -5.0 to 14.3; Dumanian 2019).

In the retrospective case series of 36 people (40 upper or lower limbs), the mean change in NRS for PLP at 12 month follow-up was 4.4 (95% CI 7.29 to 1.52, p=0.007) for upper limbs and 2.6 (95% CI 4.46 to 0.74, p=0.009) for lower limbs. People with upper limb amputation had a temporary worsening of PLP within the first 3 months. Of the 10 people with upper limb amputation, 1 was pain free at 12 months and 5 had only mild pain (NRS between 1 and 3). Of the 20 lower limb procedures, 4 people were pain free at 12 months and 3 had only mild pain (Kang 2022).

In the prospective case series of 81 people (83 upper or lower limbs), the mean worst pain score (NRS) for PLP was 2.51 at 3 months after TMR (n=53), 2.37 at 6 months (n=49), 1.05 at 12 months (n=43) and 0.96 at 18 months or more (n=23). Unadjusted pairwise analysis demonstrated a statistically significant difference in mean PLP NRS scores between 3 months and 18 months (mean difference −1.38, p=0.004), 6 months and 18 months (mean difference −1.14, p=0.02), and 12 months and 18 months or later (mean difference −1.02, p=0.04). The mean PROMIS interference score for PLP was 46.4 at 3 months after TMR and the mean PROMIS behaviour score was 47.8. The changes from 3 months onwards were not statistically significant (O'Brien 2022).

In the retrospective cohort study of 32 people (38 upper or lower limbs) who had acute or delayed TMR, the median overall PLP score for delayed TMR was 3.4 at 6 months follow-up compared with 5.5 at baseline (p=0.01). The score was 3.5 at 12 months (p=0.02), 3.0 at 18 months (p=0.03) and 3.5 at 24 months (p=0.15). The median scores for acute TMR were statistically significantly lower than for delayed TMR for all timepoints. The worst PLP score for delayed TMR was 5.5 at 6 months follow-up compared with 7.5 at baseline (p=0.06). The score was 7.0 at 12 months (p=0.19), 4.0 at 18 months (p=0.14) and 6.0 at 24 months (p=0.32). Again, the median scores for acute TMR were statistically significantly lower than for delayed TMR for all timepoints (Li 2024).

In the retrospective cohort study of 200 people who had below-knee amputation with TMR or traction neurectomy and muscle implantation, 19% of those in the TMR group had PLP at follow-up compared with 47% of those in the control group (p<0.01; Chang 2021). In the cohort study of 99 people who had through- or above-knee amputation with TMR or traction neurectomy and muscle implantation, 20% of those in the TMR group had RLP at follow-up compared with 43% of those in the control group (p=0.01; Chang 2024).

Neuroma pain

In the retrospective case series of 36 people (40 upper or lower limbs), the mean change in NRS for neuroma pain at 12 month follow-up was 5.30 (95% CI 8.61 to 2.00, p=0.006) for upper limbs and 4.35 (95% CI 6.47 to 2.23, p<0.0001) for lower limbs. Of the 10 people with upper limb amputation, all pain had resolved at 12 months. Of the 20 lower limb procedures, 10 resulted in complete resolution of neuroma pain and 2 people had only mild pain (Kang 2022).

Neuroma development

In the retrospective cohort study of 103 people (105 upper or lower limbs) who had acute or delayed TMR, neuroma development in the same nerve distributions included in the original TMR procedure was reported after 1% (1 out of 73) of acute TMR procedures and 19% (6 out of 32) of delayed TMR procedures (p<0.05). Neuroma development in a new nerve distribution was reported after 6% (4 out of 73) of acute TMR procedures and 9% (3 out of 32) of delayed TMR procedures (p=0.433). In multivariate analysis, those who had delayed TMR had 29 times greater odds of developing a subsequent neuroma compared with acute TMR, when controlling for age, sex, and extremity involved (95% CI 2.4 to 347.3; p=0.008; Goodyear 2024). In the retrospective cohort study of 200 people who had below-knee amputation with TMR or traction neurectomy and muscle implantation, 2 people in the TMR group developed symptomatic neuromas and PLP that needed a secondary TMR, 1 involving the sural nerve

and 1 involving the saphenous nerve (Chang 2021). In the retrospective study of 112 primary amputations, the rate of revision for symptomatic neuroma was 3.6% (1 out of 28) in the TMR group and 4.0% (3 out of 75) in the non-TMR group (p=0.97; Smith 2024).

Unspecified pain

In the retrospective cohort study of 200 people who had below-knee amputation with TMR or traction neurectomy and muscle implantation, 71% of those in the TMR group and 36% of those in the control group were pain free at follow-up (p<0.01). The mean pain scores for those people who had pain were 3.2 in the TMR group and 5.2 in the control group (p<0.01; Chang 2021). In the cohort study of 99 people who had through- or above-knee amputation with TMR or traction neurectomy and muscle implantation, 42% of those in the TMR group and 67% of those in the control group reported any type of pain (p=0.01). The overall pain severity in those who reported pain was 4.9 in the TMR group and 5.5 in the control group (p=0.64; Chang 2024). In the retrospective study of 112 primary amputations, the mean VAS score for pain at 2 weeks was 3.26 in those who had TMR and 3.33 in those who did not have TMR (p=0.91). At 6 weeks, the scores were 2.21 and 1.83, respectively (p=0.43). The mean decrease in VAS score between 2 and 6 weeks was 0.96 in the TMR group (p=0.06) and 1.5 in the non-TMR group (p=0.0002; Smith 2024).

Medication use

In the retrospective case series of 36 people (40 upper or lower limbs), 9 of the 18 people who were taking pregabalin before the procedure had discontinued it after 1 year. There was a mean reduction of 352 mg in daily intake over the 12 months of follow-up (p<0.01; Kang 2022). In the retrospective cohort study of 200 people who had below-knee amputation with TMR or traction neurectomy and muscle implantation, 6% of those in the TMR group and 24% of those in the control group were taking opioids within 1 month of the last follow-up (p<0.01).

The proportion of people taking neuroleptic medication at last follow-up was 42% in the TMR group and 48% in the control group (p=0.20; Chang 2021). In the cohort study of 99 people who had through- or above-knee amputation with TMR or traction neurectomy and muscle implantation, 10% of those in the TMR group and 26% of those in the control group were taking narcotics more than 1 month after amputation (p=0.05). The proportion of people taking neuroleptic medication was 56% in the TMR group and 60% in the control group (p=0.70; Chang 2024).

Functional outcomes

In the systematic review of 10 studies, 1 study reported that the OPUS score for those who had upper limb amputations and TMR increased from 53.7 to 56.4 at 1 year follow-up (p<0.01). The Neuro-QoL score for those with lower limb amputations and TMR increased from 32.9 to 35.2 (p<0.01). Both outcomes showed higher functional scores in the TMR group (Tham 2023). In the randomised controlled trial of 28 people, the lower extremity Neuro-QoL results (n=24) showed little difference between the groups at 1 year. When crossover data were included and at final follow-up, the mean score increased from 39.9 to 45.2 in the TMR cohort showing functional improvement (Dumanian 2019).

In the retrospective cohort study of 200 people who had below-knee amputation with TMR or traction neurectomy and muscle implantation, 91% of those in the TMR group and 71% of those in the control group were ambulatory at last follow-up (p<0.01). In the control group, 9 people could not ambulate because of uncontrollable pain (Chang 2021). In the cohort study of 99 people who had through- or above-knee amputation with TMR or traction neurectomy and muscle implantation, 42% of those in the TMR group and 23% of those in the control group with a minimum of 3 months follow-up were ambulatory with a prosthetic (p=0.11; Chang 2024).

Patient satisfaction

In the retrospective case series of 36 people (40 upper or lower limbs), 22 people reported data on satisfaction. Of those, 91% indicated overall satisfaction with the procedure at 12 months but only 50% felt they would have agreed to a prophylactic TMR procedure (Kang 2022).

Operative time

In the propensity score-matched study of 96 people who had below-knee amputation with or without TMR, the mean length of surgery was statistically significantly longer in the TMR group (189 minutes) than the group without TMR (88 minutes; $p<0.001$; Shammas 2022).

Safety

General complications

Complication rates ranged from 0 to 16% in the 4 studies that reported them in the systematic review of 10 studies. Complications were mostly wound site or stump infections (Tham 2023).

Readmission

Readmission was reported for 26% (8 out of 31) of people who had TMR at the same time as a below-knee amputation and 19% (12 out of 65) of people who had amputation without TMR ($p=0.21$; Shammas 2022).

Reoperation (when reported as a safety outcome)

Reoperation within 60 days was reported for 19% (6 out of 31) of people who had TMR at the same time as a below-knee amputation and 11% (7 out of 65) of people who had amputation without TMR ($p=0.13$; Shammas 2022). Operative stump revision was reported for 15% of those in the TMR and 33% in the control group ($p=0.22$) in the cohort study of 99 people who had through- or above-knee

amputation with TMR or traction neurectomy and muscle implantation (Chang 2024).

Admission to intensive care unit

Admission to an intensive care unit was reported for 7% (2 out of 31) of people who had TMR at the same time as a below-knee amputation and 11% (7 out of 65) of people who had amputation without TMR (p=0.41; Shammas 2022).

Mortality

All-cause mortality was 3% (1 out of 31) for those who had TMR at the same time as a below-knee amputation and 9% (6 out of 65) for those who had amputation without TMR (p=0.34; Shammas 2022). Mortality at 12 months was 5% in the TMR group and 6% in the control group (p=0.80) in the cohort study of 200 people (Chang 2021). Mortality at 3 months was 12% in the TMR group and 3% in the control group (p value not reported) in the cohort study of 99 people (Chang 2024).

Wound healing complication

Wound healing complications were reported for 45% (14 out of 31) of people who had TMR at the same time as a below-knee amputation and 34% (22 out of 65) of people who had amputation without TMR (p=0.25; Shammas 2022). In the case series of 36 people (11 upper and 29 lower limbs), wound dehiscence, haematoma and seroma were each reported after 1 upper limb procedure. In the lower limb group, there were 3 reports of wound dehiscence, 2 reports each of haematoma and ulceration and 1 report each of seroma and lymphatic discharge (Kang 2022). Haematoma was reported after 1% (1 out of 73) of acute TMR procedures and 3% (1 out of 32) of delayed TMR procedures in the cohort study of 103 people. In the same study, dehiscence was reported in 4% (3 out of 73) of acute TMR procedures and 3% (1 out of 32) of delayed TMR procedures and superficial dehiscence was reported in 11% (8 out of 73) and 6% (2 out of 32),

respectively (Goodyear 2024). One person had a haematoma that needed surgical evacuation and debridement after acute TMR and 1 person had delayed wound healing that needed debridement after delayed TMR, in the cohort study of 32 people (Li 2024).

Infection

Infection was reported for 10% (3 out of 31) of people who had TMR at the same time as a below-knee amputation and 6% (4 out of 65) of people who had amputation without TMR ($p<0.001$; Shammas 2022). In the case series of 36 people (11 upper and 29 lower limbs), infection was reported after 4 upper limb procedures and 7 lower limb procedures (Kang 2022). Infection was reported after 6% (4 out of 73) of acute TMR procedures and abscess was reported after 6% (2 out of 32) of delayed TMR procedures in the cohort study of 103 people. Minor abscess was reported in 1% (1 out of 73) of acute TMR procedures and 6% (2 out of 32) of delayed TMR procedures (Goodyear 2024). One person had an infection that needed surgical debridement after delayed TMR, in the cohort study of 32 people (Li 2024). Stump wounds or infections that needed surgical debridement and revision were reported in 16% of the group who had TMR and 30% of the group who did not have TMR ($p=0.02$) in the cohort study of 200 people (Chang 2021).

Paraesthesia

In the case series of 36 people who had TMR (11 upper and 29 lower limbs), paraesthesia was reported after 1 upper limb procedure and 4 lower limb procedures (Kang 2022).

Unmasking of neuroma

In the case series of 36 people who had TMR (11 upper and 29 lower limbs), unmasking of neuromas was reported after 12 lower limb procedures. This

typically happened within a few weeks of surgery and 4 people needed an additional TMR procedure (Kang 2022).

Cellulitis

Minor cellulitis was reported after 6% (4 out of 73) of acute TMR procedures and 3% (1 out of 32) of delayed TMR procedures in the cohort study of 103 people (Goodyear 2024).

Anecdotal and theoretical adverse events

Expert advice was sought from consultants who have been nominated or ratified by their professional society or royal college. They were asked if they knew of any other adverse events for this procedure that they had heard about (anecdotal), which were not reported in the literature. They were also asked if they thought there were other adverse events that might possibly occur, even if they had never happened (theoretical).

They listed the following anecdotal or theoretical adverse events:

- Neuroma in continuity
- Worsening of pain
- Insensate stump
- Loss of function of target muscles
- Muscle wasting leading to change in stump shape, making it necessary to refit the socket.

Eleven professional expert questionnaires for this procedure were submitted. Find full details of what the professional experts said about the procedure in the specialist advice questionnaires for this procedure.

Validity and generalisability

- Most of the evidence was from the US but there is some data from the UK.

- The evidence includes people who had upper or lower limb amputation for a variety of reasons. There were different levels of amputation and the TMR procedures involved different nerves.
- The reason for amputation may have an impact on the outcomes. In particular, the presence of peripheral vascular disease may be a confounding factor. In 3 studies, the main reasons for amputation were infection and ischaemia and these all noted a high level of comorbidity in the study population (Shammas 2022, Chang 2021, Chang 2024).
- Some TMR procedures were done prophylactically at the same time as the amputation rather than to treat refractory pain afterwards. Two studies were designed to compare the 2 approaches (Goodyear 2024, Li 2024).
- Most of the studies were small and many were retrospective.
- The randomised controlled trial by Dumanian et al. (2019) was stopped early with recruitment of 28 patients rather than the intended sample size of 200.
- Although the mean follow-up was less than a year in several studies, there were some reports with longer follow-up.
- It may be difficult for patients to distinguish RLP from PLP.
- The authors of Dumanian et al. (2019) noted that the 3 supplemental PROMIS item banks that were included in their outcome measures had not yet been validated in people living with chronic postamputation pain.

Ongoing trials

- A Randomized Controlled Trial of Targeted Muscle Reinnervation in Patients Requiring Lower Extremity Amputation (NCT05408520); RCT; US; n=50; completion date May 2025
- Patient Reported Outcomes Following Targeted Muscle Reinnervation in Major Limb Amputees (NCT04658368); observational; US; n=60; completion date Jan 2025

- A Randomized Trial Comparing Surgical Treatments for Neuroma Pain in Amputees (NCT04204668); RCT; US; n=90; completion date April 2028
- Surgical Treatments for Postamputation Pain (NCT05009394); RCT; US, Australia, Canada, Chile, Italy, Sweden, UK; n=110; completion date June 2028. This is a double-blind randomised controlled trial.

Related NICE guidance

Interventional procedures

Nerve transfer to partially restore upper limb function in tetraplegia (2018) NICE interventional procedures guidance 610 (Recommendation: special arrangements)

Percutaneous image-guided cryoablation of peripheral neuroma for chronic pain (2023) NICE interventional procedures guidance 747 (Recommendation: research)

NICE guidelines

Rehabilitation after traumatic injury (2022) NICE guideline 211

Professional societies

- British Orthopaedic Association
- British Limb Reconstruction Society
- British Association of Plastic, Reconstructive and Aesthetic Surgeons
- The Society of British Neurological Surgeons
- British Pain Society
- British Association of Prosthetists and Orthotists.

References

1. Tham J-L, Sood A, Saffari TM et al. (2023) The effect of targeted muscle reinnervation on post-amputation pain and functional outcomes: a systematic review and meta-analysis. European Journal of Plastic Surgery 46: 475–97
2. Dumanian GA, Potter BK, Mioton LM et al. (2019) Targeted muscle reinnervation treats neuroma and phantom pain in major limb amputees: a randomized clinical trial. Annals of Surgery 270: 238–46
3. Shammas RL, Azoury SC, Sergesketter AR et al. (2022) Primary targeted muscle reinnervation after below-knee amputation is not associated with an increased risk of major or minor surgical complications: a multi-institutional, propensity score-matched analysis. Plastic and Reconstructive Surgery 150: 589–98
4. O'Brien AL, West JM, Gokun Y et al. (2022) Longitudinal durability of patient-reported pain outcomes after targeted muscle reinnervation at the time of major limb amputation. Journal of the American College of Surgeons 234: 883–89
5. Kang NV, Woollard A, Michno DA et al. (2022) A consecutive series of targeted muscle reinnervation (TMR) cases for relief of neuroma and phantom limb pain: UK perspective. Journal of Plastic, Reconstructive & Aesthetic Surgery 75: 960–69
6. Goodyear EG, O'Brien AL, West JM et al. (2024) Targeted muscle reinnervation at the time of amputation decreases recurrent symptomatic neuroma formation. Plastic and Reconstructive Surgery 153: 154–63
7. Chang BL, Mondshine J, Attinger CE et al. (2021) Targeted muscle reinnervation improves pain and ambulation outcomes in highly comorbid amputees. Plastic and Reconstructive Surgery 148: 376–86
8. Li AT, Garcia N, Angliss M et al. (2024) Acute versus non-acute targeted muscle reinnervation for pain control following major limb amputation: A comparative study. Journal of Plastic, Reconstructive & Aesthetic Surgery 94: 229–37
9. Chang BL, Hill AL, Mondshine J et al. (2024) Primary targeted muscle reinnervation in above-knee amputations in patients with unsalvageable limbs from limb-threatening ischemia or infection. Journal of Reconstructive Microsurgery 40: 109–117
10. Smith TP, Cognetti DJ, Cook A et al. (2024) Similar rates of reoperation for neuroma after transtibial amputations with and without targeted muscle reinnervation. OTA International 7: e297

Appendix A: Methods and literature search strategy

Methods and literature search strategy

NICE has identified studies and reviews relevant to targeted muscle reinnervation for refractory pain after limb amputation from the medical literature.

Search strategy design and peer review

This search report is informed by the Preferred Reporting Items for Systematic reviews and Meta-Analyses literature search extension (PRISMA-S).

A NICE information specialist ran the literature searches on 02/08/2024. See the search strategy history for the full search strategy for each database. Relevant published studies identified during consultation or resolution that are published after this date may also be considered for inclusion.

The principal search strategy was developed in MEDLINE ALL (Ovid interface). It was adapted for use in each of the databases listed in table 4a, taking into account the database's size, search functionality and subject coverage. The MEDLINE ALL strategy was quality assured by a NICE senior information specialist. All translated search strategies were peer reviewed to ensure their accuracy. The quality assurance and peer review procedures were adapted from the Peer Review of Electronic Search Strategies (PRESS) 2015 evidence-based checklist.

Review management

The search results were managed in EPPI-Reviewer version 5 (EPPI-R5). Duplicates were removed in EPPI-R5 using a 2-step process. First, automated deduplication was done using a high-value algorithm. Second, manual deduplication was used to assess low-probability matches. All decisions about inclusion, exclusion and deduplication were recorded and stored.

Limits and restrictions

The search was not limited by date or language.

The CENTRAL database search removed trial registry records and conference material. The Embase search excluded conference material.

The limit to remove animal studies in the searches is standard NICE practice, which has been adapted from Dickersin K, Scherer R, Lefebvre C (1994) Systematic Reviews: Identifying relevant studies for systematic reviews. BMJ 309(6964): 1286.

Main search

Table 4a Main search results

Database	Date searched	Database platform	Database segment or version	Number of results downloaded
Cochrane Central Register of Controlled Trials (CENTRAL)	02/0824	Wiley	Issue 8 of 12, August 2024	120
Cochrane Database of Systematic Reviews (CDSR)	02/08/24	Wiley	Issue 7 of 12, July 2024	Review 41 Protocol 3
Embase	02/08/24	Ovid	1974 to August 05, 2024	438
INAHTA International HTA Database	02/08/24	https://database.inahta.org/	-	1
MEDLINE ALL	02/08/24	Ovid	1946 to August 01, 2024	386

MEDLINE ALL search strategy

1 , targeted muscle reinnervation.tw. , 294

2 , TMR.tw. , 2,815

3 , Nerve Transfer/ , 2,661

4 , (nerve* adj4 (transfer* or transplant* or re-rout* or rerout* or crossover* or dock* or regenerat*)).tw. , 18,294

5 , neurotizat*.tw. , 884

6 , Muscle, Skeletal/ir [Innervation] , 12,541

7 , (muscle* adj4 (skeletal* or voluntary or tibial or gastrocnemius or plantaris or soleus)).tw. , 158,412

8 , Peripheral Nerves/su , 2,315

9 , ((peripheral* adj4 nerve*) or endoneurium* or epineurium* or perineurium*).tw. , 54,304

10 , or/1-9 , 235,304

11 , exp Amputation, Surgical/ , 25,111

12 , exp Amputation Stumps/ , 3,261

13 , Amputation, Traumatic/ , 5,141

14 , Amputat*.tw. , 51,676

15 , (nerve* adj4 cut*).tw. , 7,351

16 , or/11-15 , 70,063

17 , Phantom Limb/ , 2,134

18 , (phantom adj (Limb* or pain* or sensation*)).tw. , 2,534

19 , (residual* adj Limb* adj4 (pain* or sensation*)).tw. , 252

20 , Pseudomelia*.tw. , 0

21 , exp Pain, Intractable/ , 6,430

22 , (Pain* adj4 (refract* or intractab* or severe* or constant* or debilitating*)).tw. , 48,538

23 , Neuritis/ , 5,100

24 , Neuralgia/ , 18,610

25 , (Neurit* or Neuralg* or polyneurit* or neurodynia*).tw. , 62,634

26 , Chronic Pain/ , 24,934

27 , (((chronic* or persist* or continual* or constant* or nerve*) and neuropath*) adj4 pain).tw. , 20,967

28 , or/17-27 , 164,444

29 , 10 and 16 and 28 , 448

30 , Animals/ not Humans/ , 5,210,707

31 , 29 not 30 , 386

Embase search strategy

1 , muscle reinnervation/ , 2,028

2 , TMR.tw. , 3,21

3 , nerve transplantation/ , 5,404

4 , (nerve* adj4 (transfer* or transplant* or re-rout* or rerout* or crossover* or dock* or regenerat*)).tw. , 21,27

5 , neurotizat*.tw. , 966

6 , innervation/ , 40,102

7 , (muscle* adj4 skeletal*).tw. , 170,288

8 , peripheral nerve/su [Surgery] , 463

9 , (peripheral* adj4 nerve*).tw. , 68,075

10 , innervat*.tw. , 72,854

11 , or/1-10 , 345,840

12 , exp amputation/ , 60,084

13 , amputat*.tw. , 65,926

14 , exp amputation stump/ , 2,30

15 , (nerve adj4 cut*).tw. , 6,954

16 , or/12-15 , 90,781

17 , phantom limb/ , 476

18 , ((Phantom* or residual*) adj Limb* adj4 (pain* or sensation*)).tw. , 2,207

19 , ((Phantom* or residual*) adj Limb* adj4 (pain* or sensation* or syndrom*)).tw. , 2,27

20 , exp intractable pain/ , 5,752

21 , (Pain adj4 (refract* or intractab* or severe* or constant* or debilitating*)).tw. , 74,768

22 , neuritis/ , 5,761

23 , neuralgia/ , 9,897

24 , (Neurit* or Neuralg* or polyneurit* or neurodynia*).tw. , 78,921

25 , chronic pain/ , 83,303

26 , ((chronic* or persist* or continual* or constant*) adj4 pain).tw. , 156,389

27 , or/17-26 , 318,208

28 , 11 and 16 and 27 , 719

29 , Nonhuman/ not Human/ , 5,503,992

30 , 28 not 29 , 659

31 , (conference abstract* or conference review or conference paper or conference proceeding).db,pt,su. , 5,993,676

32 , 30 not 31 , 438

Cochrane Library (CDSR and CENTRAL) search strategy

#1 targeted muscle reinnervation 19

#2 TMR 221

#3 MeSH descriptor: [Nerve Transfer] this term only 37

#4 (nerve* near/4 (transfer* or transplant* or re-rout* or rerout* or crossover* or dock* or regenerat*)) 710

#5 neurotizat* 22

#6 MeSH descriptor: [Muscle, Skeletal] this term only and with qualifier(s): [innervation - IR] 599

#7 (muscle* near/4 (skeletal* or voluntary or tibial or gastrocnemius or plantaris or soleus)) 18972

#8 MeSH descriptor: [Peripheral Nerves] explode all trees and with qualifier(s): [surgery - SU] 410

#9 ((peripheral* near/4 nerve*) or endoneurium* or epineurium* or perineurium*) 4729

#10 #1 or #2 or #3 or #4 or #5 or #6 or #7 or #8 or #9 24596

#11 MeSH descriptor: [Amputation, Surgical] explode all trees 685

#12 MeSH descriptor: [Amputation Stumps] explode all trees 71

#13 MeSH descriptor: [Amputation, Traumatic] this term only 71

#14 Amputat* 4479

#15 (nerve* near/4 cut*) 682

#16 #11 or #12 or #13 or #14 or #15 5145

#17 MeSH descriptor: [Phantom Limb] this term only 194

#18 (phantom near (Limb* or pain* or sensation*)) 526

#19 (residual* near Limb* near/4 (pain* or sensation*)) 55

#20 Pseudomelia* 0

#21 MeSH descriptor: [Pain, Intractable] this term only 349

#22 (Pain* near/4 (refract* or intractab* or severe* or constant* or debilitating*)) 13341

#23 MeSH descriptor: [Neuritis] this term only 107

#24 MeSH descriptor: [Neuralgia] this term only 1734

#25 (Neurit* or Neuralg* or polyneurit* or neurodynia*) 5259

#26 MeSH descriptor: [Chronic Pain] this term only 4667

#27 (((chronic* or persist* or continual* or constant* or nerve*) and neuropath*) near/4 pain) 3880

#28 #17 or #18 or #19 or #20 or #21 or #22 or #23 or #24 or #25 or #26 or #27 51283

#29 #10 AND #16 AND #28 165

Note: (CDSR 44, CENTRAL 120, Clinical Answers 1 [not exported])

INAHTA search strategy

1 , targeted muscle reinnervation , 1

2 , TMR , 6

3 , "Nerve Transfer"[mh] , 6

4 , (nerve* AND (transfer* or transplant* or re-rout* or rerout* or crossover* or dock* or regenerat*)) , 16

5 , neurotizat* , 0

6 , "Muscle, Skeletal"[mh] , 3

7 , (muscle* AND (skeletal* or voluntary or tibial or gastrocnemius or plantaris or soleus)) , 13

8 , "Peripheral Nerves"[mhe] , 94

9 , ((peripheral* AND nerve*) or endoneurium* or epineurium* or perineurium*) , 37

10 , #9 OR #8 OR #7 OR #6 OR #5 OR #4 OR #3 OR #2 OR #1 , 156

11 , "Amputation, Surgical"[mhe] , 10

12 , "Amputation Stumps"[mhe] , 3

14 , Amputat* , 84

15 , (nerve* AND cut*) , 9

16 , #15 OR #14 OR #13 OR #12 OR #11 , 94

17 , "Phantom Limb"[mh] , 2

18 , phantom AND (Limb* or pain* or sensation*)) , 5

19 , (residual* AND Limb* AND (pain* or sensation*)) , 1

20 , Pseudomelia* , 0

24 , "Neuralgia"[mh] , 49

25 , (Neurit* or Neuralg* or polyneurit* or neurodynia*) , 44

26 , "Chronic Pain"[mh] , 77

27 , (((chronic* or persist* or continual* or constant* or nerve*) and neuropath*) AND pain) , 36

28 , #27 OR #26 OR #25 OR #24 OR #23 OR #22 OR #21 OR #20 OR #19 OR #18 OR #17 , 381

29 , #28 AND #16 AND #10 , 165

Inclusion criteria

The following inclusion criteria were applied to the abstracts identified by the literature search.

Publication type: clinical studies were included with emphasis on identifying good quality studies. Abstracts were excluded if they did not report clinical outcomes. Reviews, editorials, and laboratory or animal studies, were also excluded and so were conference abstracts, because of the difficulty of appraising study methodology, unless they reported specific adverse events not available in the published literature.

People with upper or lower limb amputation.

Intervention or test: TMR.

Outcome: articles were retrieved if the abstract contained information relevant to the safety, efficacy, or both.

If selection criteria could not be determined from the abstracts the full paper was retrieved.

Potentially relevant studies not included in the main evidence summary are listed in Appendix B: Other relevant studies

Find out more about how NICE selects the evidence for the committee.

Appendix B: Other relevant studies

Other potentially relevant studies that were not included in the main evidence summary (tables 2 and 3) are listed in table 5 below.

Observational studies with fewer than 20 people were excluded.

Table 5 additional studies identified

Study	Number of people and follow up	Direction of conclusions	Reason study was not included in main evidence summary
Alexander JH, Jordan SW, West JM et al. (2019) Targeted muscle reinnervation in oncologic amputees: Early experience of a novel institutional protocol. Journal of Surgical Oncology 120: 348–58	Retrospective cohort study Upper and lower limbs. Primary TMR. n=85 (27 TMR) Follow-up: mean 14.7 months	TMR reduced patient-reported PLP and RLP behaviour and interference compared to unselected general oncologic amputee controls beyond the clinically meaningful threshold for this population.	More recent studies with a larger population or longer follow up are included. Study is included in systematic review by Tham et al. (2023).
Bascone CM, Sulkar RS, McGraw JR et al. (2023) Bringing the below-knee amputation out of the Civil War era: Utilization of the neurovascularized lateral compartment flap, TMR, and RPNI. Orthoplastic Surgery 13: 10–16	Retrospective cohort study n=25 Below-knee amputations with TMR or RPNI	The potential use of TMR and RPNI, which have both shown to be effective in preventing neuroma formation and associated neuropathic pain, will be a contributing factor in decreasing opioid dependency in this population. Additionally, the use of these reconstructive techniques may enable patients to take advantage of new advances in myoelectric prosthetics.	Studies with more people or longer follow up are included.

Berger LE, Shin S, Haffner ZK et al. (2023) The application of targeted muscle reinnervation in lower extremity amputations: A systematic review. Microsurgery 43: 736–47	Systematic review n=318 limbs (11 articles) Lower limb Primary or secondary TMR	The application of TMR to lower limb amputations is effective in reducing PLP and RLP with limited complications. Quantifying standardised patient reported pain and functional outcomes stratified by amputation indication and anatomic location are warranted to better realise this potential.	No meta-analysis.
Bishay J, Yeap I, Wang T (2024) The effectiveness of targeted muscle reinnervation in reducing pain and improving quality of life for patients following lower limb amputation. Journal of Plastic, Reconstructive & Aesthetic Surgery: JPRAS; 92: 288–98	Systematic review n=778 limbs (20 studies) Primary or secondary TMR	This systematic review highlights TMR's capacity to significantly reduce both residual and PLP, reduce opioid dependency, increase ambulation rates as well as enhance the use of prosthetic devices. However, further research is needed to address the limitations and challenges associated with TMR and to establish standardised protocols for patient selection, surgical techniques, and postoperative rehabilitation.	No meta-analysis.
Bowen JB, Ruter D, Wee C et al. (2019) Targeted muscle reinnervation technique in below-knee amputation. Plastic and Reconstructive Surgery 143: 309–12	Case series n=22 Below-knee amputations Primary or secondary TMR Follow-up: 6 months	TMR may be a reliable technique for the treatment and prevention of below-knee amputation PLP at all amputation levels, without additional morbidity to the traditional below-knee amputation procedure.	Studies with more people or longer follow up are included.

de Lange JWD, Hundepool CA, Power DM et al. (2022) Prevention is better than cure: Surgical methods for neuropathic pain prevention following amputation - A systematic review. Journal of plastic, reconstructive & aesthetic surgery: JPRAS; 75: 948–59	Systematic review 5 articles on TMR	For major limb amputation, TMR and RPNI are beneficial techniques to prevent neuropathic pain and PLP. Based on the current literature, considering what the results of the techniques were on the treatment of symptomatic neuroma, the authors conclude that during amputation, techniques to prevent neuropathic pain and PLP should be performed.	Review includes a variety of techniques for preventing neuropathic pain and there is no meta-analysis.
ElAbd R, Dow T, Jabori S et al. (2024) Pain and functional outcomes following targeted muscle reinnervation: A systematic review. Plastic and Reconstructive Surgery 153: 494–508	Systematic review n=1,165 (449 TMR) 39 studies Upper and lower limbs Primary or secondary TMR	The current evidence in the literature suggests that TMR is a promising novel therapeutic strategy for improving pain, prosthesis use, and functional outcomes following major limb amputation when performed as an immediate or delayed procedure.	No meta-analysis.
Frantz TL, Everhart JS, West JM et al. (2020) Targeted muscle reinnervation at the time of major limb amputation in traumatic amputees. JBJS Open Access 5: e0067	Prospective case series n=25 Upper and lower limbs Primary TMR Follow-up: mean 14.1 months	The data suggest that TMR for orthopaedic trauma amputees was associated with low overall pain scores at follow-up, decreased overall opioid and neuromodulator medication use, and an overall high rate of daily prosthetic use.	Studies with more people or longer follow up are included. Study is included in systematic review by Tham et al. (2023).
Fulton ZW, Boothby BC, Phillips SA (2022) Targeted muscle reinnervation for trauma-related amputees: a	Systematic review n=125 6 studies	In this systematic review of TMR in the trauma-related amputee population, there was a high rate of neuroma pain	A more recent systematic review with more papers is included.

systematic review. Cureus 14: e28474	Upper or lower limbs Primary or secondary TMR	prevention, reduction, and resolution. There was a high rate of overall pain resolution or reduction. No differences were seen between TMR as a primary or secondary procedure for either of these outcomes. Prosthetic wear rates were also high, while post-TMR opioid use was low. All these data points indicate that TMR is a promising procedure that deserves wider consideration in the traumatic amputee population.	
Hagiga A, Aly M, Gumaa M et al. (2023) Targeted muscle reinnervation in managing post-amputation related pain: A systematic review and meta-analysis. Pain Practice 23: 922–32	Systematic review and meta-analysis n=127 5 studies Upper and lower limbs Primary or secondary TMR	There is limited evidence of good quality favouring TMR in reducing postamputation PLP and RLP pain compared with standard care. Randomised clinical trials are encouraged to compare the efficacy of different surgical techniques.	The same studies are included in the systematic review by Tham et al. (2023).
Hoyt B, Gibson J, Potter B et al. (2021) Practice patterns and pain outcomes for targeted muscle reinnervation: an informed approach to targeted muscle reinnervation use in the acute amputation setting. Journal of Bone and Joint Surgery 103: 681–87	Retrospective cohort study n=74 TMR, RPNI or both Lower limbs Primary or secondary Follow-up: median 14 months	The data suggest that a targeted approach featuring concurrent use of TMR and RPNI in the acute setting can be safely used to prevent neuroma pain and avoid revision surgical procedures.	Studies with more people or longer follow up are included. Study is included in systematic review by Tham et al. (2023).

Lambie CJ, Moura SP Eftekari SC et al. (2024) Social media analysis of pain outcomes following targeted muscle reinnervation. Journal of Plastic, Reconstructive & Aesthetic Surgery 91: 236–40	Social media survey n=43	Forty-three individuals commented on their TMR experience. Among them, 31 had favourable surgical outcomes, 7 felt that the surgery worsened their pain or there was no notable change in their pain levels, and 5 commented during the initial postoperative period. Among the 28 people who commented on overall reduction in chronic pain, 24 reported that TMR reduced their pain, whereas 4 reported no change or worsened pain.	Social media review with small sample size.
Mauch JT, Kao DS, Friedly JL et al. (2023) Targeted muscle reinnervation and regenerative peripheral nerve interfaces for pain prophylaxis and treatment: A systematic review. PM & R: The Journal of Injury, Function, and Rehabilitation 15: 1457–65	Systematic review n=441 17 studies TMR or RPNI Upper or lower limbs Primary or secondary Follow-up: range 4 to 27.6 months	Both TMR and RPNI may be beneficial for preventing and treating pain originating from peripheral nerve dysfunction compared to traditional techniques. Randomised trials with longer term follow-up are needed to directly compare the effectiveness of TMR and RPNI with traditional nerve management techniques.	No meta-analysis.
McNamara CT, Iorio ML (2020) Targeted muscle reinnervation: outcomes in treating chronic pain secondary to extremity amputation and phantom limb syndrome. Journal of Reconstructive Microsurgery 36: 235–40	Systematic review n=149 5 articles Upper or lower limbs	For TMR at the time of amputation, all studies reported a minimal development of symptomatic neuromas (27%). For secondary TMR, near-complete resolution of previous pain was found (90%).	A more recent systematic review is included.

	Primary or secondary TMR	Phantom pain was noted to improve over time with both primary (average drop of 3.5 out of 10 points on the numerical rating scale) and secondary (diminishing from 72% of patients to 13% over 6 months) operations.	
Mioton LM, Dumanian GA, Shah N et al. (2020) Targeted muscle reinnervation improves residual limb pain, phantom limb pain, and limb function: a prospective study of 33 major limb amputees. Clinical Orthopaedics and Related Research 478: 2161–67	Prospective case series n=33 Upper or lower limbs Secondary TMR Follow-up: 1 year	Targeted muscle reinnervation demonstrates improvement in RLP and PLP parameters in major limb amputees. It should be considered as a first-line surgical treatment option for chronic amputation-related pain in patients with major limb amputations. Additional investigation into the effect on function and quality of life should be performed.	Studies with more people or longer follow up are included. The main results from this study are included in the meta-analysis by Tham et al. (2023).
O'Brien AL, Jordan SW, West JM et al. (2021) Targeted muscle reinnervation at the time of upper-extremity amputation for the treatment of pain severity and symptoms. The Journal of Hand Surgery 46: 72e1–e10	Retrospective non-randomised comparative study n=71 (16 TMR) Upper limbs Primary TMR Follow-up: mean 23.1 months	62% of those who had early TMR were without PLP compared with 24% of controls. Half were free of RLP compared with 36% of controls. The median PROMIS PLP intensity score for the general sample was 47 versus 38 in the early TMR sample. Patients who had early TMR reported reduced pain behaviours and interference specific to PLP (50 versus 53 and 41 versus 50, respectively). The PROMIS RLP intensity	Studies with more people or longer follow up are included. The main results from this study are included in the meta-analysis by Tham et al. (2023).

		score was lower in patients with early TMR (36 versus 47).	
Pet MA, Ko JH, Friedly JL et al. (2014) Does targeted nerve implantation reduce neuroma pain in amputees? Clinical Orthopaedics and Related Research 472: 2991–3001	Retrospective cohort study n=35 (12 primary targeted nerve implantation) Upper or lower limbs Follow-up: mean 22 months	Targeted nerve implantation performed either primarily at the time of acute amputation or secondarily for the treatment of established symptomatic neuroma is associated with a low frequency of neuroma-related pain. By providing a distal target for regenerating axons, the procedure may offer an effective strategy for the prevention and treatment of neuroma pain in amputees.	More recent studies are included.
Reid RT, Johnson CC, Gaston RG et al. (2024) Impact of timing of targeted muscle reinnervation on pain and opioid intake following major limb amputation. Hand 19: 200–205	Prospective registry data n=43 (44 limbs) Primary or secondary TMR	TMR is an effective procedure to reduce pain following major limb amputation. Patients with TMR performed acutely had significantly lower VAS pain scores at both intermediate and final follow-up than patients with TMR performed in a delayed setting.	Studies with more people or longer follow up are included.
Roubaud MS, Hassan AM, Shin A et al. (2023) Outcomes of targeted muscle reinnervation and regenerative peripheral nerve interfaces for chronic pain control in the oncologic amputee population. Journal of the American College of Surgeons 237: 644–54	Retrospective cohort study n=63 (28 TMR alone, 4 RPNI alone, 31 combined TMR and RPNI) Upper and lower limbs Primary	At final follow-up, patients had an average NRS score of 1.3 for RLP and 1.9 for PLP. The final average raw PROMIS measures were pain intensity 6.2 (T-score 43.5), pain interference 14.6 (T-score 55.0), and pain behaviour 39.0 (T-score 53.4). Patient opioid use decreased from	Studies with more people or longer follow up are included.

	Follow-up: mean 11 months	86% to 38% and morphine milligram equivalents decreased from a mean of 52.4 preoperatively to 20.2 postoperatively.	
Salminger S, Sturma A, Roche AD et al. (2019) Outcomes, challenges, and pitfalls after targeted muscle reinnervation in high-level amputees: is it worth the effort? Plastic and Reconstructive Surgery 144: 1037e–1043e	Cohort study n=30 Upper limbs Follow-up: at least 6 months	Targeted muscle reinnervation has improved prosthetic control and revolutionised neuroma treatment in upper limb amputees. Still, the rate of abandonment even after targeted muscle reinnervation surgery has been high, and several advances within the biotechnological interface will be needed to improve prosthetic function and acceptance in these patients.	Studies with more people or longer follow up are included.
Souza JM, Cheesborough JE, Ko JH et al. (2014) Targeted muscle reinnervation: a novel approach to postamputation neuroma pain. Clinical Orthopaedics and Related Research 472: 2984–90	Retrospective cohort study n=26 Upper limbs	All patients had TMR to improve myoelectric control. None of the 26 patients who had TMR demonstrated evidence of new neuroma pain after the procedure, and all but 1 of the 15 patients who had preoperative neuroma pain experienced complete relief of pain in the distribution of the transferred nerves.	Studies with more people or longer follow up are included.
Valentine L, Weidman AA, Foppiani J et al. (2024) A national analysis of targeted muscle reinnervation following major upper extremity amputation.	Retrospective database survey (US) n=8,945 upper extremity	The proportion of people who had TMR was low (3.5%). Length of stay was statistically significantly shorter for patients who had TMR compared to those who	Other studies with more relevant outcomes are included.

Plastic and Reconstructive Surgery doi: 10.1097/ PRS.0000000000011439	amputations (310 TMR) Primary TMR	did not (10.6 versus 14.8, p=0.012).	
Valerio IL, Dumanian GA, Jordan SW et al. (2019) Preemptive treatment of phantom and residual limb pain with targeted muscle reinnervation at the time of major limb amputation. Journal of the American College of Surgeons 228: 217–26	Cohort study n=489 (51 TMR) Upper or lower limbs Primary TMR Follow-up: at least 3 months	Patients who had TMR had less PLP and RLP compared with untreated amputee controls, across all subgroups and by all measures. Median "worst pain in the past 24 hours" for the TMR cohort was 1 out of 10 compared to 5 (PLP) and 4 (RLP) out of 10 in the control population (p=0.003 and p<0.001, respectively). Median PROMIS t-scores were lower in TMR patients for both PLP (pain intensity [36.3 versus 48.3], pain behaviour [50.1 versus 56.6], and pain interference [40.7 versus 55.8]) and RLP (pain intensity [30.7 versus 46.8], pain behaviour [36.7 versus 57.3], and pain interference [40.7 versus 57.3]). Targeted muscle reinnervation was associated with 3.03 (PLP) and 3.92 (RLP) times higher odds of decreasing pain severity compared with general amputee participants.	The main results from this study are included in the meta-analysis by Tham et al. (2023).
Vonu PM, Shekouhi R, Crawford K et al. (2024) Targeted muscle reinnervation: factors predisposing to	Retrospective cohort study n=40 (47 limbs)	TMR demonstrated favourable pain score reduction across all studied groups in the cohort. Patients	Small retrospective study.

successful pain score reduction. Annals of Plastic Surgery 92: 426-s431	Upper or lower limbs Primary or secondary TMR	younger than 50 years and females had more dramatic improvements in pain score reduction. This study adds to the existing published literature supporting TMR as the standard of care in neuroma mitigation following major limb amputation.	
Walsh AR, Lu J, Rodriguez E et al. (2023) The current state of targeted muscle reinnervation: a systematic review. Journal of Reconstructive Microsurgery 39: 238–44	Systematic review n=338 (341 limbs) 13 articles Upper or lower limbs Primary or secondary TMR Follow-up: mean 22.3 months	There is a substantial body of evidence that supports the use of TMR to maximise quality of life for limb amputees. Once a novel approach with the potential to ameliorate pain, the evidence suggests that TMR should now be standard of care for patients at the time of amputation or thereafter.	No meta-analysis.
Yuan M, Gallo M, Gallo L et al. (2024) Targeted muscle reinnervation and regenerative peripheral nerve interfaces versus standard management in the treatment of limb amputation: a systematic review and meta-analysis. Plastic Surgery 32 (2) 253–64	Systematic review and meta-analysis n=1,419 (418 TMR or RPNI); 11 studies Primary	Observational study evidence suggests that TMR or RPNI results in a statistically significant reduction in incidence, pain scores and PROMIS scores of PLP and RLP. Decreased incidence of neuromas favoured primary TMR or RPNI, but this did not achieve statistical significance (p=0.07). Included studies had moderate to critical risk of bias.	Review includes RPNI as well as TMR. There is some study overlap with the systematic review by Tham et al. (2023).