

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

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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

Information about the condition, current treatments, unmet need and the procedure is available in [section 2 of NICE's interventional procedures guidance on targeted muscle reinnervation for managing limb amputation pain](#).

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.

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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.

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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 900 TMR procedures from 2 systematic reviews (Tham 2023, Zimbulis 2025), 1 randomised controlled trial (Dumanian 2019), 1 retrospective propensity score-matched study (Shammas 2022), 1 prospective case series (O'Brien 2022), 2 prospective cohort studies (Raasveld 2024a, Raasveld 2024b) and 6 retrospective case series or

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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 reviews (Dumanian 2019; O'Brien 2022 and Chang 2021). There was some overlap in papers between the 2 systematic reviews. 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 13 studies as the key evidence in [table 2](#) and [table 3](#), and lists 31 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 (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 systematic review by Zimbulis (2025) included 11 studies, 8 of which were also in Tham (2023). It compared patient-reported and functional outcomes following amputation with either TMR or standard neurological treatment, and also compared primary and secondary TMR. All studies included were deemed as having low to moderate risk of bias overall.

The randomised controlled trial reported by Dumanian (2019), which was also included in the systematic reviews, 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

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could choose to have TMR. The trial was intended to recruit 200 people, but it was stopped early with recruitment of 28 people, 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 people 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 Shammass (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.

There were 2 prospective cohort studies by Raasveld (2024), 1 on delayed TMR and 1 on primary TMR. They both included people with upper or lower limb amputations with mixed indications for amputation including trauma, infection, vascular, and malignancy. The median age was 54 years in both studies and there was a higher proportion of males. The median follow-up period was 2 years for both studies.

The prospective case series by O'Brien (2022), which was also in the systematic review by Tham (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 (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 (2024) and Li (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 (2021 and 2024) compared TMR with traction neurectomy and muscle implantation. The 2021 study was also included in the systematic review by Tham (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

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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 (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.

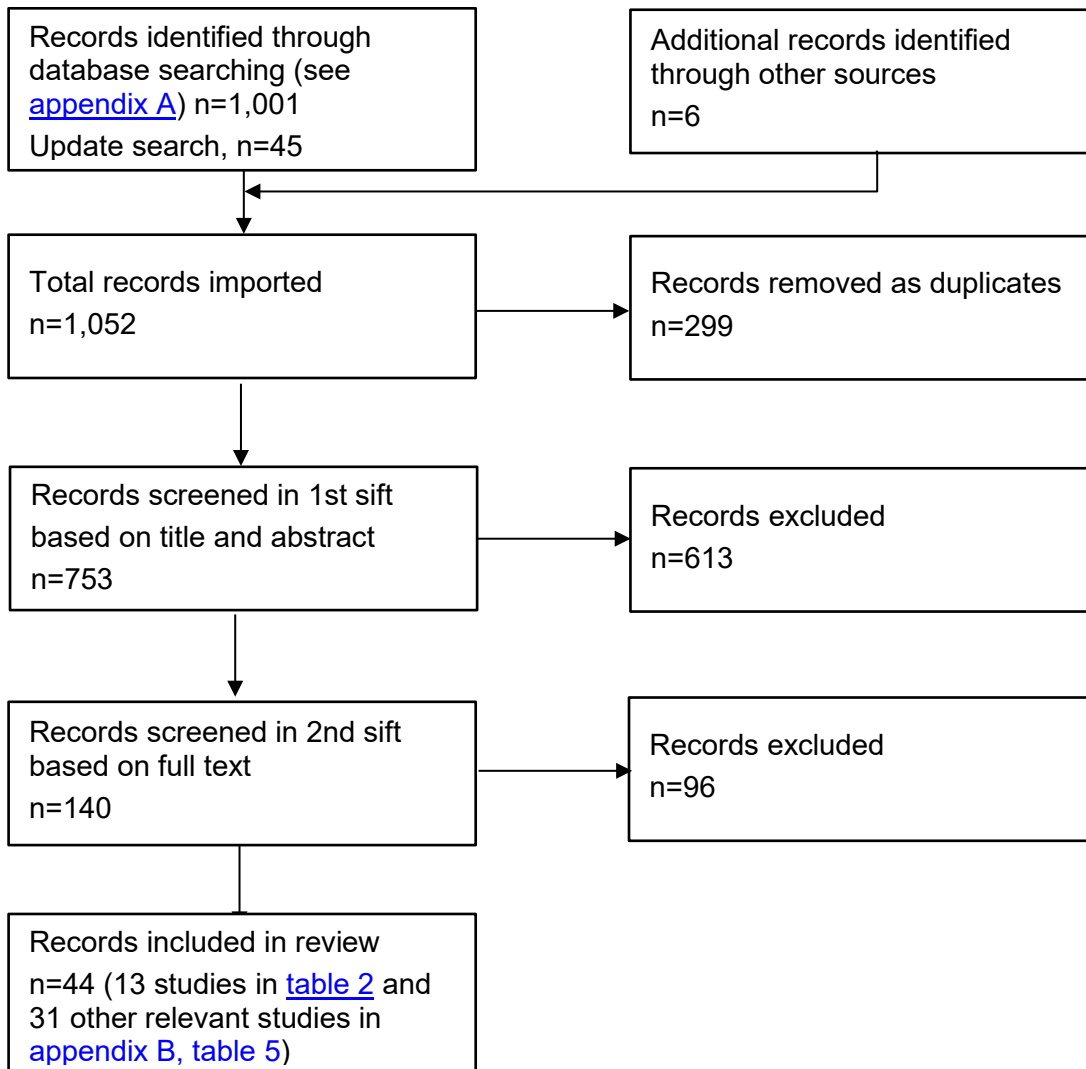
Figure 1 Flow chart of study selection

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 participants ranged from 13 to 100 in the TMR group, and	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.	Mean 17.9 months (range 9.6 to 24.0).

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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 to 438 in the control group. Most studies included amputations from any cause, but 1 study only included people who had amputations because of cancer.			The TMR was done either at the same time as the amputation or later, as a secondary procedure.	
2	Zimbulis A, 2025 Countries of included studies not reported.	n=1,117 (409 TMR, 708 controls; 11 studies) Proportion of males in TMR group ranged from 50 to 85%. Upper or lower limbs.	Systematic review and meta-analysis. Search date: March 2023 Of the 11 included studies, 10 were cohort studies (5 comparative) and 1 was a randomised controlled trial.	Adults who had amputation of an upper or lower limb for any reason. All English language studies published in peer-reviewed journals and comparing the outcomes of TMR against standard neurological	In 6 comparative studies: • TMR (n=216) • Standard neurological treatment (n=708) In the other 5 studies, primary TMR was	Not reported.

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Study no.	First author, date country	Characteristics of people in the study (as reported by the study)	Study design	Inclusion criteria	Intervention	Follow up
				treatment, or the outcomes of primary TMR against secondary TMR, were eligible for inclusion. People who had alternate reinnervation strategies, such as RPNI, were excluded from the comparison.	compared to secondary TMR.	
3	Dumanian G, 2019 US Included in Tham (2023) and Zimbulis (2025)	n=28 (30 limbs) Mean age (years): - TMR=39.6 - Control=45.3 Male (%) - TMR=86% - Control=57%	Randomised controlled trial (single blinded for 1 year). Treatment allocation was done in the operating room using sealed envelopes and a	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	- TMR (n=15 limbs) - Standard neuroma treatment of neuroma excision and muscle burying (n=15 limbs)	Mean (months) - TMR=17.7 - Control=19.3

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Study no.	First author, date country	Characteristics of people in the study (as reported by the study)	Study design	Inclusion criteria	Intervention	Follow up
		71% in both groups were described as Caucasian. 26 lower limbs, 4 upper limbs Trauma was the reason for most (90%) amputations.	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.	after their initial amputation.	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.	
4	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%	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	Below-knee amputation with or without TMR at the same time. A small proportion of TMR procedures (19%) used a	60 days

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Study no.	First author, date country	Characteristics of people in the study (as reported by the study)	Study design	Inclusion criteria	Intervention	Follow up
		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 (26% compared to 48%).		converted to an above-knee amputation, had an incomplete amputation, or had bilateral amputations were excluded from analysis.	2-incision approach. An incisional vacuum-assisted closure at the time of closure was commonly used after TMR.	

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Study no.	First author, date country	Characteristics of people in the study (as reported by the study)	Study design	Inclusion criteria	Intervention	Follow up
5	Raasveld F, 2024a US	n=101 Median age at time of TMR was 54.4 years (IQR 41.6 to 64.9) Female=39% Most amputations were transtibial followed by transfemoral. The most frequent indication for amputation was trauma. Other indications included infection or sepsis, malignancy, a painful or dysfunctional limb, and dysvasculature.	Prospective cohort study	People who had TMR as a separate operation from the index amputation more than 14 days after amputation, at a specialised amputee clinic at a tertiary care centre, were prospectively enrolled. All had a diagnosis of symptomatic neuroma, according to established criteria. For most people, this included a diagnostic nerve block.	Delayed TMR (done more than 14 days after the index amputation).	Median 2 years (IQR 1.1 to 3.4)

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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 median delay between amputation and TMR was 5.7 years (IQR 2.4 to 15.9).				
6	Raasveld F, 2024b US	n=75 Median age at time of TMR=54.4 years (IQR 38.8 to 67.4) Female=36% Most amputations (88%) were lower limbs. The most common indication for amputation was trauma (35%). Other indications included infection (16%), dysvascularity	Prospective cohort study	All included participants were being treated by the Interdisciplinary Care for Amputees Network (ICAN). This includes physicians and physician assistants from the fields of plastic surgery, orthopaedic surgery, physical medicine and rehabilitation, and psychiatry.	Primary TMR	Median=2 years (IQR 1.5 to 2.7)

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Study no.	First author, date country	Characteristics of people in the study (as reported by the study)	Study design	Inclusion criteria	Intervention	Follow up
		(18%), malignancy (12%), dysfunctional limb (14%) and congenital deformity (3%).				
7	O'Brien A, 2022 US Included in Tham (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)	Prospective single-centre case series People 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. People were included if they had completed at least one survey. People were excluded if they were enrolled in concurrent trials for neuropathic pain or had metastatic or	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).

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Study no.	First author, date country	Characteristics of people in the study (as reported by the study)	Study design	Inclusion criteria	Intervention	Follow up
		Upper limb (including shoulder disarticulation)=19% (16/83) Reason for amputation: • Cancer=52% • Infection=14% • Trauma=20% • Ischaemia=1% • Other=14%.		recurrent cancer or open wounds at the time of survey.		
8	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)	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

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Study no.	First author, date country	Characteristics of people in the study (as reported by the study)	Study design	Inclusion criteria	Intervention	Follow up
		Reasons for amputation: • trauma (64%) • peripheral vascular disease (8%) • tumour (6%) • infection (8%) • unknown (14%). Mean ASA score=2.33				
9	Goodyear E, 2024 US	n=103 (105 limbs) Mean age at surgery=53 years Male=58% (61/105) Lower limb=82% (86/105) Upper limb=18% (19/105)	Retrospective cohort study Study period: October 2015 to December 2020	People were excluded if they were younger than 18 years, had a cognitive impairment, were enrolled in another neuropathic pain	Acute (n=73 procedures; 71 people) or delayed (n=32) TMR. Acute TMR was defined as TMR done within 14 days of major extremity amputation. Delayed TMR was	The mean time to survey was 18 months for the acute TMR cohort and 22.9 months for the delayed TMR cohort.

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Study no.	First author, date country	Characteristics of people in the study (as reported by the study)	Study design	Inclusion criteria	Intervention	Follow up
		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%.		trial, or died within 6 months of TMR.	defined as TMR done secondary to the development of a symptomatic neuroma.	

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Study no.	First author, date country	Characteristics of people in the study (as reported by the study)	Study design	Inclusion criteria	Intervention	Follow up
10	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%	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	Acute (n=16 people, 22 limbs) or delayed (n=16 people, 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	Median length of follow-up was 24 months for acute TMR and 21 months for delayed TMR (p=0.65).

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Study no.	First author, date country	Characteristics of people in the study (as reported by the study)	Study design	Inclusion criteria	Intervention	Follow up
		Upper and lower limbs=6%		contraindications to the extra operating time required for the procedure (up to 2 hours) and were expected to survive the injury or disease process leading to the amputation. Delayed TMR was offered to people with significant peripheral nerve component to their chronic amputation pain.	delayed TMR (p<0.001).	
11	Chang B, 2021 US Included in Tham (2023) and	n=200 (100 TMR procedures) Mean age (years) • TMR=59.7 • Non-TMR=58.8	Retrospective, single-centre, cohort study TMR procedures were done between January	The first 100 people who had primary TMR at the time of below-knee amputation were included.	- Below knee amputation with TMR (n=100) - Below knee amputation with traction	For the TMR group, mean follow-up was 9.6 months, compared to 18.5 months for the

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Study no.	First author, date country	Characteristics of people in the study (as reported by the study)	Study design	Inclusion criteria	Intervention	Follow up
	Zimbulis (2025)	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. The mean Charlson Comorbidity Index was 5.3, and 57% of people had a Charlson Comorbidity Index greater than 5.	2018 and December 2019. The control group had amputations between January 2015 and December 2017.	The 100 people who had below knee amputation immediately before the initiation of the TMR protocol were included as a cohort for comparison of outcomes.	neurectomy and muscle implantation of all identified nerves (n=100).	non-TMR group (p<0.01).

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Study no.	First author, date country	Characteristics of people in the study (as reported by the study)	Study design	Inclusion criteria	Intervention	Follow up
12	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.	People who had primary TMR at the time of through- or above-knee amputation were included. People 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).

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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.				
13	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	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 people with and without TMR.	- Primary transtibial amputation with TMR (n=29) - Primary transtibial amputation without TMR (n=83) - Revision transtibial amputation (n=51)	Median=1.2 years (range 0 to 7.2 years).

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Study no.	First author, date country	Characteristics of people in the study (as reported by the study)	Study design	Inclusion criteria	Intervention	Follow up
		revision traumatic amputations or failed limb salvage (n=72, 64%), osteomyelitis or infection (n=31, 28%), oncology (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			Primary TMR was defined by its occurrence at the time of initial amputation or in the setting of the same initial hospitalisation. Of the 51 revision amputations, 23 (21%) were in people who had primary transtibial amputation at the study institution.	

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		ossification or bony prominence, 4 (8%) for instability, 4 (8%) for myodesis or myoplasty failure, and 1 (2%) for seroma.				

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; $I^2 = 51\%$)	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

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First author, date	Efficacy outcomes	Safety outcomes
	Residual limb pain – PROMIS <i>Intensity</i> 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]; $I^2=61\%$) <i>Behavioural</i> 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]; $I^2=87\%$) <i>Interference</i> 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 <i>Intensity</i> 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]; $I^2=61\%$)	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, $p=0.02$). Dumanian et al. (2019) reported no surgical complications (0%).

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First author, date	Efficacy outcomes	Safety outcomes
	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.	
Zimbulis A, 2025	Phantom limb pain	No safety outcomes were reported.

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First author, date	Efficacy outcomes	Safety outcomes
	Phantom limb pain was a primary outcome measure in 7 studies, 2 of which were included in a random effects meta-analysis (Valerio 2019, O'Brien 2021). • PROMIS Pain Intensity PLP scores: mean difference between TMR and control groups= -12.03 (95% CI -13.97 to -10.08; $I^2=0\%$). • PROMIS Pain Behaviour PLP scores: mean difference between TMR and control groups=-9.37 (95% CI -12.25 to -6.49; $I^2=0\%$). • PROMIS Pain Interference PLP scores: mean difference between TMR and control groups= -6.42 (95% CI -12.27 to -0.57). • NRS scores of worst PLP: mean difference between TMR and control groups= -2.52 (95% CI -3.48 to -1.55). Residual limb pain (reported in 5 studies, 2 of which were included in a random effects meta-analysis, Valerio 2019 and O'Brien 2021) • PROMIS Intensity RLP scores: mean difference between TMR and SNT groups= -11.63 (95% CI -17.82 to -5.43; $I^2=70\%$)	

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First author, date	Efficacy outcomes	Safety outcomes
	- PROMIS Pain Behaviour RLP scores: mean difference between TMR and control groups= -11.57 (95% CI -20.46 to -2.68; $I^2=76\%$) - PROMIS Pain Interference RLP scores: mean difference between TMR and control groups= -4.78 (95% CI -10.93 to 1.37). - NRS scores of worst RLP: mean difference between TMR and control groups= -2.61 (95% CI -3.32 to -1.91). Random effects meta-analysis of postoperative VAS pain scores found a mean difference of -1.70 in favour of primary TMR when compared to secondary TMR (95% CI -3.13 to -0.28, $p=0.01$) People having primary TMR had an OR of 2.09 (95% CI 0.30 to 14.32, $p=0.75$) of being “pain-free” post-treatment compared to those having secondary TMR. Symptomatic Neuroma Formation (2 studies) Alexander (2019) reported reductions in both frequency and intensity of neuroma symptoms for TMR compared to standard treatment.	

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First author, date	Efficacy outcomes	Safety outcomes
	Pet (2014) reported that most people having primary TMR and secondary TMR (92% and 87%, respectively) were free of palpation-induced neuroma pain at final follow up. Quality of life (2 studies) Dumanian (2019) reported on NEURO-QOL scores in a cohort of lower extremity amputees, with better scores at final follow-up in those who had TMR. Chang (2021) assessed ambulation status as a measure of functional improvement after surgery and found a statistically significantly higher rate of ambulation in the TMR group compared to controls (90.9% and 70.5% respectively, $p < 0.01$). Opioid use (4 studies) Alexander (2019) reported a 34% reduction in opioid use at 1 year in people who had TMR. O'Brien (2021) reported that 80% of people who had TMR were weaned off opioids at final follow up. When comparing opioid use between primary and secondary TMR, Hoyt (2021) reported a statistically significant decrease in opioid consumption with primary TMR compared to secondary TMR,	

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First author, date	Efficacy outcomes	Safety outcomes
	whereas Reid (2024) found no statistically significant differences between the groups (consumption of opioids at final follow-up had decreased to 21% and 12% in those who had primary and secondary TMR, respectively).	
Dumanian G, 2019	Worst pain score (NRS) in the last 24 hours (0 to 10), at baseline and 1 year (primary outcome); mean (SD) <i>Phantom limb pain</i> • 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) • Mean (Adjusted 95% CI) difference of change scores=3.4 (-0.1 to 6.9) <i>Residual limb pain</i> • 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)	There were no surgical complications.

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First author, date	Efficacy outcomes	Safety outcomes
	Worst pain score (NRS) in the last 24 hours at last follow-up, intention to treat; mean (SD) <i>Phantom limb pain</i> • 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) <i>Residual limb pain</i> • 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) • 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	

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First author, date	Efficacy outcomes	Safety outcomes
	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) <i>Phantom limb pain - intensity</i> • 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) <i>Phantom limb pain – behaviour</i> • Baseline: TMR=58.3 (11.8), control=58.5 (9.7) • 1 year: TMR=50.7 (9.9), control=52.0 (8.4)	

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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) <i>Phantom limb pain – interference</i> • 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) <i>Residual limb pain - intensity</i> • 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) <i>Residual limb pain – behaviour</i> • 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)	

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First author, date	Efficacy outcomes	Safety outcomes
	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) - 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	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)

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First author, date	Efficacy outcomes	Safety outcomes
	• 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	• 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) • 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

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First author, date	Efficacy outcomes	Safety outcomes
		• 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
Raasveld, 2024a	Pain remission (primary outcome - defined as achieving the minimally clinically important difference, using an upper threshold of 3 for the difference in NRS within the 2-year follow-up period)=63.4% (64/101) Those who had pain remission had statistically significantly lower pain over the entire postoperative trajectory (p<0.001).	No safety outcomes were reported.

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First author, date	Efficacy outcomes	Safety outcomes
	67.6% (25/37) of those who did not reach the threshold for pain remission had a statistically significantly lower pain at final follow-up compared to pain at baseline ($p<0.05$). Sustained mild pain, which could be achieved in addition to pain remission, was achieved by 45.8% of people, with 17.8% of these having complete pain disappearance. No patients reported an increase in pain from baseline. Multivariable analysis of factors associated with pain remission • Lower preoperative pain scores: OR=1.6, 95% CI 0.76 to 11.4, $p=0.034$ • Absence of depression: OR=3.3, 95% CI 2.9 to 9.3, $p=0.024$ • No preoperative opioid use: OR=4.4, 95% CI 2.3 to 7.5, $p=0.013$ • Lower Elixhauser Comorbidity Index: OR=2.5, 95% CI 0.63 to 6.1, $p=0.042$	

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First author, date	Efficacy outcomes	Safety outcomes
Raasveld, 2024a	Sustained pain prophylaxis over 2 year follow-up=57.3% (43/75) (defined as well controlled pain if the patient reported an NRS of 3 or less for at least 3 months, until their most recent follow-up) Pain disappearance=26.7% (20/75) Multivariable analysis of factors associated with pain prophylaxis • Absence of psychiatric comorbidities: OR=3.4; 95% CI 1.1 to 5.6, p=0.039 • Distal amputation levels: OR=3.4; 95% CI 0.1 to 4.2, p=0.036 • Lower Elixhauser Comorbidity Index: OR=2.7; 95% CI 0.5 to 3.9, p=0.001 Multivariable analysis of factors associated with pain disappearance • Absence of psychiatric conditions: OR=1.9; 95% CI 0.2 to 3.8, p=0.045 • Distal amputation levels: OR=2.1; 95% CI 0.1 to 5.5, p=0.049	No safety outcomes were reported.

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First author, date	Efficacy outcomes	Safety outcomes
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) • RLP: mean=45.55 (SD 9.31), median=40.7 (IQR 40.7 to 47.9)	No safety outcomes were reported.

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First author, date	Efficacy outcomes	Safety outcomes
	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)	

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First author, date	Efficacy outcomes	Safety outcomes
	• 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) • 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	

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First author, date	Efficacy outcomes	Safety outcomes
	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.	
Kang, 2022	Mean change in NRS at 12 months after TMR <i>Upper limb – neuroma pain (n=10)</i> Change=5.30 (SD 4.62), 95% CI 8.61 to 2.00, $p=0.006$ All pain had resolved at 12 months. <i>Upper limb – phantom limb pain (n=10)</i> 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 participants, 1 was pain free at 12 months and 5 had only mild pain (NRS between 1 and 3). <i>Lower limb – neuroma pain (n=20)</i> Change=4.35 (SD 4.53), 95% CI 6.47 to 2.23, $p<0.0001$	Complications There were 46 complications in 28 out of 40 TMR procedures (70%). Of the 36 people, 13 had more than 1 complication. Complications occurred in 23 lower limb procedures (79%) and 5 upper limb procedures (45%). Number of complications <i>Upper limbs</i> • Infection, $n=4$ • Paraesthesia, $n=1$ • Wound dehiscence, $n=1$

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First author, date	Efficacy outcomes	Safety outcomes
	Of the 20 procedures, 10 resulted in complete resolution of neuroma pain and 2 people 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 people 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 people 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 people (61%, 9 upper limb and 13 lower limb). 91% of these responses indicated overall satisfaction with the procedure at 12 months (9 upper limb and 11 lower limb). However, out of 22 people, only 50% (6 upper limb, 5 lower limb) felt they would have agreed to a prophylactic (preventive) TMR procedure.	• 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 people needed an additional TMR procedure) • Infection, n=7 • Bursa, n=6 • Paraesthesia, n=4 • Wound dehiscence, n=3 • Haematoma, n=2 • Ulceration, n=2 • 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

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First author, date	Efficacy outcomes	Safety outcomes
		limbs and longer if there is any delay to wound healing, to reduce the risk of complications.
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) - Haematoma=3.1% (1/32) - Dehiscence=3.1% (1/32) Minor complications – acute TMR - Superficial dehiscence=11.0% (8/73)

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First author, date	Efficacy outcomes	Safety outcomes
		- 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	<i>Comparison of PROMs between paired baseline and follow-up surveys for delayed TMR</i> 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)	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.

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First author, date	Efficacy outcomes	Safety outcomes
	- Baseline=5.5 (2.5 to 6.8) - 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)	

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First author, date	Efficacy outcomes	Safety outcomes
	- 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) - 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)	

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First author, date	Efficacy outcomes	Safety outcomes
	• 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) • 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	

IP overview: targeted muscle reinnervation for managing limb amputation pain

First author, date	Efficacy outcomes	Safety outcomes
	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 <i>Comparison of acute versus delayed TMR</i> Overall PLP score at 6 months, median (IQR) - Acute TMR=0.0 (0.0 to 1.6) - Delayed TMR=3.4 (1.6 to 4.6), p<0.001	

IP overview: targeted muscle reinnervation for managing limb amputation pain

First author, date	Efficacy outcomes	Safety outcomes
	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)	

IP overview: targeted muscle reinnervation for managing limb amputation pain

First author, date	Efficacy outcomes	Safety outcomes
	• 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) • 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	

IP overview: targeted muscle reinnervation for managing limb amputation pain

First author, date	Efficacy outcomes	Safety outcomes
	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) • 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)	

IP overview: targeted muscle reinnervation for managing limb amputation pain

First author, date	Efficacy outcomes	Safety outcomes
	• 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) • 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)	

IP overview: targeted muscle reinnervation for managing limb amputation pain

First author, date	Efficacy outcomes	Safety outcomes
	- 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) <i>Overall PLP scores=-2.18 (-3.4 to -0.93), $p=0.001$</i> <i>Overall RLP scores=-1.81 (-2.9 to -0.72), $p=0.001$</i> <i>Worst PLP scores=-3.02 (-4.8 to -1.2), $p=0.001$</i> <i>Worst RLP scores=-2.42 (-4.1 to -0.74), $p=0.01$</i> <i>Pain interference=-2.23 (-4.1 to -0.38), $p=0.02$</i> <i>Pain catastrophisation=-7.88 (-16.0 to 0.25), $p=0.06$</i>	
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%, $p=0.02$

IP overview: targeted muscle reinnervation for managing limb amputation pain

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	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%, $p=0.80$

IP overview: targeted muscle reinnervation for managing limb amputation pain

First author, date	Efficacy outcomes	Safety outcomes
	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.	
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, $p=0.64$	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

IP overview: targeted muscle reinnervation for managing limb amputation pain

First author, date	Efficacy outcomes	Safety outcomes
	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	• 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)
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 safety outcomes were reported

IP overview: targeted muscle reinnervation for managing limb amputation pain

First author, date	Efficacy outcomes	Safety outcomes
	• 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	

IP overview: targeted muscle reinnervation for managing limb amputation pain

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 studies included in the systematic reviews (Tham 2023 and Zimbulis 2025), 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 (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 (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 prospective cohort study of 101 people who had delayed TMR more than 14 days after lower or upper limb amputation, pain remission was reported for 63% (64/101) at 2-year follow-up (Raasveld 2024a). Of the 37 people who did not reach the threshold for pain remission, 25 (68%) had a statistically significantly lower pain at follow-up compared to baseline ($p < 0.05$). Sustained mild pain, which could be in addition to pain remission, was reported by 46% of people, with 18% of these having complete pain disappearance.

In the prospective cohort study of 75 people who had primary TMR at the same time as lower or upper limb amputation, sustained pain prophylaxis was reported for 57% (43/75) at 2-year follow-up (Raasveld 2024b). Pain disappearance was reported in 27% (20/75) of people.

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 systematic review by Zimbulis (2025), 4 studies reported on opioid use. In 1 of these, there was a 34% reduction in opioid use at 1 year after TMR. In another, 80% of people who had TMR were weaned off opioids at final follow-up. When comparing primary and secondary TMR, 1 study reported a statistically significant decrease in opioid use for primary TMR compared to secondary TMR and 1 study reported no difference between the groups.

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; $p < 0.001$; Shamma 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 ($p = 0.21$; Shamma 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 ($p = 0.13$; Shamma 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 ($p=0.41$; Shamma 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 ($p=0.34$; Shamma 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 ($p=0.25$; Shamma 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 ($p < 0.001$; Shamma 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.

Fourteen 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 people 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.
- [Prevention of Post Amputation Pain with Targeted Muscle Reinnervation \(PreventPAP trial\)](#) (NL-OMON57141); RCT; the Netherlands; n=203; expected completion date November 2028

Related NICE guidance

Interventional procedures

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

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[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

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2. Zimbulis AJ, An VVG, Symes M et al. (2025) Targeted muscle reinnervation compared to standard peripheral nerve management following amputation: a systematic review and meta-analysis. *Hand* doi:10.1177/15589447241284811
3. 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

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5. Raasveld FV, Mayrhofer-Schmid M, Johnston BR et al. (2024) Pain remission following delayed targeted muscle reinnervation in amputees. *Microsurgery* 44: e31258
6. Raasveld FV, Mayrhofer-Schmid M, Johnston BR et al. (2024) Targeted muscle reinnervation at the time of amputation to prevent the development of neuropathic pain. *Journal of Plastic, Reconstructive & Aesthetic Surgery* 97: 13–22
7. 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
8. 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
9. 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
10. 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
11. 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
12. 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

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13. 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 and updated them on 10/02/2025. 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 EPPIReviewer version 5 (EPPIR5).

Duplicates were removed in EPPIR5 using a 2step 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)	02/08/24	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

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Table 4b Update search results

Database	Date searched	Database platform	Database segment or version	Number of results downloaded
Cochrane Central Register of Controlled Trials (CENTRAL)	10/02/2025	Wiley	Issue 2 of 12, February 2025	6
Cochrane Database of Systematic Reviews (CDSR)	10/02/2025	Wiley	Issue 12 of 12, December 2024	2
Embase	10/02/2025	Ovid	1946 to February 07, 2025	19
INAHTA International HTA Database	10/02/2025	https://database.inahta.org/	-	0
MEDLINE ALL	10/02/2025	Ovid	1974 to February 07, 2025	18

Update search

For the updated searches there was no change to the strategy apart from the date limit [from 02 August 2024 to 28 February 2025]. So, the rerun strategies have not been included.

MEDLINE ALL search strategy

- 1 , targeted muscle reinnervation.tw. , 294
- 2 , TMR.tw. , 2,815

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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

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- 2 , TMR.tw. , 3,214
- 3 , nerve transplantation/ , 5,404
- 4 , (nerve* adj4 (transfer* or transplant* or re-rout* or rerout* or crossover* or dock* or regenerat*)).tw. , 21,279
- 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/ , 2,308
- 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. , 2,271
- 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

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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) 38809
 #28 #17 or #18 or #19 or #20 or #21 or #22 or #23 or #24 or #25 or #26 or #27 51283

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#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

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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 limb amputations.

Intervention or test: targeted muscle reinnervation.

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 reviews by Tham (2023) and Zimbulis (2025).
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,	Studies with more people or longer follow up are included.

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		the use of these reconstructive techniques may enable people to take advantage of new advances in myoelectric prosthetics.	
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.
Best CSW, Kung TA (2024) Current and future directions for upper extremity amputations: comparisons between regenerative peripheral nerve interface and targeted muscle reinnervation surgeries. Clinics in Plastic Surgery 51: 583–92	Review	Pain from symptomatic neuromas is a substantial cause of morbidity in people with upper extremity amputation. Regenerative peripheral nerve interface (RPNI) surgery and targeted muscle reinnervation (TMR) surgery are effective in reducing chronic postamputation pain including residual limb pain and phantom pain. The main difference between RPNI and TMR	Review without a meta-analysis. All relevant cited studies on TMR are already included in the overview.

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		surgeries is the surgical technique; however, both strategies rely on physiological processes such as nerve regeneration and muscle reinnervation.	
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)	Systematic review	For major limb amputation, TMR and RPNI are beneficial	Review includes a variety of techniques for

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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	5 articles on TMR	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.	preventing neuropathic pain and there is no meta-analysis.
EIAbd 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 (2023).
Fulton ZW, Boothby BC, Phillips SA (2022) Targeted muscle	Systematic review	In this systematic review of TMR in the trauma-related	A more recent systematic review with

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reinnervation for trauma-related amputees: a systematic review. Cureus 14: e28474	n=125 6 studies Upper or lower limbs Primary or secondary TMR	amputee population, there was a high rate of neuroma pain 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.	more papers is included.
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 (2023).
Hoyt B, Gibson J, Potter B et al. (2021) Practice patterns and pain outcomes for targeted	Retrospective cohort study n=74	The data suggest that a targeted approach featuring concurrent use of TMR and RPNI	Studies with more people or longer follow up are included.

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muscle reinnervation: an informed approach to targeted muscle reinnervation use in the acute amputation setting. Journal of Bone and Joint Surgery 103: 681–87	TMR, RPNI or both Lower limbs Primary or secondary Follow-up: median 14 months	in the acute setting can be safely used to prevent neuroma pain and avoid revision surgical procedures.	Study is included in systematic review by Tham (2023) and Zimbulis (2025).
Lambie CJ, Moura SP Eftehari 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.
Laizon JC, Boyd KU, Dudek NL (2024) What to expect following targeted muscle reinnervation/regenerative peripheral nerve interface: Pain outcomes in an amputee population. Journal of Plastic, Reconstructive &	Retrospective cohort study n=22 (16 primary, 6 secondary) Follow up: at least 6 months	There appears to be a decrease in pain levels and pain medication use over time in people with major limb amputations who have TMR or RPNI for neuropathic pain management. Several individuals had an increase in pain or	Studies with larger sample size or longer follow up are included.

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Aesthetic Surgery 99: 373–76		required an increase in pain medications in the first 3 months before ultimately seeing an improvement over time. There were better outcomes for primary procedures compared to secondary procedures.	
Mathieu L, Redais C, Diner C et al. (2025) Curative and preemptive treatment of amputee pain by targeted muscle reinnervation: experience from a French military trauma center. European Journal of Trauma and Emergency Surgery 51: 37	Prospective non-randomised comparative study n=45 (18 TMR; 10 primary, 8 secondary) Follow up: median 13 months	The results confirmed the benefits of TMR for the curative treatment of residual limb pain and phantom limb pain. However, within the limits of this small sample size, preemptive TMR did not show added value. TMR appears to be a complex technique that requires a learning curve.	Studies with larger sample size or longer follow up are included.
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	No meta-analysis.

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		management techniques.	
McNamara CT, Iorio ML (2020) Targeted muscle reinnervation: outcomes in treating chronic pain secondary to extremity amputation and phantom limb syndrome. <i>Journal of Reconstructive Microsurgery</i> 36: 235–40	Systematic review n=149 5 articles Upper or lower limbs Primary or secondary TMR	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%). 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 people to 13% over 6 months) operations.	A more recent systematic review is included.
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. <i>Clinical Orthopaedics and Related Research</i> 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 people 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 (2023).
Obinero CG, Green JC, Swiekatowski KR et al. (2024) Surgical	Retrospective case series	The incidence of postoperative complications was	Small case series reporting safety outcomes

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complications after targeted muscle reinnervation at a safety-net hospital. Journal of Reconstructive Microsurgery https://doi.org/10.1055/a-2435-7410	n=32 (18 TMR and RPNI, 11 TMR only and 3 RPNI only) Follow up: median 107.5 days	47%, with infection being the most common (31%), followed by wound dehiscence (25%). One person had a postoperative haematoma (3%). There were no cases of postoperative symptomatic neuroma or reoperation within 6 months. The risk of postoperative complications after lower extremity amputation with TMR, RPNI or both should be weighed against the potential benefits that these techniques offer, including decreased rates of residual and PLP as well as decreased opioid use and cost.	that are already included in the key evidence.
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. People who had early TMR reported reduced pain behaviours and	Studies with more people or longer follow up are included. The main results from this study are included in the meta-analysis by Tham (2023) and Zimbulis (2025).

		interference specific to PLP (50 versus 53 and 41 versus 50, respectively). The PROMIS RLP intensity score was lower in people 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. Study is included in systematic review by Zimbulis (2025).
Raasveld FV, Hao D, Gomez-Eslava B et al. (2024) Predictive value of preoperative pain sketches in lower extremity amputees undergoing secondary targeted muscle reinnervation for treatment of neuropathic pain. Journal of the American College of Surgeons 239: 588–99	Prospective cohort study n=58 (all secondary) Follow up: median 1.4 years	In lower extremity amputees who had secondary TMR, preoperative pain sketches could serve as a helpful tool in predicting pain outcomes. Radiating pain sketches seemed to be associated with worse outcomes and focal pain sketches with the most improvement.	Study focuses on use of preoperative pain sketches.

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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. People with TMR performed acutely had significantly lower VAS pain scores at both intermediate and final follow-up than people 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 Follow-up: mean 11 months	At final follow-up, people 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). Opioid use decreased from 86% to 38% and morphine milligram equivalents decreased from a mean of 52.4 preoperatively to 20.2 postoperatively.	Studies with more people or longer follow up are included.

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 people had TMR to improve myoelectric control. None of the 26 people who had TMR demonstrated evidence of new neuroma pain after the procedure, and all but 1 of the 15 people 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 people who had TMR compared to those who	Other studies with more relevant outcomes are included.

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Plastic and Reconstructive Surgery doi: 10.1097/PRS.00000000000011439	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	People 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 people who had TMR, 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	The main results from this study are included in the meta-analyses by Tham (2023) and Zimbulis (2025).

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		general amputee participants.	
Vonu PM, Shekouhi R, Crawford K et al. (2024) Targeted muscle reinnervation: factors predisposing to successful pain score reduction. <i>Annals of Plastic Surgery</i> 92: 426-s431	Retrospective cohort study n=40 (47 limbs) Upper or lower limbs Primary or secondary TMR	TMR demonstrated favourable pain score reduction across all studied groups in the cohort. People 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.	Small retrospective study.
Walsh AR, Lu J, Rodriguez E et al. (2023) The current state of targeted muscle reinnervation: a systematic review. <i>Journal of Reconstructive Microsurgery</i> 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 people 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-	Systematic review and meta-analysis n=1,419 (418 TMR or RPNI); 11 studies	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	Review includes RPNI as well as TMR. There is some study overlap with the systematic review by Tham (2023).

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analysis. Plastic Surgery 32 (2) 253–64	Primary	favoured primary TMR or RPNI, but this did not achieve statistical significance ($p=0.07$). Included studies had moderate to critical risk of bias.	
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