National Institute for Health and Care Excellence

Final

Fractures (complex): assessment and management

[A] Evidence review for negative pressure wound therapy for temporary closure of open fractures

NICE guideline NG37

Evidence review underpinning recommendation 1.2.31 and research recommendation 1 in the NICE guideline

November 2022

This evidence review was developed by Guideline Development Team B

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1.1 Review question

Is negative pressure wound therapy more clinically and cost effective than other dressings for temporary management of open fractures after surgical debridement (including wound excision) when immediate definitive soft tissue cover has not been performed?

1.1.1 Introduction

Results from the Wound management of Open Lower Limb Fractures (WOLLF) study indicate that negative pressure wound therapy (NPWT) does not provide any benefits in terms of clinical and cost-effectiveness compared to standard dressing therapy, in people with an open fracture of the lower limb.

NICE guideline NG37 currently states in recommendation 1.2.31 that negative pressure wound therapy could be considered after debridement if immediate definitive soft tissue cover has not been performed. This recommendation was based on two small studies considered to be at high risk of bias and the quality of the body of the evidence identified was considered low to very low.

Topic experts consulted during the exceptional surveillance review of the guideline noted that the use of NWTP is widely used in clinical practice for the treatment of open fracture. They highlighted that the results of the WOLFF study are directly applicable to the UK context and may provide stronger evidence in this area than the evidence previously available.

1.1.2 Summary of the protocol

Table 1: PICOS inclusion criteria

Eligibility criterion	Content
Population	Children, young people, and adults with an open long bone fracture who have had surgical debridement (including wound excision) but definitive soft tissue cover has not been performed
Interventions	Negative pressure wound therapy, alone or in combination with antiseptic or antibiotic dressing.
Comparator	Other dressing (including dry, saline, antiseptic, antibiotic, occlusive and biological dressings, and dermal substitutes) without negative pressure wound therapy.
Outcomes	• Function e.g. Lower Extremity Functional scale, Disability rating index or other validated measures • Health-related quality of life e.g. EQ-5D-5L or other validated measures • Wound healing by 6 weeks • Being able to return to life roles • Appearance • Deep infection • Wound infection • Re-operation/amputation • Tissue necrosis • Pain or discomfort • Length of stay • Frequency of dressing/bedding changes

Eligibility criterion	Content
Study type	Randomised controlled trials (RCTs) Cost-effectiveness studies (Systematic reviews of RCTs included for reference checking)

For the full protocol see appendix A.

1.1.3 Methods and process

This evidence review was developed using the methods and process described in Developing NICE guidelines: the manual. Methods specific to this review question are described in the review protocol in appendix A and the methods appendix (appendix K).

Declarations of interest were recorded according to NICE's conflicts of interest policy.

1.1.3.1 Search methods

The searches for the clinical effectiveness evidence were run on 30-06-2022. The following databases were searched: Central Register of Controlled Trials (Wiley), CINAHL (Ebsco), Cochrane Database of Systematic Reviews (Wiley), Embase (Ovid), Emcare (Ovid), Epistemonikos, MEDLINE (Ovid), MEDLINE-in-Process (Ovid) and MEDLINE Epub Ahead-of-Print (Ovid). Full search strategies for each database are provided in appendix B.

The searches for the cost effectiveness evidence were run on 30-06-2022. The following databases were searched: EconLit (Ovid), Embase (Ovid), INAHTA, MEDLINE (Ovid), MEDLINE-in-Process (Ovid) and MEDLINE Epub Ahead-of-Print (Ovid). Full search strategies for each database are provided in appendix B.

A NICE information specialist conducted the searches. The MEDLINE strategy was quality assured by a trained NICE information specialist and all translated search strategies were peer reviewed to ensure their accuracy. Both procedures were adapted from the 2016 PRESS Checklist.

1.1.3.2 Protocol deviations

1. 2 Studies (Sagy 2020 and Rasool 2013) reporting post-hoc analyses relating to granulation. These outcomes were not included in the study protocol but have been extracted into GRADE tables because they may be of interest to the committee, as this outcome was included in the previous evidence review relating to this guideline. The outcomes have been downgraded once for indirectness to reflect this.
2. Three additional studies were identified from reference lists of systematic reviews that appeared to have been eligible for inclusion in the previous version of this review. The studies were not indexed in MEDLINE and therefore were likely not found in the previous searches. These studies were assessed for inclusion in this review. 2 of the 3 studies were included (Gupta 2013, Jayakumar 2013), one was excluded (Sinha 2013 – see appendix I for details of excluded studies along with reasons for exclusion).

1.1.4 Effectiveness evidence

1.1.4.1 Included studies

A systematic search carried out to identify potential studies found 390 references after deduplication (see appendix B for the literature search strategy). Three additional studies were added (see 1.1.3.2) to give a total of 393.

These 393 references were screened at title and abstract level against the review protocol to identify RCTs that matched the PICO. Systematic reviews were also included at this stage

for the purpose of checking the inclusion list for possible additional studies. 359 references were excluded at this level. 10% double screening was undertaken for quality assurance with 100% agreement between the two screeners.

The full texts of 34 studies (including the 3 additional studies described in 1.1.3.2) were ordered for closer inspection. Out of these, 11 papers (describing 9 studies) met the criteria specified in the review protocol (appendix A). For a summary of the 9 included studies see table 2. The 9 studies included two of the additional 3 studies described in 1.1.3.2 (Gupta 2013 and Jayakumar 2013), and both of the studies included in the previous review (Stannard 2009 and Rasool 3013).

The clinical evidence study selection is presented as a PRISMA diagram in appendix C.

See section 1.1.11 References – included studies for the full references of the included studies.

1.1.4.2 Excluded studies

See appendix I for a list of studies excluded at full text along with the reasons for exclusion.

1.1.5 Summary of RCTs included in the effectiveness evidence

Table 2: Summary of RCTs included in the effectiveness evidence review

Study	Setting	Population	Intervention	Comparator	Outcome(s)
Arti (2016)	University hospital, Iran	90 people (15 – 55 years) with grade IIIB fractures.	Intermittent or continuous NPWT	Conventional dressing (no further detail provided)	• Wound healing • Infection • Length of stay Duration of follow up: 1 month
Costa (2018)[1]	24 Major trauma hospitals, UK	625 people (>=16 years) with grade II or III open fracture of the lower limb	NPWT – exact details at discretion of surgeon.	Sterile dressings sealed from external contamination (details were left to the discretion of the healthcare team)	• Superficial surgical site infection at 30 days • Patient-reported Disability Rating Index (DRI): 3, 6, 9, 12 months and 2, 3, 4, 5 years • Health-related quality of life: EQ-5D VAS, EQ-5D MAU, SF-12 PCS, SF-12 MCS at 3, 6, 9, 12 months and ED-5DL-3L and EQ-VAS at 2, 3, 4 and 5 years

Study	Setting	Population	Intervention	Comparator	Outcome(s)
					• Deep infection at 30 days • Wound healing by 6 weeks • Further surgical interventions Length of follow up: 5 years
Gupta (2013)	Krishna Institute of Medical Sciences, India	30 people (over 18 years) with open musculoskeletal injuries in the extremities that required coverage.	Intermittent NPWT	Sterile dressings (no further information reported)	• Infection • Length of hospitalisation • Wound healing by 6 weeks Length of follow up not reported
Jayakumar (2013)	Government medical college hospital, India	50 people (aged 20-60) with grade IIIA and IIIB open fractures of both leg bones	Intermittent NPWT	Sterile dressings (no further information reported)	• Infection • Wound healing by 6 weeks • Length of hospitalisation Length of follow up not reported
Rasool (2013)	Department of Orthopaedics, Pakistan Ordnance Factories Hospital	50 people (age 10-40 years) with grade II, IIIA or IIIB open tibial fracture.	Continuous NPWT	Normal saline dressing	• Wound healing Reported maximum number of days to wound closure was 40 days.
Sagy (2020)	Hospital orthopaedic department, India	100 people (age NR) with primary long bone fractures requiring surgical debridement where closure was not possible.	NPWT	Dressings using combination of H_2O_2, saline and iodine	• Length of hospitalisation • Time to 100% granulation Length of follow up not reported
Sibin (2017)	Government medical college hospital, India	30 patients (over 18 years) with grade III tibia fractures treated by	Intermittent NPWT	Sterile dressings (no further information reported)	• Infection • Length of hospitalisation • Wound healing by 6 weeks

Study	Setting	Population	Intervention	Comparator	Outcome(s)
		external fixation.			Length of follow up not reported
Stannard (2009)	Division of orthopaedic surgery, University of Alabama, USA	58 people (aged over 18) with severe open fracture *(note: includes fracture that are not long bone)*	NPWT	Saline wet-to-moist dressings	• Infection • Health-related quality of life • SF-36 • Deep infection • Acute infection • Amputation Mean follow-up is 28 months, with a range of 14–67 months
Virani 2016	India (no further detail provided)	93 people (aged over 18) with open tibial fractures	NPWT	Daily cleaning, dressing and debridement	• Infection • Deep infection Follow up mean 23 ± 6 weeks

Footnotes

[1] Secondary publications: Costa (2018b), Costa (2022)

See appendix D for full evidence tables.

Table 3: Additional information about included studies

Study (year)	Bone fractured	Gustilo and Anderson classification	Co-interventions	Days until closure/coverage		Details of intervention	Details of comparator	Details of wound management	
				NPWT	Control			NPWT	Control
Arti (2016)	Long bone: Tibia & fibula = 60 (67%) Femur = 20 (22%) Humerus = 5 (5%) Radius & unlna = 5 (5%)	Grade IIIB	Open fracture in both wounds underwent debridement before treatment.	9.7 ± 2.3	11.2 ± 3.1	Sponge foam was placed on the wound and was covered by an adhesive drape. A suction tube was inserted in the dead wound space and connected to the VAC. Negative pressure continued for 10-14 days at 125 mm Hg continuously or intermittently 5 minutes on two minutes off. Wounds were examined weekly. VAC therapy was terminated when adequate granulation base was achieved to allow for change to conventional dressing, split-thickness skin graft, or flap closure.	Conventional dressing (no further detail provided)	Wound dressings were changed usually every 48 hours.	Not reported

Study (year)	Bone fractured	Gustilo and Anderson classification	Co-interventions	Days until closure/coverage		Details of intervention	Details of comparator	Details of wound management	
				NPWT	Control			NPWT	Control
Costa (2018)	Open fractures of the leg. 82% tibia (reported) 18% Femur (implied)	Grade II = 64 (14%) Grade III = 351 (76%) Grade III+IV = 45 (7%)	All participants received a general or regional anaesthetic, wound debridement and fracture treated with either internal or external fixation. After the initial operation, if the open fracture wound could not be closed, patients were randomised to study groups. Both groups of participants then followed standard local post-op management of patients with an open fracture of the leg with an open wound. Normally this meant a second operation between 48 and 72 h after the first, with further	48 - 72 hours, prespecified	49 - 72 hours, prespecified	The dressing used an 'open-cell' solid foam or gauze and an adherent dressing. Exact details of dressing and pressure were left to the discretion of the treating healthcare team. Most of the participants (74%) received pump pressure of 125 mmHg, 17% participants did not and in 9.5% the pressure used is not known. The majority of participants (77%) received continuous NPWT operation; 6% received intermittent use and for 17% the type of use was not known.	Standard non-adhesive dressing layer applied directly to the wound covered by a sealed dressing or bandage at the discretion of the treating surgeon as per routine care.	Both groups of patients then followed the normal postoperative management of patients with an open fracture of the lower limb. This usually involved a 'second-look' operation between 48 and 72 hours, at which time a further debridement was performed and the wound closed with sutures or a soft-tissue reconstruction as necessary. Depending on the specific injury and depending on the treating surgeon's normal practice, the wound may have been redressed again pending further surgery.	

Study (year)	Bone fractured	Gustilo and Anderson classification	Co-interventions	Days until closure/coverage		Details of intervention	Details of comparator	Details of wound management	
				NPWT	Control			NPWT	Control
			debridement performed and the wounds closed or soft tissue reconstruction performed as necessary. Any further dressing to open wounds followed the allocated treatment until definitive closure/cover of the wound.						

Study (year)	Bone fractured	Gustilo and Anderson classification	Co-interventions	Days until closure/coverage		Details of intervention	Details of comparator	Details of wound management	
				NPWT	Control			NPWT	Control
Gupta (2013)	Not reported. Described as fractures in extremities	Not reported. Fractures needed to be open and require coverage procedures.	All ppts treated with tetanus prophylaxis, standard antibiotics and 'other supportive measures'. All underwent wound debridement and fracture fixation.	87% achieved coverage in <3 weeks	20% achieved coverage in <3 weeks	After adequate haemostasis was achieved sterile, open-pore foam dressing (400–600 microns size with hydrophobic open cell structured network) was placed into the wound cavity. The site was then sealed with an adhesive drape covering the foam and tubing and at least three to five centimetres of surrounding healthy tissue to ensure a seal. The pump delivered an intermittent negative pressure of −125mmHg. The cycle was of nine minutes in which pump was on for six minutes and off for three minutes	Sterile dressing. No further information given.	The dressings were changed on third or fourth day depending upon the amount of drain	Not reported.

Study (year)	Bone fractured	Gustilo and Anderson classification	Co-interventions	Days until closure/coverage		Details of intervention	Details of comparator	Details of wound management	
				NPWT	Control			NPWT	Control
Jayakumar (2013)	Described as 'both bones leg'	Grade IIIA and IIIB	All cases were treated with tetanus prophylaxis, standard antibiotics and 'other supportive measures'. All underwent wound debridement and external fixator application	16/20 (80%) covered within 3 weeks	3/20 (15%) covered within 3 weeks.	Polyurethane open celled sponge obtained from an upholstery shop was autoclaved and cut to match the shape of the wound. The pore size of the sponge is approximately between 400- 600 micrometre. A suction tube of a standard negative suction drain of 16 mm ending in a round pad with holes was placed on the sponge and allowed to exit the dressing parallel to the surface of the sponge. The entire dressing was covered by an adherent clear plastic film to make it air tight and connected to the suction drain. This suction drain operates cyclically to get cyclical negative pressure at the wound site.	Sterile dressings. No further information given.	Not reported	Not reported

Study (year)	Bone fractured	Gustilo and Anderson classification	Co-interventions	Days until closure/coverage		Details of intervention	Details of comparator	Details of wound management	
				NPWT	Control			NPWT	Control
Rasool (2013)	Tibia	Grade II, IIIA and IIIB	All patients received irrigation, sharp debridement, tetanus prophylaxis and empirical systemic antibiotics against staphylococci before VAC or saline dressing.	Wound healing (defined as appearance of 100% granulation tissue) in 84% before 20 days and 100% before 30 days.	Wound healing (defined as appearance of 100% granulation tissue) in 4% before 20 days, 52% before 30 days and 100% before 40 days.	Continuous negative pressure of 125mmHg from wall mounted suction machine.	Saline dressing. No further details reported	Change 3 times a week.	Change 3 times a week.

Study (year)	Bone fractured	Gustilo and Anderson classification	Co-interventions	Days until closure/coverage		Details of intervention	Details of comparator	Details of wound management	
				NPWT	Control			NPWT	Control
Sagy (2020)	Tibia = 91 Femur - 9	"Patients with fresh compound fractures where primary closure was not possible and who required surgical debridement"	Patients underwent initial debridement	14.88	25	After adequate hemostasis, a foam band dressing was applied over the wound. The foam dressing was connected to a VAC unit via a drain tube. Sub-atmospheric pressure was delivered to the wound.	A local traditional combination of hydrogen peroxide, normal saline and povidone iodine.	Dressing was changed every 4 days as per VAC application guidelines and wound inspection was conducted at this time	Dressings were changed daily for patients in traditional dressing group by using combination of hydrogen peroxide, normal saline and povidone iodine in a sequential manner

Study (year)	Bone fractured	Gustilo and Anderson classification	Co-interventions	Days until closure/coverage		Details of intervention	Details of comparator	Details of wound management	
				NPWT	Control			NPWT	Control
Sibin (2017)	Tibia	Grade III fractures Grade IIIA = 9 (30%) Grade IIIB = 21 (70%) Grade IIIC were excluded	All patients treated with wound debridement and external fixation followed by application of VAC or sterile dressing. Infected wounds were treated with wound care and parenteral antibiotics based on pus culture and sensitivity report.	66.7% attained wound coverage by 3 weeks	33.3% attained wound coverage by 3 weeks	VAC: • A polyurethane open celled sponge (having pore size approximately between 400-600 mm) obtained from upholstery shop, was cut to match the shape of the wound and autoclaved. •The suction tube of a standard negative suction apparatus was placed on the sponge and allowed to exit the dressing parallel to the surface of the sponge. •The dressing was covered by an adherent clear plastic film. •The apparatus operated cyclically 20 minutes every 2 hours to get cyclical negative pressure at the wound site.	Sterile dressing. No further information given	Not reported	Not reported

Study (year)	Bone fractured	Gustilo and Anderson classification	Co-interventions	Days until closure/coverage		Details of intervention	Details of comparator	Details of wound management	
				NPWT	Control			NPWT	Control
Stannard (2009)	Tibia = 26 Pilon = 8 Femur = 10 Radius = 2 Humerus = 3 Calcaneus = 1 Talus = 1 Ankle = 5 Radius & ulna = 2 Olecranon = 1 Foot = 2	Most participants had Grade IIIA or IIIB fractures. Grade II = 5 (8%) Grade IIIA = 27 (43.5%) Grade IIIB = 27 (43.5%) Grade IIIC = 3 (5%)	All fractures had an irrigation, debridement and skeletal stabilisation of the injury. This was followed by a second surgery that included irrigation and debridement of the open fracture wound within 36-72 hours of the initial procedure. This procedure was repeated as needed until all wounds achieved grade A status (abundant granulation tissue and ready for closure or coverage). All participants received prophylactic IV antibiotics (the type depended on the level of contamination) until 24 h after	3.2	4	NPWT VAC dressing at 125mmHg5. No other details given.	Saline wet to moist dressings. No further details	Open wounds were closed when they achieved a grade A wound (abundant granulation tissue, ready for closure). All others had the assigned dressing replaced and underwent an additional surgical irrigation and debridement 36–72 hours later. This protocol was repeated until the wound achieved a grade A status and was ready for closure or coverage.	

Study (year)	Bone fractured	Gustilo and Anderson classification	Co-interventions	Days until closure/coverage		Details of intervention	Details of comparator	Details of wound management	
				NPWT	Control			NPWT	Control
			closure or coverage.						
Virani 2016	Tibia	Most participants had Grade IIIA or IIIB fractures. Grade II = 5 (11%) Grade IIIA = 15 (34.8%) Grade IIIB = 22 (51.1%) Grade IIIC = 1 (2.3%)	All participants underwent debridement and received perioperative antibiotic coverage. These antibiotics were continued post-operatively. Serial irrigation and debridement was continued till the wounds were ready for closure or coverage.	8.3	9.8 (ns)	Dressing consisted of a custom cut open cell foam and gauze that was put over the wound under an adhesive occlusive dressing. VAC dressing and negative pressure of about 125 mmHg applied intermittently. VAC dressing and negative pressure of about 125 mmHg applied intermittently.	Daily cleaning, dressing and debridement	The wound was opened every fourth day for reapplication of dressing.	Daily cleaning, dressing and debridement

1.1.6 Summary of the effectiveness evidence

Table 4: Summary of effectiveness evidence for short term outcomes

Negative pressure wound therapy (NPWT) compared to standard dressing for open fractures

Patient or population: People with an open fracture of a long bone following surgical debridement but before definitive cover.

Intervention: NPWT **Comparison:** Standard dressing

Outcomes: Short term (less than 6 months)

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	№ of participants (studies)	Certainty of the evidence (GRADE)	Summary of effect
	Risk with Standard dressing	Risk with NPWT				
Wound healing						
Wound healing by 6 weeks	452 per 1,000	**1000 per 1,000** (452 to 1,000)	**RR 2.50** (1.00 to 6.26)	455 (4 RCTs)[a]	⨁◯◯◯ Very low[b,c,h]	Favours NPWT
Wound infection						
Wound infection - Acute infection subgroup	53 per 1,000	**10 per 1,000** (1 to 78)	**RR 0.18** (0.02 to 1.46)	155 (2 RCTs)[e]	⨁◯◯◯ Very low[d,f,g]	Could not differentiate
Wound infection - Deep infection subgroup	105 per 1,000	**65 per 1,000** (40 to 108)	**RR 0.62** (0.38 to 1.03)	705 (4 RCTs)[j]	⨁⨁◯◯ Low[b,h]	Could not differentiate
Wound infection - All infections subgroup	580 per 1,000	**278 per 1,000** (168 to 470)	**RR 0.48** (0.29 to 0.81)	100 (3 RCTs)[j]	⨁◯◯◯ Very low[f,h,k]	Favours NPWT
Superficial surgical site infection	141 per 1,000	**155 per 1,000** (100 to 240)	**RR 1.10** (0.71 to 1.70)	460 (1 RCT)[l]	⨁◯◯◯ Very low[d,m,n]	Could not differentiate
Deep infection by G&I grade						
Deep infection - G&A subgroup analysis - II	not estimable	not estimable	not pooled	5 (1 RCT)[q]	⨁◯◯◯ Very low[g,n,r,s]	Could not differentiate
Deep infection - G&A subgroup analysis - IIIA	417 per 1,000	**67 per 1,000** (8 to 496)	**RR 0.16** (0.02 to 1.19)	27 (1 RCT)[q]	⨁◯◯◯ Very low[g,h,n,r]	Could not differentiate
Deep infection - G&A subgroup analysis - IIIB	333 per 1,000	**57 per 1,000** (7 to 460)	**RR 0.17** (0.02 to 1.38)	27 (1 RCT)[q]	⨁◯◯◯ Very low[d,g,n,r]	Could not differentiate

Negative pressure wound therapy (NPWT) compared to standard dressing for open fractures

Patient or population: People with an open fracture of a long bone following surgical debridement but before definitive cover.

Intervention: NPWT **Comparison:** Standard dressing

Outcomes: Short term (less than 6 months)

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	№ of participants (studies)	Certainty of the evidence (GRADE)	Summary of effect
	Risk with Standard dressing	**Risk with NPWT**				
Deep infection - G&A subgroup analysis - IIIC	500 per 1,000	**250 per 1,000** (20 to 1,000)	**RR 0.50** (0.04 to 7.10)	3 (1 RCT)[q]	⨁◯◯◯ Very low[d,g,n,r]	Could not differentiate
Duration of hospital stay						
Duration of hospital stay [days] [MID 8.7]	The mean duration of hospital stay [days] [MID 8.7] was **0**	MD **7.55 lower** (20.25 lower to 5.15 higher)	-	560 (2 RCT)[t,l]	⨁◯◯◯ Very low[h,c,y]	Could not differentiate
Hospital stay less than 1 month	180 per 1,000	**779 per 1,000** (423 to 1,000)	**RR 4.33** (2.35 to 7.98)	100 (3 RCTs)[j]	⨁⨁⨁◯ Moderate[b]	Favours NPWT
Post-operative pain						
Postoperative pain	47 per 1,000	**35 per 1,000** (15 to 86)	**RR 0.75** (0.31 to 1.84)	460 (1 RCT)[o]	⨁◯◯◯ Very low[d,n,p]	Could not differentiate
Post hoc analyses of granulation tissue proliferation						
Post-hoc - Time for appearance of 100% granulation tissue [MID 1]	The mean post-hoc - Time for appearance of 100% granulation tissue [MID 1] was **0**	MD **9.04 lower** (9.83 lower to 8.25 lower)	-	100 (1 RCT)[t]	⨁◯◯◯ Very low[n,u]	Favours NPWT
Post-hoc - appearance of 100% granulation tissue in less than 21 days	40 per 1,000	**840 per 1,000** (122 to 1,000)	**RR 21.00** (3.05 to 144.39)	50 (1 RCT)[v]	⨁◯◯◯ Very low[n,w,x]	Favours NPWT

*__The risk in the intervention group__ (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).

CI: confidence interval; **MD:** mean difference; **RR:** risk ratio

Negative pressure wound therapy (NPWT) compared to standard dressing for open fractures

Patient or population: People with an open fracture of a long bone following surgical debridement but before definitive cover.

Intervention: NPWT **Comparison:** Standard dressing

Outcomes: Short term (less than 6 months)

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	№ of participants (studies)	Certainty of the evidence (GRADE)	Summary of effect
	Risk with Standard dressing	**Risk with NPWT**				

GRADE Working Group grades of evidence
High certainty: we are very confident that the true effect lies close to that of the estimate of the effect.
Moderate certainty: we are moderately confident in the effect estimate: the true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different.
Low certainty: our confidence in the effect estimate is limited: the true effect may be substantially different from the estimate of the effect.
Very low certainty: we have very little confidence in the effect estimate: the true effect is likely to be substantially different from the estimate of effect.

Explanations

a. Gupta 2013, WOLLF, Jayakumar 2013, Sibin 2017

b. greater than 33.3% of studies at high risk of bias

c. I^2 greater than 66.7%

d. 95% CI crosses both MIDs

e. Stannard 2009, Virani 2016

f. greater than 33% of studies at high risk of bias

g. Stannard 2009 indirectly applicable as not all fractures were long bone.

h. 95% CI crosses one MID

i. Arti 2016, WOLLF, Stannard 2009, Virani 2016

j. Gupta 2013, Jayakumar 2013, Sibin 2017

k. I^2 greater than 33.3% but less than 66.7%

l. WOLLF

m. Some concerns due to attrition and subjective outcome

n. Single study analysis

o. WOLLF trial (Costa 2018, 2018b, 2022)

p. Some concerns due to self-reported outcomes without blinding

q. Stannard 2009

r. Very serious concerns due to lack of information around allocation concealment, self-reported outcome measures where blinding was not possible, and bias in selection of the reported result,

s. No effect size available

t. Sagy 2020

u. Very serious concerns due to concerns around randomisation as there was no information about allocation concealment or the method of randomisation, and concerns around measurement of the outcome as this was likely assessed by unblinded assessors.

v. Rasool 2013

w. Very serious concerns as alternation was used, and it is likely that allocation was not concealed until all participants were enrolled and assigned to interventions. There were also concerns around measurement of the outcome as subjective assessment was likely carried out by an unblinded assessor. There are also no details about a trial protocol,

x. Outcome measure not in PICO for this review

y. greater than 33.3% of studies at moderate or high risk of bias

Table 5: Summary of effectiveness evidence for functional outcomes

Negative pressure wound therapy (NPWT) compared to standard dressing for open fractures

Patient or population: People with an open fracture of a long bone following surgical debridement but before definitive cover.

Intervention: NPWT **Comparison:** Standard dressing

Outcomes: Functional outcomes (measured with DRI)

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	№ of participants (studies)	Certainty of the evidence (GRADE)	Summary of effect
	Risk with Standard dressing	**Risk with NPWT**				
Function - DRI - 3 months assessed with: Disability Rating Index [MID 8]	The mean function - DRI - 3 months was **0**	MD **1.3 lower** (5.75 lower to 3.15 higher)	-	354 (1 RCT)[a]	⨁⨁⨁◯ Moderate[b,c]	Could not differentiate
Function - DRI- 6 months assessed with: Disability Rating Index [MID 8]	The mean function - DRI- 6 months was **0**	MD **2.9 higher** (2.28 lower to 8.08 higher)	-	329 (1 RCT)[a]	⨁⨁◯◯ Low[b,c,d]	Could not differentiate
Function - DRI - 9 months assessed with: Disability Rating Index [MID 8]	The mean function - DRI - 9 months was **0**	MD **3.8 higher** (1.86 lower to 9.46 higher)	-	314 (1 RCT)[a]	⨁⨁◯◯ Low[b,c,d]	Could not differentiate
Function - DRI - 12 months assessed with: Disability Rating Index [MID 8]	The mean function - DRI - 12 months was **0**	MD **3.1 higher** (2.23 lower to 8.43 higher)	-	374 (1 RCT)[a]	⨁⨁◯◯ Low[b,c,d]	Could not differentiate
Function - DRI - 2 years assessed with: Disability Rating Index [MID 8]	The mean function - DRI - 2 years was **0**	MD **2.52 lower** (11.76 lower to 6.72 higher)	-	125 (1 RCT)[a]	⨁⨁◯◯ Low[b,c,d]	Could not differentiate
Function - DRI - 3 years assessed with: Disability Rating Index [MID 8]	The mean function - DRI - 3 years was **0**	MD **0.27 higher** (10.6 lower to 11.14 higher)	-	88 (1 RCT)[a]	⨁◯◯◯ Very low[b,c,e]	Could not differentiate

Negative pressure wound therapy (NPWT) compared to standard dressing for open fractures

Patient or population: People with an open fracture of a long bone following surgical debridement but before definitive cover.

Intervention: NPWT **Comparison:** Standard dressing

Outcomes: Functional outcomes (measured with DRI)

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	№ of participants (studies)	Certainty of the evidence (GRADE)	Summary of effect
	Risk with Standard dressing	**Risk with NPWT**				
Function - DRI - 4 years assessed with: Disability Rating Index [MID 8]	The mean function - DRI - 4 years was **0**	MD **1.56 lower** (10.85 lower to 7.73 higher)	-	122 (1 RCT)[a]	⨁⨁◯◯ Low[b,c,d]	Could not differentiate
Function - DRI - 5 years assessed with: Disability Rating Index [MID 8]	The mean function - DRI - 5 years was **0**	MD **3.52 lower** (11.71 lower to 4.67 higher)	-	131 (1 RCT)[a]	⨁⨁◯◯ Low[b,c,d]	Could not differentiate

***The risk in the intervention group** (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).

CI: confidence interval; **MD:** mean difference; **RR:** risk ratio

GRADE Working Group grades of evidence
High certainty: we are very confident that the true effect lies close to that of the estimate of the effect.
Moderate certainty: we are moderately confident in the effect estimate: the true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different.
Low certainty: our confidence in the effect estimate is limited: the true effect may be substantially different from the estimate of the effect.
Very low certainty: we have very little confidence in the effect estimate: the true effect is likely to be substantially different from the estimate of effect.

Explanations

a. WOLLF trial (Costa 2018, 2018b, 2022)

b. Some concerns due to self-reported outcomes without blinding

c. Single study analysis

d. 95% CI crosses one the MID of 8 points [taken from Costa 2018]

e. 95% confidence interval crosses both MIDs (set at 8 points by Costa 2018)

Table 6: Summary of effectiveness evidence for quality-of-life outcomes

Negative pressure wound therapy (NPWT) compared to standard dressing for open fractures

Patient or population: People with an open fracture of a long bone following surgical debridement but before definitive cover.

Intervention: NPWT **Comparison:** Standard dressing

Outcomes: Health related quality of life

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	№ of participants (studies)	Certainty of the evidence (GRADE)	Summary of effect
	Risk with Standard dressing	**Risk with NPWT**				
HRQoL- EQ-5D-3L (utility) - post-injury [MID 0.15]	The mean hRQoL- EQ-5D-3L (utility) - post-injury [MID 0.15] was **0**	MD **0** (0.06 lower to 0.06 higher)	-	436 (1 RCT)[b]	⨁⨁⨁◯ Moderate[c,d]	Could not differentiate
HRQoL - EQ-5D-3L (utility) - 3 months [MID 0.16]	The mean hRQoL - EQ-5D-3L (utility) - 3 months [MID 0.16] was **0**	MD **0** (0.07 lower to 0.07 higher)	-	327 (1 RCT)[b]	⨁⨁⨁◯ Moderate[c,d]	Could not differentiate
HRQoL - EQ-5D-3L (utility)- 6 months [MID 0.16]	The mean hRQoL - EQ-5D-3L (utility)- 6 months [MID 0.16] was **0**	MD **0** (0.07 lower to 0.07 higher)	-	312 (1 RCT)[b]	⨁⨁⨁◯ Moderate[c,d]	Could not differentiate
HRQoL - EQ-5D-3L (utility)- 9 months [MID 0.15]	The mean hRQoL - EQ-5D-3L (utility)- 9 months [MID 0.15] was **0**	MD **0.03 higher** (0.04 lower to 0.1 higher)	-	298 (1 RCT)[b]	⨁⨁⨁◯ Moderate[c,d]	Could not differentiate
HRQoL - EQ-5D-3L (utility) - 12 months [MID 0.16]	The mean hRQoL - EQ-5D-3L (utility) - 12 months [MID 0.16] was **0**	MD **0.01 higher** (0.06 lower to 0.08 higher)	-	364 (1 RCT)[b]	⨁⨁⨁◯ Moderate[c,d]	Could not differentiate
HRQoL - EQ-5D-3L (utility) - 2 years [MID 0.13]	The mean hRQoL - EQ-5D-3L (utility) - 2 years [MID 0.13] was **0**	MD **0.03 lower** (0.12 lower to 0.06 higher)	-	123 (1 RCT)[b]	⨁⨁⨁◯ Moderate[c,d]	Could not differentiate
HRQoL - EQ-5D-3L (utility) - 3 years [MID 0.16]	The mean hRQoL - EQ-5D-3L (utility) - 3 years [MID 0.16] was **0**	MD **0.04 lower** (0.17 lower to 0.08 higher)	-	87 (1 RCT)[b]	⨁⨁◯◯ Low[a,c,d]	Could not differentiate
HRQoL - EQ-5D-3L (utility) - 4 years [MID 0.14]	The mean hRQoL - EQ-5D-3L (utility) - 4 years [MID 0.14] was **0**	MD **0.06 lower** (0.16 lower to 0.05 higher)	-	119 (1 RCT)[b]	⨁⨁◯◯ Low[a,c,d]	Could not differentiate

Negative pressure wound therapy (NPWT) compared to standard dressing for open fractures

Patient or population: People with an open fracture of a long bone following surgical debridement but before definitive cover.

Intervention: NPWT **Comparison:** Standard dressing

Outcomes: Health related quality of life

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	№ of participants (studies)	Certainty of the evidence (GRADE)	Summary of effect
	Risk with Standard dressing	**Risk with NPWT**				
HRQoL - EQ-5D-3L (utility) - 5 years [MID 0.14]	The mean hRQoL - EQ-5D-3L (utility) - 5 years [MID 0.14] was **0**	MD **0.03 lower** (0.13 lower to 0.07 higher)	-	132 (1 RCT)[b]	⨁⨁⨁◯ Moderate[c,d]	Could not differentiate
HRQoL - EQ-5D VAS - post-injury [MID 12]	The mean hRQoL - EQ-5D VAS - post-injury [MID 12] was **0**	MD **0.91 lower** (5.36 lower to 3.54 higher)	-	433 (1 RCT)[b]	⨁⨁⨁◯ Moderate[c,d]	Could not differentiate
HRQoL - EQ-5D VAS - 3 months [MID 12]	The mean hRQoL - EQ-5D VAS - 3 months [MID 12] was **0**	MD **3.28 higher** (1.55 lower to 8.11 higher)	-	326 (1 RCT)[b]	⨁⨁⨁◯ Moderate[c,d]	Could not differentiate
HRQoL - EQ-5D VAS - 6 months [MID 12]	The mean hRQoL - EQ-5D VAS - 6 months [MID 12] was **0**	MD **0.5 higher** (4.62 lower to 5.62 higher)	-	309 (1 RCT)[b]	⨁⨁⨁◯ Moderate[c,d]	Could not differentiate
HRQoL - EQ-5D VAS - 9 months [MID 12]	The mean hRQoL - EQ-5D VAS - 9 months [MID 12] was **0**	MD **1.7 higher** (3.56 lower to 6.96 higher)	-	295 (1 RCT)[b]	⨁⨁⨁◯ Moderate[c,d]	Could not differentiate
HRQoL - EQ-5D VAS - 12 months [MID 12]	The mean hRQoL - EQ-5D VAS - 12 months [MID 12] was **0**	MD **0.6 higher** (4.22 lower to 5.42 higher)	-	364 (1 RCT)[b]	⨁⨁⨁◯ Moderate[c,d]	Could not differentiate
HRQoL - EQ-5D VAS - 2 years [MID 11]	The mean hRQoL - EQ-5D VAS - 2 years [MID 11] was **0**	MD **2.91 lower** (10.42 lower to 4.6 higher)	-	125 (1 RCT)[b]	⨁⨁⨁◯ Moderate[c,d]	Could not differentiate
HRQoL - EQ-5D VAS - 3 years [MID 10]	The mean hRQoL - EQ-5D VAS - 3 years [MID 10] was **0**	MD **0.07 lower** (9.04 lower to 8.9 higher)	-	87 (1 RCT)[b]	⨁⨁⨁◯ Moderate[c]	Could not differentiate

Negative pressure wound therapy (NPWT) compared to standard dressing for open fractures

Patient or population: People with an open fracture of a long bone following surgical debridement but before definitive cover.

Intervention: NPWT **Comparison:** Standard dressing

Outcomes: Health related quality of life

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	№ of participants (studies)	Certainty of the evidence (GRADE)	Summary of effect
	Risk with Standard dressing	**Risk with NPWT**				
HRQoL - EQ-5D VAS - 4 years [MID 11]	The mean hRQoL - EQ-5D VAS - 4 years [MID 11] was **0**	MD **6.49 lower** (14.18 lower to 1.2 higher)	-	118 (1 RCT)[b]	⨁⨁◯◯ Low[a,c,d]	Could not differentiate
HRQoL - EQ-5D VAS - 5 years [MID 10]	The mean hRQoL - EQ-5D VAS - 5 years [MID 10] was **0**	MD **0.89 lower** (7.88 lower to 6.1 higher)	-	132 (1 RCT)[b]	⨁⨁⨁◯ Moderate[c,d]	Could not differentiate
HRQoL - SF-12 - PCS - 3 months [MID 6]	The mean hRQoL - SF-12 - PCS - 3 months [MID 6] was **0**	MD **0.5 higher** (2.23 lower to 3.23 higher)	-	302 (1 RCT)[b]	⨁⨁⨁◯ Moderate[c,d]	Could not differentiate
HRQoL - SF-12 - PCS - 6 months [MID 8]	The mean hRQoL - SF-12 - PCS - 6 months [MID 8] was **0**	MD **0.1 higher** (3.33 lower to 3.53 higher)	-	288 (1 RCT)[b]	⨁⨁⨁◯ Moderate[c,d]	Could not differentiate
HRQoL - SF-12 - PCS - 9 months [MID 8]	The mean hRQoL - SF-12 - PCS - 9 months [MID 8] was **0**	MD **0.2 higher** (3.75 lower to 4.15 higher)	-	267 (1 RCT)[b]	⨁⨁⨁◯ Moderate[c,d]	Could not differentiate
HRQoL - SF-12 - PCS - 12 months [MID 8]	The mean hRQoL - SF-12 - PCS - 12 months [MID 8] was **0**	MD **0.5 higher** (3.08 lower to 4.08 higher)	-	329 (1 RCT)[b]	⨁⨁⨁◯ Moderate[c,d]	Could not differentiate
HRQoL - SF-12 - MCS - 3 months [MID 5]	The mean hRQoL - SF-12 - MCS - 3 months [MID 5] was **0**	MD **0.4 higher** (1.64 lower to 2.44 higher)	-	302 (1 RCT)[b]	⨁⨁⨁◯ Moderate[c,d]	Could not differentiate
HRQoL - SF-12 - MCS - 6 months [MID 5]	The mean hRQoL - SF-12 - MCS - 6 months [MID 5] was **0**	MD **0.4 lower** (2.57 lower to 1.77 higher)	-	288 (1 RCT)[b]	⨁⨁⨁◯ Moderate[c,d]	Could not differentiate

Negative pressure wound therapy (NPWT) compared to standard dressing for open fractures

Patient or population: People with an open fracture of a long bone following surgical debridement but before definitive cover.

Intervention: NPWT **Comparison:** Standard dressing

Outcomes: Health related quality of life

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	№ of participants (studies)	Certainty of the evidence (GRADE)	Summary of effect
	Risk with Standard dressing	**Risk with NPWT**				
HRQoL - SF-12 - MCS - 9 months [MID 4]	The mean hRQoL - SF-12 - MCS - 9 months [MID 4] was **0**	MD **1.5 higher** (0.56 lower to 3.56 higher)	-	267 (1 RCT)[b]	⨁⨁⨁◯ Moderate[c]	Could not differentiate
HRQoL - SF-12 - MCS - 12 months [MID 4]	The mean hRQoL - SF-12 - MCS - 12 months [MID 4] was **0**	MD **0.4 lower** (2.2 lower to 1.4 higher)	-	329 (1 RCT)[b]	⨁⨁⨁◯ Moderate[c,d]	Could not differentiate

***The risk in the intervention group** (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).

CI: confidence interval; **MD:** mean difference; **RR:** risk ratio

GRADE Working Group grades of evidence
High certainty: we are very confident that the true effect lies close to that of the estimate of the effect.
Moderate certainty: we are moderately confident in the effect estimate: the true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different.
Low certainty: our confidence in the effect estimate is limited: the true effect may be substantially different from the estimate of the effect.
Very low certainty: we have very little confidence in the effect estimate: the true effect is likely to be substantially different from the estimate of effect.

Explanations

a. 95% CI crosses one MID

b. WOLLF trial (Costa 2018, 2018b, 2022)

c. Some concerns due to self-reported outcomes without blinding

d. Single study analysis

Table 7: Summary of effectiveness evidence for reoperation/amputation outcomes

Negative pressure wound therapy (NPWT) compared to standard dressing for open fractures

Patient or population: People with an open fracture of a long bone following surgical debridement but before definitive cover.

Intervention: NPWT **Comparison:** Standard dressing

Outcomes: Re-operation or amuptation

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	№ of participants (studies)	Certainty of the evidence (GRADE)	Summary of effect
	Risk with Standard dressing	Risk with NPWT				
Amputation/reoperation within 12 months - Revision fixation	64 per 1,000	**79 per 1,000** (41 to 154)	**RR 1.24** (0.64 to 2.40)	460 (1 RCT)[c]	⨁◯◯◯ Very low[a,d,e]	Could not differentiate
Amputation/reoperation within 12 months - Wound management	90 per 1,000	**84 per 1,000** (47 to 153)	**RR 0.94** (0.52 to 1.70)	460 (1 RCT)[c]	⨁◯◯◯ Very low[a,d,e]	Could not differentiate
Amputation/reoperation within 12 months - Bone graft	77 per 1,000	**45 per 1,000** (21 to 94)	**RR 0.58** (0.27 to 1.22)	460 (1 RCT)[c]	⨁⨁◯◯ Low[b,d,e]	Could not differentiate
Amputation/reoperation within 12 months - Amputation	26 per 1,000	**18 per 1,000** (5 to 62)	**RR 0.69** (0.20 to 2.41)	460 (1 RCT)[c]	⨁◯◯◯ Very low[a,d,e]	Could not differentiate
Re-operation/amputation - 2-year follow-up - Metalwork removal	152 per 1,000	**238 per 1,000** (114 to 492)	**RR 1.57** (0.75 to 3.25)	125 (1 RCT)[c]	⨁◯◯◯ Very low[a,d,e]	Could not differentiate
Re-operation/amputation - 2-year follow-up - Surgery for nonunion	136 per 1,000	**102 per 1,000** (38 to 269)	**RR 0.75** (0.28 to 1.97)	125 (1 RCT)[c]	⨁◯◯◯ Very low[a,d,e]	Could not differentiate
Re-operation/amputation - 2-year follow-up - Surgery to revise/augment fixation	91 per 1,000	**34 per 1,000** (7 to 162)	**RR 0.37** (0.08 to 1.78)	125 (1 RCT)[c]	⨁◯◯◯ Very low[a,d,e]	Could not differentiate
Re-operation/amputation - 2-year follow-up - Amputation	0 per 1,000	**0 per 1,000** (0 to 0)	**RR 5.58** (0.27 to 113.99)	125 (1 RCT)[c]	⨁◯◯◯ Very low[a,d,e]	Could not differentiate
Re-operation/amputation - 2-year follow-up - Other treatment	106 per 1,000	**102 per 1,000** (36 to 285)	**RR 0.96** (0.34 to 2.69)	125 (1 RCT)[c]	⨁◯◯◯ Very low[a,d,e]	Could not differentiate

Negative pressure wound therapy (NPWT) compared to standard dressing for open fractures

Patient or population: People with an open fracture of a long bone following surgical debridement but before definitive cover.

Intervention: NPWT **Comparison:** Standard dressing

Outcomes: Re-operation or amputation

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	№ of participants (studies)	Certainty of the evidence (GRADE)	Summary of effect
	Risk with Standard dressing	**Risk with NPWT**				
Re-operation/amputation - 3-year follow-up - Metalwork removal	102 per 1,000	**103 per 1,000** (30 to 356)	**RR 1.01** (0.29 to 3.49)	88 (1 RCT)[c]	⨁◯◯◯ Very low[a,d,e]	Could not differentiate
Re-operation/amputation - 3-year follow-up - Surgery for nonunion	61 per 1,000	**11 per 1,000** (1 to 206)	**RR 0.18** (0.01 to 3.36)	88 (1 RCT)[d]	⨁◯◯◯ Very low[a,c,e]	Could not differentiate
Re-operation/amputation - 3-year follow-up - Surgery to revise/augment fixation	41 per 1,000	**51 per 1,000** (8 to 348)	**RR 1.26** (0.19 to 8.52)	88 (1 RCT)[c]	⨁◯◯◯ Very low[a,d,e]	Could not differentiate
Re-operation/amputation - 3-year follow-up - Amputation	0 per 1,000	**0 per 1,000** (0 to 0)	**RR 3.75** (0.16 to 89.59)	88 (1 RCT)[c]	⨁◯◯◯ Very low[a,d,e]	Could not differentiate
Re-operation/amputation - 3-year follow-up - Other treatment	20 per 1,000	**26 per 1,000** (2 to 397)	**RR 1.26** (0.08 to 19.45)	88 (1 RCT)[c]	⨁◯◯◯ Very low[a,d,e]	Could not differentiate
Re-operation/amputation - 4-year follow-up - Metalwork removal	16 per 1,000	**89 per 1,000** (11 to 742)	**RR 5.71** (0.69 to 47.46)	120 (1 RCT)[c]	⨁◯◯◯ Very low[a,d,e]	Could not differentiate
Re-operation/amputation - 4-year follow-up - Surgery for nonunion	47 per 1,000	**71 per 1,000** (17 to 306)	**RR 1.52** (0.36 to 6.52)	120 (1 RCT)[c]	⨁◯◯◯ Very low[a,d,e]	Could not differentiate
Re-operation/amputation - 4-year follow-up - Surgery to revise/augment fixation	0 per 1,000	**0 per 1,000** (0 to 0)	**RR 10.26** (0.56 to 186.53)	120 (1 RCT)[c]	⨁◯◯◯ Very low[a,d,e]	Could not differentiate
Re-operation/amputation - 4-year follow-up - Amputation	16 per 1,000	**6 per 1,000** (0 to 143)	**RR 0.38** (0.02 to 9.15)	120 (1 RCT)[c]	⨁◯◯◯ Very low[a,d,e]	Could not differentiate

Negative pressure wound therapy (NPWT) compared to standard dressing for open fractures

Patient or population: People with an open fracture of a long bone following surgical debridement but before definitive cover.

Intervention: NPWT **Comparison:** Standard dressing

Outcomes: Re-operation or amputation

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	№ of participants (studies)	Certainty of the evidence (GRADE)	Summary of effect
	Risk with Standard dressing	**Risk with NPWT**				
Re-operation/amputation - 4-year follow-up - Other treatment	78 per 1,000	**71 per 1,000** (20 to 253)	**RR 0.91** (0.26 to 3.24)	120 (1 RCT)[c]	⨁◯◯◯ Very low[a,d,e]	Could not differentiate
Re-operation/amputation - 5-year follow-up - Metalwork removal	69 per 1,000	**47 per 1,000** (12 to 188)	**RR 0.68** (0.17 to 2.71)	136 (1 RCT)[c]	⨁◯◯◯ Very low[a,d,e]	Could not differentiate
Re-operation/amputation - 5-year follow-up - Surgery for nonunion	42 per 1,000	**7 per 1,000** (0 to 127)	**RR 0.16** (0.01 to 3.05)	136 (1 RCT)[c]	⨁◯◯◯ Very low[a,d,e]	Could not differentiate
Re-operation/amputation - 5-year follow-up - Surgery to revise/augment fixation	28 per 1,000	**6 per 1,000** (0 to 128)	**RR 0.22** (0.01 to 4.59)	136 (1 RCT)[c]	⨁◯◯◯ Very low[a,d,e]	Could not differentiate
Re-operation/amputation - 5-year follow-up - Amputation	0 per 1,000	**0 per 1,000** (0 to 0)	**RR 3.37** (0.14 to 81.27)	136 (1 RCT)[c]	⨁◯◯◯ Very low[a,d,e]	Could not differentiate
Re-operation/amputation - 5-year follow-up - Other treatment	69 per 1,000	**63 per 1,000** (17 to 223)	**RR 0.90** (0.25 to 3.21)	136 (1 RCT)[c]	⨁◯◯◯ Very low[a,d,e]	Could not differentiate
Re-operation/amputation - any year - Metalwork removal	191 per 1,000	**246 per 1,000** (139 to 437)	**RR 1.29** (0.73 to 2.29)	170 (1 RCT)[c]	⨁◯◯◯ Very low[a,d,e]	Could not differentiate
Re-operation/amputation - any year - Surgery for nonunion	191 per 1,000	**111 per 1,000** (52 to 235)	**RR 0.58** (0.27 to 1.23)	170 (1 RCT)[c]	⨁⨁◯◯ Low[b,d,e]	Could not differentiate
Re-operation/amputation - any year - Surgery to revise/augment fixation	112 per 1,000	**99 per 1,000** (40 to 238)	**RR 0.88** (0.36 to 2.12)	170 (1 RCT)[c]	⨁◯◯◯ Very low[a,c,e]	Could not differentiate

Negative pressure wound therapy (NPWT) compared to standard dressing for open fractures

Patient or population: People with an open fracture of a long bone following surgical debridement but before definitive cover.

Intervention: NPWT **Comparison:** Standard dressing

Outcomes: Re-operation or amuptation

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	№ of participants (studies)	Certainty of the evidence (GRADE)	Summary of effect
	Risk with Standard dressing	Risk with NPWT				
Re-operation/amputation - any year - Amputation	34 per 1,000	**25 per 1,000** (4 to 144)	**RR 0.73** (0.13 to 4.27)	170 (1 RCT)[c]	⨁◯◯◯ Very low[a,d,e]	Could not differentiate
Re-operation/amputation - any year - Other treatment	191 per 1,000	**160 per 1,000** (84 to 309)	**RR 0.84** (0.44 to 1.62)	170 (1 RCT)[c]	⨁◯◯◯ Very low[a,d,e]	Could not differentiate

***The risk in the intervention group** (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).

CI: confidence interval; **MD:** mean difference; **RR:** risk ratio

GRADE Working Group grades of evidence
High certainty: we are very confident that the true effect lies close to that of the estimate of the effect.
Moderate certainty: we are moderately confident in the effect estimate: the true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different.
Low certainty: our confidence in the effect estimate is limited: the true effect may be substantially different from the estimate of the effect.
Very low certainty: we have very little confidence in the effect estimate: the true effect is likely to be substantially different from the estimate of effect.

Explanations

a. 95% CI crosses both MIDs

b. 95% CI crosses one MID

c. WOLLF trial (Costa 2018, 2018b, 2022)

d. Some concerns due to attrition

e. Single study analysis

See appendix F for full GRADE tables for all outcomes.

1.1.7 Economic evidence

1.1.7.1 Included studies

A single search was performed to identify published economic evaluations. This search retrieved 42 studies. Based on title and abstract screening, 40 of the studies could confidently be excluded. One study was excluded following full text review. Thus, one paper was included from the existing literature. See appendix B for literature search strategies and appendix G for a summary of study selection.

1.1.7.2 Excluded studies

See appendix I for a list of references for excluded studies, with reason for exclusion.

1.1.8 Summary of included economic evidence

Table 8: Economic evidence profile

Study	Applicability	Limitations	Other comments	Incremental			Uncertainty
				Cost (£)	Effects (QALYs)	ICER (£/QALY)	
Petrou et al 2019	Directly applicable	Minor limitations	Absolute costs were not presented in the analysis.	£719[(a)] (95% CI: -£1,147 to £2,584)	0.002 (95% CI: -0.054 to 0.059)	£283,997[(a)] (This figure is the ICER value from the paper that has been rounded and uprated to 2022 values. If one instead calculates the ICER by dividing the incremental costs that have been rounded and uprated, £719, by the incremental effects, 0.002, this will return a different ICER value than £283,997.)	Deterministic: None Probabilistic: Probability that NPWT is cost effective at £20,000 threshold was 24.4%. Probability that NPWT is cost effective does not exceed 27% at any threshold. Scenario: Restricting the analysis to patients with full data resulted in NPWT being the dominant treatment (NPWT is less costly and more effective).

(a) Costs uprated to 2022 using EPPI-Centre Cost Converter https://eppi.ioe.ac.uk/costconversion/default.aspx

See appendix H for a full evidence table.

Evidence Statement

- One study was found which compared negative pressure wound therapy (NPWT) with standard wound management. Using NICE's £20,000 per QALY threshold, this study found that NPWT was unlikely to be a cost-effective strategy for improving outcomes in adult patients with severe open fractures of the lower limb.

1.1.9 The committee's discussion and interpretation of the evidence

1.1.9.1. The outcomes that matter most

The committee noted the range of outcomes both short and long term. However, the committee agreed that there were key short-term outcomes relating to patient acceptability and resource use that were not included in the evidence, and that this made it difficult to establish a full picture of the clinical effectiveness of negative pressure wound therapy (NPWT) in the context of open fracture management in the UK system. They agreed that the long-term outcomes in terms of function and quality of life were not as relevant because they did not expect dressing choice for a maximum of 72 hours (before definitive coverage) to have much impact on long term outcomes. They agreed that the shorter-term outcomes were more relevant, but that the most important outcomes would be patient outcomes, such as acceptability of dressings, or resource impact outcomes, such as the number of times the dressing needed to be changed or supplemented and the amount of nursing time that this involved. None of the included studies addressed these issues.

1.1.9.2 The quality of the evidence

The committee were concerned that most of the studies were conducted in the Indian subcontinent and one was conducted in Iran, and that the results of these studies were probably not generalisable to the UK context. In these studies, time to definitive soft tissue closure was not prespecified, and NPWT was used as a primary therapeutic to achieve granulation, rather than as a bridging intervention between initial wound excision and definitive cover. This varies from the UK context, where NPWT would only be used for the recommended 72 hours before definitive cover takes place. Additionally, the committee were concerned that nutritional status is a key factor in wound healing, and although cases of malnourishment are not limited to the Indian subcontinent, it may affect the generalisability of these studies to the UK. The committee were also concerned that Stannard 2009, which was conducted in the US, may not be generalisable to the UK context, as multiple wound excisions were performed, which would not be typical of UK practice. Therefore, the committee felt that they could only use evidence from WOLLF study (Costa 2018, Costa et al 2022 and the Costa 2018 HTA) for the purposes of making any recommendations, as this study was conducted in the UK where NPWT is used as a bridging treatment and coverage is normally performed within 72 hours as specified in this guideline.

As the committee felt that only results from Costa 2018 were applicable to the UK context, they were confident in the single-study analyses for the long-term outcomes of HR-QoL, function, and reoperation/amputation (measured at multiple timepoints from 3 months to 5 years). These results showed no difference between NPWT and standard dressing for all of the long-term outcomes. The committee was confident in evidence of HR-QoL outcomes that were mostly of moderate GRADE certainty and were only downgraded due to concerns around risk of bias from self-reported outcome measures. For the outcomes of function and reoperation/amputation, most of the evidence was low and very low quality respectively, mainly due to risk of bias due to self-reported outcomes and imprecision, and for attrition and imprecision, respectively.

The committee were less certain about the value of evidence relating to short- and medium-term outcomes of wound healing by 6 weeks, wound infection, deep infection and hospital stay, where GRADE rating were mostly low of very low, and heterogeneity was high for the outcome of wound healing by 6 weeks. The high level of heterogeneity for the outcome of wound healing by 6 weeks is likely due to the differences in treatment pathways associated with the studies. In the UK context of the WOLLF study, definitive wound coverage would mostly have been performed within 72 hours, whereas in the other studies, time to definitive coverage was generally longer, or definitive coverage did not take place. This means that differences in time to wound healing between NPWT and conventional dressings would be less for the WOLLF study compared with the other studies in the meta-analysis. In addition

to the low and very low GRADE ratings, the committee did not feel that they could make a recommendation based on studies other than Costa 2018, as these studies used NPWT as a therapeutic intervention rather than a bridging method. The committee discussed that when NPWT is used as a therapeutic intervention, it is more likely to show a greater benefit for infection outcomes compared with studies carried out in the UK context, as the wounds are open for longer, and therefore at increased risk of infection. Similarly, the increased rates of granulation promoted by NPWT would show a greater improvement in hospital stay, and wound healing outcomes in studies where NPWT is used as a therapeutic intervention rather than a bridging intervention. In the UK where definitive coverage is recommended within 72 hours for all open fractures, the impact on hospital stay would not occur.

Overall, the committee were satisfied that the results of Costa 2018 were directly applicable to the UK context and of sufficient quality to be used to update the recommendation. However, from experience, the committee agreed that there were important benefits to using NPWT in some circumstances (for example, in a wound that is exuding heavily), such as fewer associated dressing changes and supplementations. Generally in the UK context NPWT dressings would not need to be changed at all. The committee agreed that this was important, as using dressings that would need to be changed or supplemented would result in pain and distress for patients and would increase associated nursing time. As the important outcomes of patient acceptability and resource use in the first 72 hours from fixation and wound excision were not reported by Costa 2018, the committee did not feel that they could make a strong recommendation against the use of NPWT based on the outcomes reported. The committee agreed that there were other dressings available that could accommodate heavy exudate and not need to be changed during the 72 hours, but it was unclear which of these dressings were the most clinically and cost-effective. The committee discussed whether to make a research recommendation on specific temporary dressing for open fractures after wound excision or excision but before definitive soft tissue cover (see appendix J). Since they could not be sure that this evidence did not already exist (because it was not searched for as part of this update) they agreed to ask stakeholders at consultation,so that when this guideline is updated they can provide clearer guidance on which dressings should be used. Stakeholders did not raise any objection and so the committee proceeded to make a research recommendation.

1.1.9.3 Benefits and harms

There was no evidence that NPWT worsened any of the outcomes described in the protocol when compared with conventional dressings. As described in section 1.1.9.2, the committee only felt able to consider evidence from Costa 2018 to inform the update of the recommendation. Evidence from Costa 2018 showed no improvement in any of the outcomes measured, including function, HR-QoL, reoperation/amputation, post-operative pain, wound healing at 6 weeks, deep infection, and superficial surgical site infection at a range of timepoints from post-injury to 5 years. Therefore, the committee felt that the lack of any evidence of improved relative effectiveness of NPWT vs conventional dressings for any outcomes reported in the WOLLF trial meant that the weak recommendation around use of NPWT in the 2016 guideline should be changed. However, the committee felt that in practice there were benefits to using NPWT that were not captured in the evidence, including reduced dressing and bedding changes (which were not reported in any of the studies), reduced nursing time in the 72 hours following fixation and wound excision, decreased pain, and increased acceptability. Due to the lack of evidence around these outcomes, the committee did not feel able to make a recommendation not to use NPWT. The committee believed from experience that most of the benefit of NPWT came from it being a dressing that would normally remain in situ until definitive coverage, whereas standard dressing might require several changes or supplementations in the same time period. The committee discussed that dressing changes and supplementations can be associated with pain and discomfort and reducing the number of dressing changes or supplementations may reduce distress felt by patients. The committee also discussed that reducing the number of dressing changes or

supplementations would also reduce associated nursing time. They agreed that the key is to avoid desiccation and limit the number of dressing changes, and highlighted that there are dressings available other than NPWT that can be left on for 72 hours. They agreed that part of the effectiveness of a dressing was also due to its proper application. Poorly applied dressings may not be as effective or last as long, and may lead to an increased risk of infection. The committee also noted that there may be cases where it is most appropriate to use NPWT, for example with heavily exuding wounds, and in these cases it should be left to clinician discretion to use NPWT if they deem it more appropriate than conventional dressings. Taking these factors into account, the committee decided that it was more important to recommend to use a dressing that avoids desiccation and reduces the number of dressing changes, without mentioning NPWT due to there being no evidence of effectiveness for the recommendation.

1.1.9.4 Cost effectiveness and resource use

Cost-effectiveness evidence was available from only one study (Petrou 2019), which was based on data from the WOLLF trial (Costa 2018). This study found that NPWT was unlikely to be cost effective for improving outcomes in adult patients with severe open fractures of the lower limb, with a base case ICER of £283,997 (uprated to the year 2022) per QALY gained.

The committee were concerned that cost-effectiveness analysis was based on longer-term DRI outcomes, and it would have been more appropriate to have used important outcomes that were measured in the first 72 hours when NPWT was used as a temporary dressing. The committee felt that the benefits of NPWT are likely to be found during the period that it is being used, and using a 12-month time horizon may mean these benefits would be outweighed by the longer term QALYs. The committee discussed that the additional costs associated with NPWT dressing changes are relatively low, especially when considering other costs associated with complex fractures, and the main reason that the ICER was so high is because there was a very small difference in effectiveness (QALYs) between NPWT and standard dressing.

The committee also discussed that the WOLLF trial began before the publication of NG37, and that although the analysis included 2.05 as the mean number of NPWT dressing changes, it is unlikely that there would be any NPWT dressing changes in current practice. While reducing the number of dressings would reduce the cost, it is unknown what effect this would have on the QALYs. Also, for the ICER to become cost effective at NICE's £20,000 per QALY threshold, the incremental cost would have to drop from £678 to around £40; reducing the number of dressings would not reduce the incremental cost enough for NPWT to be considered cost effective. Therefore, it is unlikely that the number of dressings would affect the conclusions of the analysis.

The committee further discussed that NPWT was dominant under complete case analysis, however, this analysis was only done in a small sample (NPWT n=65; standard dressing n=79). This scenario analysis differs from the base case analysis in that it only used complete case data, whereas the base case used multiple imputation using chained equations to handle missing data. Under these circumstances, it was not preferable to form any policy conclusions or clinical recommendations on the complete case analysis, but the committee were unsure that they could say that NPWT was 'definitely' not cost-effective given their concerns with the analysis. The committee acknowledged that the base case had a significant amount of missing data, but the missingness were handled through a widely recommended multiple imputation techniques that address the inherent biases associated with estimating effects on the basis of complete data. This, in addition to the size of the base case ICER, led to the consensus that NPWT should not be routinely recommended.

1.1.9.5 Other factors the committee took into account

Based on the clinical and cost-effectiveness evidence, the committee did not feel that NPWT should be recommended for all patients, however, it should remain an option for patients who clinicians felt would benefit from the intervention (such as in heavy exuding wounds). The committee agreed that it would be inappropriate to make a recommendation that NPWT should not be routinely used, as they felt that this may deter some clinicians from providing NPWT, which may create variations in care, and prevent access for patients who may benefit from NPWT. The committee also discussed equality considerations and felt that it was important that NPWT could be used as an option for people with learning disabilities or cognitive impairments, children and young people in order to reduce the number of dressing changes and associated distress, and that the recommendation reflects the need for clinicians to be able to make this decision.

1.1.10 Recommendations supported by this evidence review

This evidence review supports recommendation 1.2.31.

1.1.11 References – included studies

1.1.11.1 Effectiveness

Primary publications

Arti, H.; Khorami, M.; Ebrahimi-Nejad, V. (2016) Comparison of negative pressure wound therapy (NPWT) & conventional wound dressings in the open fracture wounds. Pakistan Journal of Medical Sciences 32(1): 65-69

Costa, Matthew L, Achten, Juul, Bruce, Julie et al. (2018) Effect of Negative Pressure Wound Therapy vs Standard Wound Management on 12-Month Disability Among Adults With Severe Open Fracture of the Lower Limb: The WOLLF Randomized Clinical Trial. JAMA 319(22): 2280-2288

Gupta, Ketan; Mundada, A; Patil, A (2013) Comparison of vacuum assisted closure therapy with standard wound therapy for open musculoskeletal injuries. International Journal of Recent Trends in Science and Technology 9(2): 168-170

Jayakumar, M and Ajai, P (2013) A comparative study between primary vacuum assisted closure and conventional sterile dressing in treatment of soft tissue injuries associated with severe open fractures of both bones leg. Kerala Journal of Orthopaedics 26(1)

Rasool G, Ahmed MU, Iqbal M et al. (2013) Vacuum assisted wound closure and normal saline dressing in treatment of Gustilo type II, type IIIa and IIIb open fracture of tibia. Rawal Medical Journal 4(38): 382-384

Sagy, Mohammed, Singh, Jagdeep, Kalia, Anoop et al. (2020) Wound healing of open fractures: comparison of vaccum assisted dressing versus traditonal dressing. International journal of orthopaedic and trauma nursing 36: 100722

Sibin, J; Pullatttu, BR; Jose, FC (2017) Vacuum assisted closure in grade III open tibial fractures. Indian J Appl Res 7

Stannard JP, Volgas DA, Stewart R et al. (2009) Negative pressure wound therapy after severe open fractures: a prospective randomized study. Journal of orthopaedic trauma 23(8): 552-557

Virani, S.R., Dahapute, A.A., Bava, S.S. et al. (2016) Impact of negative pressure wound therapy on open diaphyseal tibial fractures: A prospective randomized trial. Journal of Clinical Orthopaedics and Trauma 7(4): 256-259

Secondary publications

Costa, Matt L, Achten, Juul, Parsons, Nick R et al. (2022) Five-year outcomes for patients sustaining severe fractures of the lower limb : mid-term results from the Wound management for Open Lower Limb Fracture (WOLLF) trial. The bone & joint journal 104b(5): 633-639

Costa, Matthew L, Achten, Juul, Bruce, Julie et al. (2018) Negative-pressure wound therapy versus standard dressings for adults with an open lower limb fracture: the WOLLF RCT. Health technology assessment (Winchester, England) 22(73): 1-162

1.1.11.2 Economic

Petrou, S; Parker, B; Masters, J et al. (2019) Cost-effectiveness of negative-pressure wound therapy in adults with severe open fractures of the lower limb: evidence from the WOLLF randomized controlled trial. The bone and joint journal. 101b(11): 1392-1401

Appendices

Appendix A – Review protocol

Review protocol for negative pressure wound therapy in open fractures after surgical debridement (including wound excision)

ID	Field	Content
1.	Review title	The effectiveness and cost-effectiveness of negative pressure wound therapy compared to standard dressing or wound therapy for temporary management of open fractures after surgical debridement (including wound excision).
2.	Review question	Is negative pressure wound therapy more clinically and cost effective than other dressings for temporary management of open fractures after surgical debridement (including wound excision) when immediate definitive soft tissue cover has not been performed?
3.	Objective	To determine whether negative pressure wound therapy is more clinically and cost effective than other dressings for temporary management of open fractures, after surgical debridement (including wound excision), but before definitive soft tissue cover
4.	Searches	**Systematic reviews** Relevant systematic reviews will be identified during the screening of database search results. High quality, up-to-date systematic reviews may be critically appraised and presented to the committee. In the event that no high quality up to date systematic reviews are identified, the studies Ied in any systematic reviews identified will be checked for potential inclusion in this review. **Database searches** The principal search strategy will be developed in MEDLINE (Ovid interface) and then adapted, as appropriate, for use in the other sources listed, taking into account their size, search

		functionality and subject coverage. The databases will be: • CINAHL • Cochrane Central Register of Controlled Trials (CENTRAL) via Wiley • Cochrane Database of Systematic Reviews (CDSR) via Wiley • EconLit via Ovid • Epistemonikos • Embase via Ovid • EMCARE via Ovid • International HTA Database via INAHTA https://database.inahta.org/ • MEDLINE ALL (including In-Process and Epub-Ahead-of-Print) via Ovid **Database search limits** Database functionality will be used, where available, to exclude: • animal studies • editorials, letters and commentaries • non English language studies Sources will be searched from 13 April 2015 to the current date. Search filters will be used if appropriate for the search and to filter economic searches.
5.	Condition or domain being studied	Assessment and management of open fractures
6.	Population	Inclusion: Children, young people, and adults with an open long bone fracture who have had surgical debridement (including wound excision) but definitive soft tissue cover has not been performed
7.	Intervention/Exposure/Test	Negative pressure wound therapy, alone or in combination with antiseptic or antibiotic dressing.
8.	Comparator/Reference standard/Confounding factors	Other dressing (including dry, saline, antiseptic, antibiotic, occlusive and biological dressings, and dermal substitutes) without negative pressure wound therapy.

9.	Types of study to be included	• RCTs • Systematic reviews of RCTs
10.	Other exclusion criteria	• Wound closure dressings
11.	Context	New evidence from a Health Technology Assessment ('Negative-pressure wound therapy versus standard dressings for adults with an open lower limb fracture: the WOLLF RCT', Costa et al. 2018) indicates that compared with standard dressings, negative pressure wound therapy for open lower limb fractures after surgical debridement does not provide a clinical or economic benefit. The relevant recommendation in the existing guideline ('Consider negative pressure wound therapy after debridement if immediate definitive soft tissue cover has not been performed') was based on 2 small studies considered to be at high risk of bias and the quality of the body of the evidence identified was considered low to very low. The original review question "What is the most clinically and cost-effective temporary dressing or wound therapy in open fractures after wound excision or surgical debridement?" was modified to be specific to NPWT during the surveillance process for this guideline since the new evidence was identified specifically in that area.
12.	Primary outcomes (critical outcomes)	• Function e.g. Lower Extremity Functional scale, Disability rating index or other validated measures • Health-related quality of life e.g. EQ-5D-5L or other validated measures • Wound healing by 6 weeks • Being able to return to life roles • Appearance • Deep infection • Wound infection • Re-operation/amputation

		• Tissue necrosis • Pain or discomfort • Length of stay • Frequency of dressing/bedding changes
13.	Secondary outcomes (important outcomes)	None
14.	Data extraction (selection and coding)	All references identified by the searches and from other sources will be uploaded into EPPI reviewer and de-duplicated. 10% of the abstracts will be reviewed by two reviewers, with any disagreements resolved by discussion or, if necessary, a third independent reviewer. The full text of potentially eligible studies will be retrieved and will be assessed in line with the criteria outlined above. A standardised form will be used to extract data from studies (see Developing NICE guidelines: the manual section 6.2). Study investigators may be contacted for missing data where time and resources allow.
15.	Risk of bias (quality) assessment	Risk of bias for RCTs will be assessed using Cochrane Risk of Bias v.2.0 and for systematic reviews using ROBIS as described in Developing NICE guidelines: the manual.
16.	Strategy for data synthesis	Pairwise meta-analyses will be performed in Cochrane Review Manager V5.3. A pooled relative risk will be calculated for dichotomous outcomes (using the Mantel–Haenszel method) reporting numbers of people having an event. A pooled mean difference will be calculated for continuous outcomes (using the inverse variance method) when the same scale will be used to measure an outcome across different studies. Where different studies presented continuous data measuring the same outcome but using different numerical scales these outcomes will be all converted to the same scale before meta-analysis is conducted on the mean differences. Where outcomes measured the same underlying construct but used different instruments/metrics, data will be

		analysed using standardised mean differences (SMDs, Hedges' g). Fixed effects models will be fitted unless there is significant statistical heterogeneity in the meta-analysis, defined as I2≥50%, or where significant between study heterogeneity in methodology, population, intervention or comparator was identified by the reviewer in advance of data analysis, when random effects models will be used instead. Where 10 or more studies are included as part of a single meta-analysis, a funnel plot will be produced to graphically assess the potential for publication bias. GRADE will be used to assess the quality of the outcomes. Outcomes using evidence from RCTs will be rated as high quality initially and downgraded from this point.
17.	Analysis of sub-groups	Where disaggregation is possible: • Age • Grade of fracture (Gustilo and Anderson) • Time from surgical debridement (including wound excision) to definitive cover • Location of fracture (lower and upper limb) • Type of NPWT (intermittent and continuous pressure) • Comparator (occlusive and non-occlusive dressings) • Type of fracture (frailty and high energy fractures) • Trauma type (single and poly)
18.	Type and method of review	☒ Intervention ☐ Diagnostic ☐ Prognostic ☐ Qualitative ☐ Epidemiologic ☐ Service Delivery ☐ Other (please specify)

19.	Language	English		
20.	Country	England		
21.	Anticipated or actual start date	July 2022.		
22.	Anticipated completion date	Consultation on draft guideline (including publication of draft review): 14/09/22 to 28/09/22		
23.	Stage of review at time of this submission	**Review stage**	**Started**	**Completed**
		Preliminary searches		
		Piloting of the study selection process		
		Formal screening of search results against eligibility criteria		
		Data extraction		
		Risk of bias (quality) assessment		
		Data analysis		
24.	Named contact	**5a. Named contact** NICE Guideline Development Team **5b Named contact e-mail** fracturesupdate@nice.org.uk **5c Organisational affiliation of the review**		

		National Institute for Health and Care Excellence (NICE) and NICE Guideline Development Team.
25.	Review team members	From the NICE Guideline Development Team: • Mr Chris Carmona, technical lead • Dr Sarah Matthews, technical analyst • Ms Steph Armstrong, health economic adviser • Ms Jemma Deane, information specialist • Ms Becky Chadwick, project manager
26.	Funding sources/sponsor	This systematic review is being completed by the NICE Guideline Development Team which is an internal team at NICE.
27.	Conflicts of interest	All guideline committee members and anyone who has direct input into NICE guidelines (including the evidence review team and expert witnesses) must declare any potential conflicts of interest in line wit' NICE's code of practice for declaring and dealing with conflicts of interest. Any relevant interests, or changes to interests, will also be declared publicly at the start of each guideline committee meeting. Before each meeting, any potential conflicts of interest will be considered by the guideline committee Chair and a senior member of the development team. Any decisions to exclude a person from all or part of a meeting will be documented. Any changes to a 'ember's declaration of interests will be recorded in the minutes of the meeting. Declarations of interests will be published with the final guideline.
28.	Collaborators	Development of this systematic review will be overseen by an advisory committee who will use the review to inform the development of evidence-based recommendations in line with section 3 of Developing NICE guidelines: the manual. Members of the guideline committee are available on the NICE website: www.nice.org.uk
29.	Other registration details	No other registrations of this protocol.

30.	Reference/URL for published protocol	
31.	Dissemination plans	NICE may use a range of different methods to raise awareness of the guideline. These include standard approaches such as: • notifying registered stakeholders of publication • publicising the guideline throug' NICE's newsletter and alerts • issuing a press release or briefing as appropriate, posting news articles on the NICE website, using social media channels, and publicising the guideline within NICE.
32.	Keywords	Systematic review; fractures, open [*therapy]; negative-pressure wound therapy [*methods]; quality of life; wound healing; wound infection [prevention & control].
33.	Details of existing review of same topic by same authors	This is a new review question that will update the section 'Definitive dressings after debridement' in NICE Guideline NG37: Fractures (complex): assessment and management (2016)
34.	Current review status	☒ Ongoing ☐ Completed but not published ☐ Completed and published ☐ Completed, published and being updated ☐ Discontinued
35..	Additional information	This review will be used to update the NICE guideline on Fractures (complex): assessment and management.
36.	Details of final publication	www.nice.org.uk

Appendix B – Literature search strategies

Background and development

Search design and peer review

A NICE information specialist conducted the literature searches for the evidence review. The searches were run on 30th June 2022. This search report is compliant with the requirements of PRISMA-S.

The MEDLINE strategy below was quality assured (QA) by a trained NICE information specialist. All translated search strategies were peer reviewed to ensure their accuracy. Both procedures were adapted from the 2016 PRESS Checklist.

The principal search strategy was developed in MEDLINE (Ovid interface) and adapted, as appropriate, for use in the other sources listed in the protocol, taking into account their size, search functionality and subject coverage.

Review management

The search results were managed in EPPI-Reviewer v5. Duplicates were removed in EPPI-R5 using a two-step process. First, automated deduplication is performed using a high-value algorithm. Second, manual deduplication is used to assess 'low-probability' matches. All decisions made for the review can be accessed via the deduplication history.

Prior work

The search strategy was based on the terms used in the NG37 NICE guideline and the Cochrane review:

Iheozor-Ejiofor Z, Newton K, Dumville JC, Costa ML, Norman G, Bruce J. Negative pressure wound therapy for open traumatic wounds. Cochrane Database of Systematic Reviews 2018, Issue 7. Art. No.: CD012522. DOI: 10.1002/14651858.CD012522.pub2.

Modifications were made to these original search strategies for the specifications in the review protocol.

Limits and restrictions

English language limits were applied in adherence to standard NICE practice and the review protocol.

Limits to exclude letters, editorials and news were applied in adherence to standard NICE practice and the review protocol.

The search was limited from 1st April 2015 to 30th June 2022 as defined in the review protocol.

The limit to remove animal studies in the searches was the 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.

Cost effectiveness searches

The following search filters were applied to the search strategies in MEDLINE and Embase to identify cost-effectiveness studies:

- Glanville J et al. (2009) Development and Testing of Search Filters to Identify Economic Evaluations in MEDLINE and EMBASE. Alberta: Canadian Agency for Drugs and Technologies in Health (CADTH)

Several modifications have been made to these filters over the years that are standard NICE practice.

Key decisions

The search strategy was developed to find evidence on for the specified population and intervention in the review protocol. It was adapted for different databases.

Clinical searches

Main search – Databases

Database	Date searched	Database Platform	Database segment or version	No. of results downloaded
Cochrane Central Register of Controlled Trials (CENTRAL)	30/06/2022	Wiley	Issue 6 of 12, June 2022	31
Cochrane Database of Systematic Reviews (CDSR)	30/06/2022	Wiley	Issue 6 of 12, June 2022	1
Embase	30/06/2022	Ovid	Embase 1974 to 2022 June 29	317
Epistemonikos	30/06/2022	Epistemonikos	-	61
MEDLINE	30/06/2022	Ovid	Ovid MIINE(R) 1946 to June 29, 2022	123
MEDLINE-in-Process	30/06/2022	Ovid	OvilEDLINE(R) In-Process & In-Data-Review Citations 1946 to June 29, 2022	0
MEDLINE Epub Ahead-of-Print	30/06/2022	Ovid	Id MEDLINE(R) Epub Ahead of Print June 29, 2022	10

Main search – Additional methods

Database	Date searched	Database Platform	Database segment or version	No. of results downloaded
CINAHL	30/06/2022	EBSCOhost	-	80
Emcare	30/06/2022	Ovid	Ovid Emcare 1995 to 2022 Week 25	126

Re-run search – Databases

Re-run searches were not requested for this update

Search strategy history

Database Medline

e 1 Fractures, Open/ (5765)
2 ((open or compound) adj4 (fracture* or break* or crack* or frx or fx)).tw. (9877)
3 1 or 2 (12202)
4 Negative-Pressure Wound Therapy/ (3704)
5 (npwt or tnp).tw. (4621)
6 (negative adj2 pressure).tw. (10353)
7 Vacuum/ (6245)
8 Suction/ (12961)
9 Drainage/ (45592)
10 (drain* or vac or vacuum* or suction*).tw. (164645)
11 or/4-10 (200795)
12 3 and 11 (437)
13 52oad52tit 12 to english language (346)
14 Animals/ not (Animals/ and Humans/) (4988972)
15 13 not 14 (329)
16 limit 15 to (letter or historical article or comment or editorial or news) (16)
17 15 not 16 (313)
18 limit 17 to ed=20150401-20220630 (123)

Database name: MedliProcess

f 1 Fractures, Open/ (0)
2 ((open or compound) adj4 (fracture* or break* or crack* or frx or fx)).tw. (0)
3 1 or 2 (0)
4 Negative-Pressure Wound Therapy/ (0)
5 (npwt or tnp).tw. (2)
6 (negative adj2 pressure).tw. (4)
7 Vacuum/ (0)
8 Suction/ (0)
9 Drainage/ (0)
10 (drain* or vac or vacuum* or suction*).tw. (25)
11 or/4-10 (28)
12 3 and 11 (0)
13 52oad52tit 12 to english language (0)
14 Animals/ not (Animals/ and Humans/) (0)
15 13 not 14 (0)
16 limit 15 to (letter or historical article or comment or editorial or news) (0)
17 15 not 16 (0)
18 limit 17 to dt=20150401-20220630 (0)

Database name:ne Epubs

g 1 Fractures, Open/ (0)
2 ((open or compound) adj4 (fracture* or break* or crack* or frx or fx)).tw. (153)
3 1 or 2 (153)

4 Negative-Pressure Wound Therapy/ (0)
5 (npwt or tnp).tw. (58)
6 (negative adj2 pressure).tw. (216)
7 Vacuum/ (0)
8 Suction/ (0)
9 Drainage/ (0)
10 (drain* or vac or vacuum* or suction*).tw. (2490)
11 or/4-10 (2677)
12 3 and 11 (10)
13 53oad53tit 12 to english language (10)
14 Animals/ not (Animals/ and Humans/) (0)
15 13 not 14 (10)
16 limit 15 to (letter or historical article or comment or editorial or news) (0)
17 15 not 16 (10)

Database Embase

h 1 open fracture/ (6784)
2 ((open or compound) adj4 (fracture* or break* or crack* or frx or fx)).tw. (12624)
3 1 or 2 (14962)
4 vacuum assisted closure/ (8871)
5 vacuum assisted closure device/ (1140)
6 vacuum/ (16415)
7 suction/ (11992)
8 drain/ or suction drain/ (9472)
9 (npwt or tnp).tw. (7142)
10 (negative adj2 pressure).tw. (15470)
11 (drain* or vac or vacuum* or suction*).tw. (269575)
12 or/4-11 (295951)
13 3 and 12 (707)
14 53oad53tit 13 to english language (601)
15 nonhuman/ not (human/ and nonhuman/) (5012277)
16 14 not 15 (588)
17 (letter or editorial).pt. (1961210)
18 16 not 17 (563)
19 limit 18 to dc=20150401-20220630 (317)

Database name: Cochrane Library (CDSR, CENTRAL)

D Search Hits
#1 MeSH descriptor: [Fractures, Open] this term only 138
#2 (((open or compound) NEAR/4 (fracture* or break* or crack* or frx or fx))):ti,ab,kw 1012
#3 #1 OR #2 1012
#4 MeSH descriptor: [Negative-Pressure Wound Therapy] this term only 259
#5 ((npwt or tnp)):ti,ab,kw 468
#6 ((negative NEAR/2 pressure)):ti,ab,kw 1825
#7 MeSH descriptor: [Vacuum] this term only 160
#8 MeSH descriptor: [Suction] this term only 953
#9 MeSH descriptor: [Drainage] this term only 1724

#10 ((drain* or vac or vacuum* or suction*)):ti,ab,kw 18976
#11 {OR #4-#10} 20070
#12 #3 AND #11 “61
#13 ” "conference":pt or (clinicaltrials or trialsearch):so 599319
#14 #12 NOT #13 with Cochrane Library publication date Between Apr 2015 and Jun 2022, in Cochrane Reviews, Cochrane Protocols 1
#15 #12 NOT #13 with Publication Year from 2015 to 2022, in Trials 31
#16 #14 OR #15 32

Database name: Epistemonikos

(title:((title:(((open OR compound) AND (fracture* OR break* OR crack* OR frx OR fx))) OR abstract:(((open OR compound) AND (fracture* OR break* OR crack* OR frx OR fx)))) AND (title:(((npwt OR tnp OR drain* OR vac OR vacuum* OR suction*) OR (negative AND pressure))) OR abstract:(((npwt OR tnp OR drain* OR vac OR vacuum* OR suction*) OR (negative AND pressure))))) OR abstract:((title:(((open OR compound) AND (fracture* OR break* OR crack* OR frx OR fx))) OR abstract:(((open OR compound) AND (fracture* OR break* OR crack* OR frx OR fx)))) AND (title:(((npwt OR tnp OR drain* OR vac OR vacuum* OR suction*) OR (negative AND pressure))) OR abstract:(((npwt OR tnp OR drain* OR vac OR vacuum* OR suction*) OR (negative AND pressure))))))

Additional search methods

Database name: CINAHL

Search ID#	Search Terms	Search Options	Last Run Via	Results
S13	S3 AN– S11	Limiters - Published Date: 20150401-2022– 631 Expanders - Apply equivalent subject– Search modes - Boolean/Phra–e	Interface - EBSCO Discovery Service– Search Screen - Advanced S–arch Database - Health and care evidence, from Health Education England	886
S12	S3 AND–S11	Expanders - Apply equivalent subject– Search modes - Boolean/Phra–e	Interface - EBSCO Discovery Service– Search Screen - Advanced S–arch Database - Health and care evidence, from Health Education England	Display
S11	S4 OR S5 OR S6 OR S7 OR S8 OR S9 OR–S10	Expanders - Apply equivalent subject– Search modes - Boolean/Phra–e	Interface - EBSCO Discovery Service– Search Screen - Advanced S–arch Database - Health and care evidence, from Health Education England	Display
S10	TI ((drain* or vac or vacuum* or suction*)) OR AB ((drain* or vac or vacuum* or suction–))	Expanders - Apply equivalent subject– Search modes - Boolean/Phra–e	Interface - EBSCO Discovery Service– Search Screen - Advanced S–arch Database - Health and care evidence, from Health Education England	D“splay
S”	(MH "Draina–e")	Expanders - Apply equivalent subject– Search modes - Boolean/Phra–e	Interface - EBSCO Discovery Service– Search Screen - Advanced S–arch Database - Health and care evidence, from Health Education England	D“splay
”S7	(MH "Vacu–m")	Expanders - Apply equivalent subject– Search modes - Boolean/Phra–e	Interface - EBSCO Discovery Service– Search Screen - Advanced S–arch Database - Health and care evidence, from Health Education England	Display

S6	TI (negative N2 pressure) OR AB (negative N2 press–re)	Expanders - Apply equivalent subject– Search modes - Boolean/Phra–e	Interface - EBSCO Discovery Service– Search Screen - Advanced S–arch Database - Health and care evidence, from Health Education England	Display
S5	TI ((npwt or tnp)) OR AB ((npwt or tn–))	Expanders - Apply equivalent subject– Search modes - Boolean/Phra–e	Interface - EBSCO Discovery Service– Search Screen - Advanced S–arch Database - Health and care evidence, from Health Education England	D“splay
S4	(MH "Negative Pressur” Wound Thera–y")	Expanders - Apply equivalent subject– Search modes - Boolean/Phra–e	Interface - EBSCO Discovery Service– Search Screen - Advanced S–arch Database - Health and care evidence, from Health Education England	Display
S3	S1 O– S2	Expanders - Apply equivalent subject– Search modes - Boolean/Phra–e	Interface - EBSCO Discovery Service– Search Screen - Advanced S–arch Database - Health and care evidence, from Health Education England	Display
S2	TI (((open or compound) N4 (fracture* or break* or crack* or frx or fx))) OR AB (((open or compound) N4 (fracture* or break* or crack* or frx or fx–))	Expanders - Apply equivalent subject– Search modes - Boolean/Phra–e	Interface - EBSCO Discovery Service– Search Screen - Advanced S–arch Database - Health and care evidence, from Health Education England	D“splay
S1	(MH ""ractures, Op–n")	Expanders - Apply equivalent subject– Search modes - Boolean/Phra–e	Interface - EBSCO Discovery Service– Search Screen - Advanced S–arch Database - Health and care evidence, from Health Education England	

Database Emcare

i 1 open fracture/ (3045)
2 ((open or compound) adj4 (fracture* or break* or crack* or frx or fx)).tw. (5187)
3 1 or 2 (6064)

4 vacuum assisted closure/ (3084)
5 vacuum assisted closure device/ (191)
6 vacuum/ (5425)
7 suction/ (2996)
8 drain/ or suction drain/ (1110)
9 (npwt or tnp).tw. (1216)
10 (negative adj2 pressure).tw. (4131)
11 (drain* or vac or vacuum* or suction*).tw. (44016)
12 or/4-11 (49914)
13 3 and 12 (281)
14 57oad57tit 13 to english language (241)
15 nonhuman/ not (human/ and nonhuman/) (447092)
16 14 not 15 (234)
17 (letter or editorial).pt. (674426)
18 16 not 17 (222)
19 limit 18 to dc=20150401-20220630 (126)

Cost-effectiveness searches

Main search – Databases

Database	Date searched	Database Platform	Database segment or version	No. of results downloaded
EconLit	30/06/2022	OVID	Econlit 1886 to June 23, 2022	0
Embase	30/06/2022	Ovid	Embase 1974 to 2022 June 29	38
INAHTA	30/06/2022	INAHTA	-	1
MEDLINE	30/06/2022	OvIOvid MEDLINE(R) 1946 to June 29, 2022	15	
MEDLINE-in-Process	30/06/2022	Id	Ovid MEDLINE(R) In-Process & In-Data-Review Citations 1946 to June 29, 2022	0
MEDLINE Epub Ahead-of-Print	30/06/2022	Ovid	Ovid MEDLINE(R) Epub Ahead of Print June 29, 2022	2

Re-run search – Databases

Re-runs were not requested for this update search

Search strategy history

Da name: Medline

j 1 Fractures, Open/ (5765)
2 ((open or compound) adj4 (fracture* or break* or crack* or frx or fx)).tw. (9877)
3 1 or 2 (12202)
4 Negative-Pressure Wound Therapy/ (3704)
5 (npwt or tnp).tw. (4621)
6 (negative adj2 pressure).tw. (10353)
7 Vacuum/ (6245)
8 Suction/ (12961)
9 Drainage/ (45592)
10 (drain* or vac or vacuum* or suction*).tw. (164645)
11 or/4-10 (200795)
12 3 and 11 (437)
13 Economics“ (27455)
14 exp "Co”ts and Cost Analysis"/ (258796)
15 Economics, Dental/ (1920)
16 exp Economics, Hospital/ (25592)
17 exp Economics, Medical/ (14343)
18 Economics, Nursing/ (4013)
19 Economics, Pharmaceutical/ (3070)
20 Budgets/ (11621)

21 exp Models, Economic/ (16124)
22 Markov Chains/ (15735)
23 Monte Carlo Method/ (31377)
24 Decision Trees/ (11978)
25 econom$.tw. (293810)
26 cba.tw. (10326)
27 cea.tw. (22820)
28 cua.tw. (1099)
29 markov$.tw. (21575)
30 (monte adj carlo).tw. (34480)
31 (decision adj3 (tree$ or analys$)).tw. (18501)
32 (cost or costs or costing$ or costly or costed).tw. (548508)
33 (price$ or pricing$).tw. (39616)
34 budget$.tw. (27101)
35 expenditure$.tw. (57161)
36 (value adj3 (money or monetary)).tw. (2547)
37 (pharmacoeconomic$ or (pharmaco adj economic$)).tw. (3800)
38 or/13-37 (1084776)
39 Cost-Benefit Analysis/ (90063)
40 Quality-Adjusted Life Years/ (14907)
41 Markov Chains/ (15735)
42 exp Models, Economic/ (16124)
43 cost*.ti. (118601)
44 (cost* adj2 utilit*).tw. (5976)
45 (cost* adj2 (effective* or assess* or evaluat* or analys* or model* or benefit* or threshold* or quality or expens* or saving* or reduc*)).tw. (208050)
46 (economic* adj2 (evaluat* or assess* or analys* or model* or outcome* or benefit* or threshold* or expens* or saving* or reduc*))59oad59ti35494)
47 (qualit* adj2 adjust* adj2 life*).tw. (14122)
48 QALY*.tw. (11211)
49 (incremental* adj2 cost*).tw. (13707)
50 ICER.tw. (4421)
51 utilities.tw. (7115)
52 markov*.tw. (21575)
53 (dollar* or USD or cents or pound or pounds or GBP or sterling* or pence or euro or euros or yen or JPY).tw. (44050)
54 ((utility or effective*) adj2 analys*).tw. (19377)
55 (willing* adj2 pay*).tw. (7130)
56 (EQ5D* or EQ-5D*).tw. (9729)
57 ((euroqol or euro-qol or euroquol or euro-quol or euroco“ ”r euro-col) adj3 ("5" or five)59oad59tio569)
58 (european“ ”dj2 quality adj3 ("5" or five)).tw. (491)
59 or/39-58 (388826)
60 38 or 59 (1127388)
61 12 and 60 (3059oad59ti limit 61 to english language (25)
63 Animals/ not (Animals/ and Humans/) (4988972)
64 62 not 63 (24)
65 limit 64 to (letter or historical article or comment or editorial or news) (0)
66 64 not 65 (24)
67 limit 66 to ed=20150401-20220630 (15)

Database nameine in Process

k 1 Fractures, Open/ (0)
2 ((open or compound) adj4 (fracture* or break* or crack* or frx or fx)).tw. (0)
3 1 or 2 (0)
4 Negative-Pressure Wound Therapy/ (0)
5 (npwt or tnp).tw. (2)
6 (negative adj2 pressure).tw. (4)
7 Vacuum/ (0)
8 Suction/ (0)
9 Drainage/ (0)
10 (drain* or vac or vacuum* or suction*).tw. (25)
11 or/4-10 (28)
12 3 and 11 (0)
13 Econo“ics/ (0)
14 exp "Co”ts and Cost Analysis"/ (0)
15 Economics, Dental/ (0)
16 exp Economics, Hospital/ (0)
17 exp Economics, Medical/ (0)
18 Economics, Nursing/ (0)
19 Economics, Pharmaceutical/ (0)
20 Budgets/ (0)
21 exp Models, Economic/ (0)
22 Markov Chains/ (0)
23 Monte Carlo Method/ (0)
24 Decision Trees/ (0)
25 econom$.tw. (52)
26 cba.tw. (0)
27 cea.tw. (1)
28 cua.tw. (0)
29 markov$.tw. (8)
30 (monte adj carlo).tw. (7)
31 (decision adj3 (tree$ or analys$)).tw. (2)
32 (cost or costs or costing$ or costly or costed).tw. (82)
33 (price$ or pricing$).tw. (7)
34 budget$.tw. (2)
35 expenditure$.tw. (3)
36 (value adj3 (money or monetary)).tw. (3)
37 (pharmacoeconomic$ or (pharmaco adj economic$)).tw. (0)
38 or/13-37 (141)
39 Cost-Benefit Analysis/ (0)
40 Quality-Adjusted Life Years/ (0)
41 Markov Chains/ (0)
42 exp Models, Economic/ (0)
43 cost*.ti. (12)
44 (cost* adj2 utilit*).tw. (3)
45 (cost* adj2 (effective* or assess* or evaluat* or analys* or model* or benefit* or threshold* or quality or expens* or saving* or reduc*)).tw. (30)
46 (economic* adj2 (evaluat* or assess* or analys* or model* or outcome* or benefit* or threshold* or expens* or saving* or redu60oad60tiw. (9)
47 (qualit* adj2 adjust* adj2 life*).tw. (6)
48 QALY*.tw. (6)
49 (incremental* adj2 cost*).tw. (9)
50 ICER.tw. (6)

51 utilities.tw. (3)
52 markov*.tw. (8)
53 (dollar* or USD or cents or pound or pounds or GBP or sterling* or pence or euro or euros or yen or JPY).tw. (7)
54 ((utility or effective*) adj2 analys*).tw. (7)
55 (willing* adj2 pay*).tw. (3)
56 (EQ5D* or EQ-5D*).tw. (2)
57 ((euroqol or euro-qol or euroquol or euro-quol or euroco“ ”r euro-col) adj3 ("5" or fi61oad61tio (2)
58 (european“ ”dj2 quality adj3 ("5" or five)).tw. (0)
59 or/39-58 (45)
60 38 or 59 (146)
61 12 and 60 (061oad61ti limit 61 to english language (0)
63 Animals/ not (Animals/ and Humans/) (0)
64 62 not 63 (0)
65 limit 64 to (letter or historical article or comment or editorial or news) (0)
66 64 not 65 (0)
67 limit 66 to dt=20150401-20220630 (0)

Database Medline Epubs

l 1 Fractures, Open/ (0)
2 ((open or compound) adj4 (fracture* or break* or crack* or frx or fx)).tw. (153)
3 1 or 2 (153)
4 Negative-Pressure Wound Therapy/ (0)
5 (npwt or tnp).tw. (58)
6 (negative adj2 pressure).tw. (214)
7 Vacuum/ (0)
8 Suction/ (0)
9 Drainage/ (0)
10 (drain* or vac or vacuum* or suction*).tw. (2488)
11 or/4-10 (2672)
12 3 and 11 (10)
13 Econo“ics/ (0)
14 exp "Co”ts and Cost Analysis"/ (0)
15 Economics, Dental/ (0)
16 exp Economics, Hospital/ (0)
17 exp Economics, Medical/ (0)
18 Economics, Nursing/ (0)
19 Economics, Pharmaceutical/ (0)
20 Budgets/ (0)
21 exp Models, Economic/ (0)
22 Markov Chains/ (0)
23 Monte Carlo Method/ (0)
24 Decision Trees/ (0)
25 econom$.tw. (7613)
26 cba.tw. (48)
27 cea.tw. (231)
28 cua.tw. (20)
29 markov$.tw. (602)
30 (monte adj carlo).tw. (838)
31 (decision adj3 (tree$ or analys$)).tw. (628)

32 (cost or costs or costing$ or costly or costed).tw. (12719)
33 (price$ or pricing$).tw. (1043)
34 budget$.tw. (549)
35 expenditure$.tw. (1045)
36 (value adj3 (money or monetary)).tw. (71)
37 (pharmacoeconomic$ or (pharmaco adj economic$)).tw. (45)
38 or/13-37 (21823)
39 Cost-Benefit Analysis/ (0)
40 Quality-Adjusted Life Years/ (0)
41 Markov Chains/ (0)
42 exp Models, Economic/ (0)
43 cost*.ti. (1815)
44 (cost* adj2 utilit*).tw. (203)
45 (cost* adj2 (effective* or assess* or evaluat* or analys* or model* or benefit* or threshold* or quality or expens* or saving* or reduc*)).tw. (5052)
46 (economic* adj2 (evaluat* or assess* or analys* or model* or outcome* or benefit* or threshold* or expens* or saving* or reduc*62oad62ti (980)
47 (qualit* adj2 adjust* adj2 life*).tw. (427)
48 QALY*.tw. (341)
49 (incremental* adj2 cost*).tw. (369)
50 ICER.tw. (144)
51 utilities.tw. (151)
52 markov*.tw. (602)
53 (dollar* or USD or cents or pound or pounds or GBP or sterling* or pence or euro or euros or yen or JPY).tw. (806)
54 ((utility or effective*) adj2 analys*).tw. (552)
55 (willing* adj2 pay*).tw. (244)
56 (EQ5D* or EQ-5D*).tw. (358)
57 ((euroqol or euro-qol or euroquol or euro-quol or euroco“ ”r euro-col) adj3 ("5" or fiv62oad62tio(99)
58 (european“ ”dj2 quality adj3 ("5" or five)).tw. (23)
59 or/39-58 (7948)
60 38 or 59 (22743)
61 12 and 60 (262oad62ti limit 61 to english language (2)
63 Animals/ not (Animals/ and Humans/) (0)
64 62 not 63 (2)
65 limit 64 to (letter or historical article or comment or editorial or news) (0)
66 64 not 65 (2)

Da name: Embase

m 1 open fracture/ (6784)
2 ((open or compound) adj4 (fracture* or break* or crack* or frx or fx)).tw. (12624)
3 1 or 2 (14962)
4 vacuum assisted closure/ (8871)
5 vacuum assisted closure device/ (1140)
6 vacuum/ (16415)
7 suction/ (11992)
8 drain/ or suction drain/ (9472)
9 (npwt or tnp).tw. (7142)

10 (negative adj2 pressure).tw. (15470)
11 (drain* or vac or vacuum* or suction*).tw. (269575)
12 or/4-11 (295951)
13 3 and 12 (707)
14 exp Health Economics/“(962486)
15 ”xp "Health Care Cost"/ (320280)
16 exp Pharmacoeconomics/ (219403)
17 Monte Carlo Method/ (46506)
18 Decision Tree/ (17676)
19 econom$.tw. (444458)
20 cba.tw. (13616)
21 cea.tw. (38738)
22 cua.tw. (1713)
23 markov$.tw. (35969)
24 (monte adj carlo).tw. (55963)
25 (decision adj3 (tree$ or analys$)).tw. (31402)
26 (cost or costs or costing$ or costly or costed).tw. (904359)
27 (price$ or pricing$).tw. (66567)
28 budget$.tw. (43806)
29 expenditure$.tw. (84497)
30 (value adj3 (money or monetary)).tw. (3952)
31 (pharmacoeconomic$ or (pharmaco adj economic$)).tw. (9271)
32 or/14-31 (2056737)
33 cost utility analysis/ (11169)
34 quality adjusted life year/ (31701)
35 cost*.ti. (180515)
36 (cost* adj2 utilit*).tw. (11379)
37 (cost* adj2 (effective* or assess* or evaluat* or analys* or model* or benefit* or threshold* or quality or expens* or saving* or reduc*)).tw. (348241)
38 (economic* adj2 (evaluat* or assess* or analys* or model* or outcome* or benefit* or threshold* or expens* or saving* or reduc*))63oad63ti59353)
39 (qualit* adj2 adjust* adj2 life*).tw. (24302)
40 QALY*.tw. (23802)
41 (incremental* adj2 cost*).tw. (25597)
42 ICER.tw. (11304)
43 utilities.tw. (13602)
44 markov*.tw. (35969)
45 (dollar* or USD or cents or pound or pounds or GBP or sterling* or pence or euro or euros or yen or JPY).tw. (65665)
46 ((utility or effective*) adj2 analys*).tw. (33763)
47 (willing* adj2 pay*).tw. (12703)
48 (EQ5D* or EQ-5D*).tw. (22155)
49 ((euroqol or euro-qol or euroquol or euro-quol or euroco“ ”r euro-col) adj3 ("5" or five)63oad63tio303)
50 (european“ ”dj2 quality adj3 ("5" or five)).tw. (810)
51 or/33-50 (574211)
52 32 or 51 (2126551)
53 13 and 52 (6863oad63ti limit 53 to english language (63)
55 nonhuman/ not (human/ and nonhuman/) (5012277)
56 54 not 55 (62)
57 (letter or editorial).pt. (1961210)
58 56 not 57 (60)
59 limit 58 to dc=20150401-20220630 (38)

Datname: EconLit

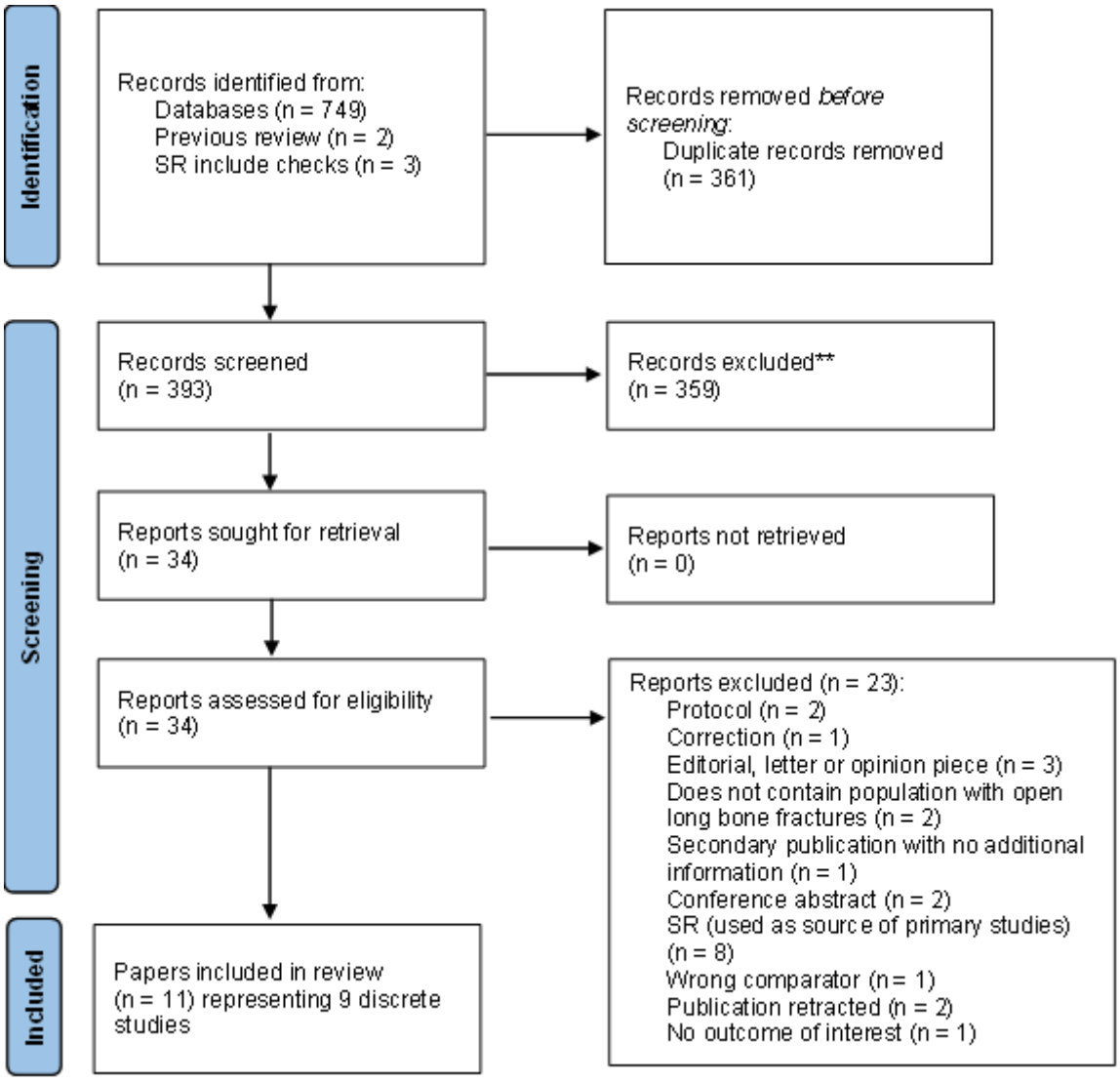
n 1 ((open or compound) adj4 (fracture* or break* or crack* or frx or fx)).tw. (43)
2 (npwt or tnp).tw. (3)
3 (negative adj2 pressure).tw. (25)
4 (drain* or vac or vacuum* or suction*).tw. (1988)
5 or/2-4 (2016)
6 1 and 5 (0)

Database name: INAHTA

Line	Query	Hits
12	#11 AND #3	1
11	#10 OR #9 OR #8 OR #7 OR #6 OR #5 OR #4	153
10	(drain* or vac or vacuum* or suction*)	93
9	"Drainage"[mh]	23
8	"Suction"[mh]	9
7	"Vacuum"[mh]	12
6	(negative) AND (pressure)	56
5	((npwt or tnp))	19
4	"Negative-P”essure Wound Therapy"[mh]	27
3	#2 OR #1	18
2	((open or compound)) AND ((fracture* or break* or crack* or frx or fx))	18
1	"Fractures, Open"[mh]	1

Date limit: 2015-2022

Appendix C – Effectiveness evidence study selection



Appendix D – Effectiveness evidence

D.1.1.1 Arti, 2016

Bibliographic Reference	Arti, H.; Khorami, M.; Ebrahimi-Nejad, V.; Comparison of negative pressure wound therapy (NPWT) & conventional wound dressings in the open fracture wounds; Pakistan Journal of Medical Sciences; 2016; vol. 32 (no. 1); 65-69

Study details

Trial registration number and/or trial name	Not reported
Study type	Randomised controlled trial (RCT)
Study location	Iran
Study setting	University hospital
Study dates	February 2013 to March 2015
Sources of funding	Not reported
Inclusion criteria	• Age: 15-55 years • Fracture type: IIIB • Accessible clean wound after debridement
Exclusion criteria	• Fracture type: type I, II or IIIA and IIIC • Need of vascular repair or reconstruction • Presence of multiple fractures in extremities • Malnutrition • Systemic disease Dermatological disease such as psoriasis • Immunosuppressive drug consumption • Existence of old fracture or implant in the fractured extremity • Previous osteomyelitis
Intervention(s)	NPWT • After detailed debridement of open fractures, sponge foam was placed on the wound and was covered by an adhesive drape. A suction tube was inserted in the dead wound space and connected to the Vacuum-Assisted closer (VAC) device. • Wound dressings were changed usually every 48 hours and negative pressure continued for 10-14 days. Pressure was maintained at 125 mm Hg continuously or intermittently 5 minutes on two minutes off. • Wounds were examined weekly.

	• VAC therapy was terminated when adequate granulation base was achieved to allow for change to conventional dressing, split-thickness skin graft, or flap closure.
Comparator	Conventional dressings (no further information provided)
Outcome me–sures	• Wound healing - Wound surface reduction • Infection (Defined as purulent discharge from the wound site or positive culture of the wound) • Length of hospitalisation - Duration of stay to coverage by skin graft or flap
Number of participants	136 patients were referred for treatment, 46 were excluded, and 90 participants were enrolled.
Duration of follow-up	1 month
Loss to follow-up	Not reported
Methods of analysis	• Analysis type (e– ITT, per-protocol) - not reported • Independent t-test for hospital stay • Paired samples t-test for wound surface reduction • Chi-square test for infection differences between two groups

Study arms

NPWT (N = 45)

Conventional wound dressing (N = 45)

Characteristics

Study-level characteristics

Characteristic	Study (N = 90)
% Female Sample size	n = 22 ; % = 22.4
Mean age (SD) (years) Mean (SD)	31.86 (9.7)

Arm-level characteristics

Characteristic	NPWT (N = 45)	Conventional wound dressing (N = 45)
Tibia and fibula fracture	n = 30 ; % = 66.7	n = 30 ; % = 66.7

Characteristic	NPWT (N = 45)	Conventional wound dressing (N = 45)
Sample size		
Femur fracture Sample size	n = 10 ; % = 22.2	n = 10 ; % = 22.2
Humerus fracture Sample size	n = 2 ; % = 4.4	n = 3 ; % = 6.7
Radius and ulna fracture Sample size	n = 3 ; % = 6.7	n = 2 ; % = 4.4

–

Critical appraisal - Cochrane Risk of Bias tool –RoB 2.0) Normal RCT - objective measure (length of stay)

Question	Answer
Risk of bias judgement	Moderate *(Some concerns around risk of bias arising from the randomisation process as there was no information on allocation concealment.)*

–

Critical appraisal - Cochrane Risk of Bias tool –RoB 2.0) Normal RCT - subjective measure (infection)

Question	Answer
Risk of bias judgement	Moderate *(Some concerns around risk of bias arising from the randomisation process as there was no information on allocation concealment. Some concerns about measurement of outcome as outcome assessors were not blinded and knowledge of allocation could have affected decisions about wound healing, and subjective aspect of infection.)*
Overall Directness	Directly applicable *(Population, intervention, comparator, and outcomes match the review protocol)*

D.1.1.2 Costa, 2022

Bibliographic Reference	Costa, Matt L; Achten, Juul; Parsons, Nick R; WOLLF, collaborators; Five-year outcomes for patients sustaining severe fractures of the lower limb : mid-term results from the Wound management for Open Lower Limb Fracture (WOLLF) trial.; The bone & joint journal; 2022; vol. 104b (no. 5); 633-639

Study details

Secondary publication of another included study- see primary study for details	Costa, Matthew L. (2018) Negative Pressure Wound Therapy forIen Fractures-Reply...Costa ML, Achten J, Bruce J, et al; UK WOLLF Collaboration. Effect of negative pressure wound therapy vs standard wound management on 12-month disability among adults with severe open fracture of the lower limb: the WOLLF randomized clinical trial. JAMA . 2018;319(22):2280-2288. JAMA: Journal of the American Medical Association 320(16): 1709-1710
Other publications associated with this study included in review	Costa, Matt L, Achten, Juul, Parsons, Nick R et al. (2022) Five-year outcomes for patients sustaining severe fractures of the lower limb : mid-term results from the Wound management for Open Lower Limb Fracture (WOLLF) trial. The bone & joint journal 104b(5): 633-63–

Critical appraisal Cochrane Risk of Bias to–l (RoB 2.0) Normal RCT - objective measure (reoperation or amputation)

Question	Answer
Risk of bias judgement	Moderate *(Some concerns due to attrition and no evidence that missingness does not bias the result. However, the proportion of missing data are similar in both arms. There was some cross-over due to unavailability of equipment, however, 95% of participants received the intervention to which they were allocated.)*
Overall Directness	Directly applicabl–

Critical appraisal Cochrane Risk of Bias to–l (RoB 2.0) Normal RCT - subjective measure (function and quality of life)

Question	Answer
Risk of bias judgement	High *(Some concerns around measurement of the outcome as this was self-reported and it was not possible to blind participants. Also, some concerns around missing outcome data due to attrition with no evidence that this did not cause bias, however, attrition was similar in both arms. There was some cross-over due to unavailability of equipment, however, 95% of participants received the intervention to which they were allocated.)*
Overall Directness	Directly applicable

D.1.1.3 Costa, 2018

Bibliographic Reference	Costa, Matthew L; Achten, Juul; Bruce, Julie; Tutton, Elizabeth; Petrou, Stavros; Lamb, Sarah E; Parsons, Nick R; UK WOLLF, Collaboration; Effect of Negative Pressure Wound Therapy vs Standard Wound Management on 12-Month Disability Among Adults With Severe Open Fracture of the Lower Limb: The WOLLF Randomized Clinical Trial.; JAMA; 2018; vol. 319 (no. 22); 2280-2288

Study details

Other publications associated with this study included in review	Costa, Matt L, Achten, Juul, Parsons, Nick R et al. (2022) Five-year outcomes for patients sustaining severe fractures of the lower limb : mid-term results from the Wound management for Open Lower Limb Fracture (WOLLF) trial. The bone & joint journal 104b(5): 633-639 Costa, Matthew L, Achten, Juul, Bruce, Julie et al. (2018) Negative-pressure wound therapy versus standard dressings for adults with an open lower limb fracture: the WOLLF RCT. Health technology assessment (Winchester, England) 22(73): 1-162
Trial registration number and/or trial name	WOLFF (ISRCTN33756652)
Study type	Randomised controlled trial (RCT)
Study location	UK
Study setting	24 major trauma hospitals representing the UK Major Trauma Network
Study dates	Randomisation between July 2012 and December 2015
Sources of funding	Funded by UK NIHR HTA Programme and supported by NIHR Oxford Biomedical Research Centre and the NIHR Collaboration for Leadership in Applied Health Research and Care in Oxford. Commercial funding in terms of excess treatment costs of NPWT was provided by Smith & Nephew and KCI Medical, by they had no part in the design, conduct, or reporting of the trial.
Inclusion criteria	Age: ≥ 16 years Fracture type: Open fracture of the lower limb as Gustillo-Anderson grade 2 or 3 (G&A grade determined by the treating surgeon at the end of the surgical debridement as per routine operative practice) Presented (or were transferred) to a trial hospital within 72 hours of injury Cases where it was not possible to safely suture the wound edges at the end of the first surgical debridement
Exclusion criteria	Contraindications to anaesthesia such that the patient was unfit for surgery Evidence that the patient was unable to adhere to the trial procedures or complete questionnaires, such as cognitive impairment

Intervention(s)	Negative-pressure wound therapy • NPWT dressing using an open-cell foam or gauze was laid on the wound followed by an adherent sealed dressing. A sealed tube was connected from the dressing to a suction pump, which created a partial vacuum over the wound. • The exact details of the dressing and pressure were left to the discretion of the healthcare team [In all participants the fracture wound was debrided, and the fracture immobilized with either internal or external fixation. If the wound could not be closed primarily, the patient was randomised to either NPWT or standard dressing. Patients had a second operation at 48 to 72 hours where a further assessment and debridement was performed, followed by closure with either primarily sutures or soft-tissue reconstruction.]
Comparator	Sterile dressings sealed from external contamination (details were left to the discretion of the healthcare team)
Outcome measures	• Infection: Superficial surgical site infection at 30 days – CDC definition • Patient-reported Disability Rating Index (DRI): 3, 6, 9, 12 months and 2, 3, 4, 5 years • Health-related quality of life: EQ-5D VAS, EQ-5D MAU, SF-12 PCS, SF-12 MCS at 3, 6, 9, 12 months and ED-5DL-3L and EQ-VAS at 2, 3, 4 and 5 years • Deep infection: Deep SSI at 30 days according to CDC criteria • Wound healing by 6 weeks: Wound photographs • Complications • Further surgical interventions
Number of participants	625 participants
Duration of follow-up	5 years
Loss to follow-up	NPWT: • 3 months: 166 completed follow-up • 6 months: 154 completed follow-ip • 9 months: 153 completed follow-up • 12 months: 179 completed follow-up • 2 years: 59 completed follow-up • 3 years: 39 completed follow-up • 4 years: 56 completed follow-up • 5 years: 64 completed follow-up Standard dressing: • 3 months: 189 completed follow-up • 6 months: 176 completed follow-ip • 9 months: 162 completed follow-up • 12 months: 195 completed follow-up • 2 years: 66 completed follow-up • 3 years: 49 completed follow-up • 4 years: 64 completed follow-up

	• 5 years: 72 completed follow-up
Methods of analysis	• A minimum clinically important difference for the DRI of 8 points was selected to power the study. • The SD of the DRI used in the sample size calculation was 25 points, allowing for 10% loss during follow-up to give a total sample size of 460 patients. Therefore, 230 patients consenting to each intervention group would provide 90% power to detect a difference of 8 points in DRI at 12 months at the 5% significance level. • ITT and per-treatment analyses were performed. • Mixed-effects regression analysis, with recruiting centre as a random effect, and fixed terms to adjust for age group, sex, baseline preinjury score, and Gustilo and Anderson grade was used to test for treatment group differences using complete case data. • Secondary end points were not adjusted for multiple comparisons. • In a post hoc sensitivity analysis for the primary outcome, missing data were imputed using the chained equation method and models fitted to give a pooled estimate of the treatment effect. • All tests were 2-sided and significance was assessed at the 5% level. • Analyses of primary and secondary outcomes used complete-case data and all analyses were implemented in R.
Additional comments	None

Study arms

NPWT (N = 311)

Standard dressing (N = 314)

Characteristics

Arm-level characteristics

Characteristic	NPWT (N = 311)	Standard dressing (N = 314)
% Female Sample size	n = 48 ; % = 21.2	n = 70 ; % = 29.9
Mean age (SD) Mean (SD)	46.1 (19.9)	44.5 (19)
Smoker, No. (%) No of events	n = 70 ; % = 31	n = 79 ; % = 33.8
Road traffic accident	n = 125 ; % = 55.3	n = 139 ; % = 59.4

Characteristic	NPWT (N = 311)	Standard dressing (N = 314)
No of events		
Low-energy fall No of events	n = 34 ; % = 15	n = 39 ; % = 16.7
High-energy fall No of events	n = 34 ; % = 15	n = 25
Crush injury No of events	n = 17 ; % = 7.5	n = 19 ; % = 8.1
Other No of events	n = 13 ; % = 5.8	n = 9 ; % = 3.8
Contact sports injury No of events	n = 3 ; % = 1.3	n = 1 ; % = 0.4
Unknown No of events	n = 0 ; % = 0	n = 2 ; % = 0.9
grade II No of events	n = 34 ; % = 15	n = 30 ; % = 12.8
grade III No of events	n = 171 ; % = 75.7	n = 180 ; % = 76.9
Grade III and IV No of events	n = 21 ; % = 9.3	n = 24 ; % = 10.3

Critical appraisal – Cochrane Risk of Bias tool (RoB 2.0) Normal RCT – objective measure (reoperation/amputation)

Question	Answer
Risk of bias judgement	Moderate *(Some concerns due to attrition and no evidence that missingness does not bias the result. However, the proportion of missing data are similar in both arms.)*
Overall Directness	Directly applicable

Critical appraisal– Cochrane Risk of Bias tool (RoB 2.0) Normal RCT – subjective measure (function, quality of life, and deep infection)

Question	Answer
Risk of bias judgement	Moderate (function, quality of life, and deep infection) *(Moderate risk of bias due to self-reported outcomes without blinding. There was also high attrition that was similar in both arms, however, there was evidence that results were not biased due to mixed-effects regression based on a complete case analysis with treatment group, age group, sex, baseline preinjury score, and wound grade as covariates (fixed effects) and recruiting centre as a random effect.)*
Overall Directness	Directly applicable

D.1.1.4 Costa, 2018b

Bibliographic Reference	Costa, Matthew L; Achten, Juul; Bruce, Julie; Davis, Sonia; Hennings, Susie; Willett, Keith; Petrou, Stavros; Jeffery, Steven; Griffin, Damian; Parker, Ben; Masters, James; Lamb, Sarah E; Tutton, Elizabeth; Parsons, Nick; Negative-pressure wound therapy versus standard dressings for adults with an open lower limb fracture: the WOLLF RCT.; Health technology assessment (Winchester, England); 2018; vol. 22 (no. 73); 1-162

Study details

Secondary publication of another included study- see primary study for details	Costa, Matthew L, Achten, Juul, Bruce, Julie et al. (2018) Effect of Negative Pressure Wound Therapy vs Standard Wound Management on 12-Month Disability Among Adults With Severe Open Fracture of the Lower Limb: The WOLLF Randomized Clinical Trial. JAMA 319(22): 2280-2288
Other publications associated with this study included in review	Costa, Matt L, Achten, Juul, Parsons, Nick R et al. (2022) Five-year outcomes for patients sustaining severe fractures of the lower limb : mid-term results from the Wound management for Open Lower Limb Fracture (WOLLF) trial. The bone & joint journal 104b(5): 633-639

Critical appraisal– Cochrane Risk of Bias tool (RoB 2.0) Normal RCT – subjective measure (quality of life, superficial surgical site infection and pain)

Question	Answer
Risk of bias judgement	Moderate (quality of life) *(Moderate for HRQOL measures: Some concerns around measurement of the outcome as this was self-reported and it was not possible to blind*

Question	Answer
	participants. Low risk of bias for missing outcome data as mixed-effects regression based on a complete-case analysis with treatment group, age group, gender, baseline score and wound grade as covariates (fixed effects) and recruiting centre as a random effect were presented, and indicated that the result was not biased by missing data. There was some cross-over due to unavailability of equipment, however, 95% of participants received the intervention to which they were allocated Moderate (wound healing by 6 weeks) *(Some concerns due to attrition and no evidence that missingness does not bias the result. However, the proportion of missing data are similar in both arms. There was some cross-over due to unavailability of equipment, however, 95% of participants received the intervention to which they were allocated. No concerns around measurement of the outcome, as photographs were reviewed blind to treatment allocation.)* Moderate (superficial infection) *(Moderate risk of bias due to self-reported outcomes without blinding. There was also high attrition that was similar in both arms, however, there was evidence that results were not biased due to mixed-effects regression based on a complete case analysis with treatment group, age group, sex, baseline preinjury score, and wound grade as covariates (fixed effects) and recruiting centre as a random effect.)* High (pain) *Some concerns around measurement of the outcome as this was self-reported and it was not possible to blind participants. Also so concerns around missing outcome data due to attrition with no evidence that this did not cause bias, however, attrition was similar in both arms. There was some cross-over due to unavailability of equipment, however, 95% of participants received the intervention to which they were allocated.)*
Overall Directness	Directly applicable *(Population, intervention, comparator, and outcomes match the review protocol)*

D.1.1.5 Gupta, 2013

Bibliographic Reference	Gupta, Ketan; Mundada, A; Patil, A; Comparison of vacuum assisted closure therapy with standard wound therapy for open musculoskeletal injuries; International Journal of Recent Trends in Science and Technology; 2013; vol. 9 (no. 2); 168-170

Study details

Trial registration number	Not reported

and/or trial name	
Study location	India
Study setting	Hospital
Study dates	Not reported
Sources of funding	Not reported
Inclusion criteria	Age Over 18 years Fracture type Open musculoskeletal injuries in the extremities that required coverage.
Exclusion criteria	Previous osteomyelitis History of diabetes mellitus Neurovascular deficit Cancer
Intervention(s)	Sterile, open-pore foam dressing was placed into the wound cavity. The site was then sealed with an adhesive drape covering the foam and tubing and at least three to five centimetres of surrounding healthy tissue to ensure a seal. Controlled pressure was applied with an intermittent negative pressure of −125mmhg. The cycle on for six minutes and off for three minutes. The dressings were changed on third or fourth day depending upon the amount of drain. [All cases were treated with tetanus prophylaxis, standard antibiotics and other supportive measures. All of them had undergone wound debridement and fracture fixation.]
Comparator	Sterile dressing. No further detail reported.
Number of participants	30
Outcome measures	Infection Primary wound coverage Wound healing by 6 weeks
Duration of follow-up	Not reported but longest timepoint is 6 weeks.

Loss to follow-up	No loss to follow up.
Methods of analysis	Recorded as binary variables in both groups - infection present or not present - healing of wound <6 weeks or > 6 weeks
Additional comments	None

Study arms

Vacuum Assisted Closure (N = 15)

Sterile dressing (N = 15)

Characteristics

Study-level characteristics

Characteristic	**Study (N =)**
Mean age (SD) (years (mean)) Mean (SD)	39 (18)

Arm-level characteristics

Characteristic	**Vacuum Assisted Closure (N = 15)**	**Sterile dressing (N = 15)**
% Female (%) Sample size	n = 4 ; % = 27	n = 3 ; % = 20–

Critical appraisal - Cochrane Risk of Bias to–l (RoB 2.0) Normal RCT - objective measure (length of hospitalisation)

Question	**Answer**
Risk of bias judgement	Moderate *(Some concerns about randomisation)*
Overall Directness	Directly applicabl–

Critical appraisal Cochrane Risk of Bias to–l (RoB 2.0) Normal RCT - subjective measure (wound healing by 6 weeks, and infection)

Question	Answer
Risk of bias judgement	Moderate *(Some concerns about randomisation and subjective judgments of infection and wound healing by unblinded clinicians)*
Overall Directness	Directly applicable

D.1.1.6 Jayakumar, 2013

Bibliographic Reference	Jayakumar, M; Ajai, P; A comparative study between primary vacuum assisted closure and conventional sterile dressing in treatment of soft tissue injuries associated with severe open fractures of both bones leg.; Kerala Journal of Orthopaedics; 2013; vol. 26 (no. 1)

Study details

Trial registration number and/or trial name	Not reported
Study type	Randomised controlled trial (RCT)
Study location	Government medical college hospital, Kerala, India
Study setting	Hospital
Study dates	Study period is 3 years, but dates not reported.
Sources of funding	Not reported.
Inclusion criteria	Age: 20 - 60 Fracture type: Grade IIIA and IIIB open fractures of both leg bones.
Exclusion criteria	Fracture type: Grade IIIC Associated neurovascular injuries Grossly infected wounds
Intervention(s)	Polyurethane open celled sponge obtained from an upholstery shop was autoclaved and cut to match the shape of the wound. The pore size of the sponge is approximately between 400- 600 micrometres. A suction tube of a standard negative suction drain of 16 mm ending in a round pad with holes was placed on the sponge and allowed to exit the dressing parallel to the surface of the sponge. The entire dressing was covered by an adherent clear plastic film to make it air tight and connected to the suction drain. This suction drain operates cyclically to get cyclical negative pressure at the wound site.

	[All cases were treated with tetanus prophylaxis, standard antibiotics and other supportive measures. All underwent wound debridement and external fixator application]
Comparator	Sterile dressings. No further information given.
Outcome measures	Length of hospitalisation (less than or more than 1 month) Primary wound coverage (less than or more than 3 weeks) Wound healing by 6 weeks
Number of participants	50, 10 lost to follow up, 40 included in analysis.
Duration of follow-up	Not reported. Longest timepoint is 6 weeks.
Loss to follow-up	10 “atients (20%). 2 died, "8 patients were lost during follow up be”ause of unknown reasons"
Methods of analysis	Chi squared test Fishers exact test
Additional comments	None

Characteristics

Study-level characteristics

Characteristic	**Study (N = 50)**
% Female Sample size	n = NR ; % = NR
Mean age (SD) (years) Range	20 to 60
Mean age (SD) (years) Mean (SD)	32 (NR–

Critical appraisal - Cochrane Risk of Bias to–l (RoB 2.0) Normal RCT - objective measure (length of hospitalisation)

Question	**Answer**
Risk of bias judgement	High *(Very serious concerns about randomisation and blinding of patients and clinicians, concerns about patients lost to follow up and not included in analysis)*
Overall Directness	Directly applicable

Critical appraisal - Cochrane Risk of Bias to–l (RoB 2.0) Normal RCT - subjective measure (wound healing by 6 weeks, and infection)

Question	Answer
Risk of bias judgement	High *(Very serious concerns about randomisation and blinding of patients and clinicians, concerns about subjective assessments undertaken by non-blinded clinicians, concerns about patients lost to follow up and not included in analysis)*
Overall Directness	Directly applicable

D.1.1.7 Rasool, 2013

Bibliographic Reference	Rasool G; Ahmed MU; Iqbal M; Khwaja Z; Vacuum assisted wound closure and normal saline dressing in treatment of Gustilo type II, type IIIa and IIIb open fracture of tibia; Rawal Medical Journal; 2013; vol. 4 (no. 38); 382-384

Study details

Trial registration number and/or trial name	Not reported
Study type	Randomised controlled trial (RCT)
Study location	Pakistan
Study setting	Department of Orthopaedics, Pakistan Ordnance Factories Hospital
Study dates	March 2010 to March 2012
Sources of funding	Not reported
Inclusion criteria	Fracture type: Gustilo type II, type IIIA and type IIIB open tibial fracture
Exclusion criteria	Fracture type: Gustilo type I and type IIIC Gunshot injuries Contraindications for wound VAC use
Intervention(s)	VAC therapy: • Continuous negative pressure of 125 mmHg • Modified form of suction drain as vacuum device mounted on wall [All patients received irrigation, sharp debridement, tetanus prophylaxis and empirical systemic antibiotics against staphylococci before VAC or saline dressing.]
Comparator	Normal saline dressing

Outcome measures	• Wound healing • Appearance of 100% granulation tissue in number of days
Number of participants	50 participants
Duration of follow-up	Reported maximum number of days to wound closure was 40 days.
Loss to follow-up	Not reported
Methods of analysis	• Type of analysis (eg ITT or per-protocol): not reported • Chis-square test used for comparison between groups with p-value <0.05 as significant
Additional comments	None

Study arms

VAC therapy (N = 25)

Saline dressing (N = 25)

Characteristics

Study-level characteristics

Characteristic	Study (N = 50)
Mean age (SD) Range	10 to 40

Arm-level characteristics

Characteristic	VAC therapy (N = 25)	Saline dressing (N = 25)
% Female n calculated from percentage by reviewer No of events	n = 8 ; % = 32	n = 7 ; % = 28–

Critical appraisal - Cochrane Risk of Bias to–l (RoB 2.0) Normal RCT - subjective measure (post hoc analysis – time to 100% granulation)

Question	Answer
Risk of bias judgement	High *(Very serious concerns as alternation was used, and it is likely that allocation was not concealed until all participants were enrolled and assigned to interventions. There were also concerns around measurement of the outcome as subjective assessment was likely carried out by unblinded assessor. There are also no details about a trial protocol, and time of wound healing was only presented as frequency of wounds healed in 10-20 and 21-30 days.)*
Overall Directness	Indirectly applicable *(Outcome measure not match outcomes in the PICO)*

D.1.1.8 Sagy, 2020

Bibliographic Reference	Sagy, Mohammed; Singh, Jagdeep; Kalia, Anoop; Dahuja, Anshul; Garg, Sorabh; Garg, RadheShyam; Wound healing of open f82oad82tes: comparison of vaccum a82oad82tionalessing versus traditonal dressing.; International journal of orthopaedic and trauma nursing; 2020; vol. 36; 100722

Study details

Trial registration number and/or trial name	Not reported
Study type	Randomised controlled trial (RCT)
Study location	India
Study setting	Department of Orthopaedics, Hospital
Study dates	January 2015 to December 2016
Sources of funding	None
Inclusion criteria	• Patients with fresh compound fractures where primary closure was not possible • Patients who required surgical debridement • Patients with no co-morbid conditions • including diabetes mellitus and obesity • No other confounding factors including old age, compliance, alcoholism and smoking • Wounds unsuitable for primary closure with associated fracture of a long bone
Exclusion criteria	• Haemophilia or haemoglobinopathies • History of diabetes mellitus • Pathological fractures with untreated osteomyelitis

	• Old compound fractures with infected wounds
Intervention(s)	Negative pressure wound therapy: • After adequate hemostasis, a foam band dressing was applied over the wound • The foam dressing was connected to a VAC unit via a drain tube (further information provided in Sagy 2020) • Sub-atmospheric pressure was delivered to the wound • dressing was changed every 4 days and wound inspection was conducted at this time [Patients underwent initial debridement]
Comparator	Traditional wound dressing: • Dressings changed daily using combination of hydrogen peroxide, normal saline and povidone iodine in a sequential manner
Outcome measures	• Length of hospitalisation • Appearance of granulation tissue • Time to 100% granulation
Number of participants	100 participants
Duration of follow-up	Until definitive wound coverage or surgeries such as split skin graft, flap surgery or secondary suturing
Loss to follow-up	Not reported
Methods of analysis	• Analysis method (eg ITT, per-protocol): not reported • Numerical data expressed as mean ± standard deviation or percent as proportionate to the sample size • Statistical significance determined using p-value - p-value less that 0.05 was considered significant
Additional comments	None

Study arms

Vacuum assisted dressing (N = 50)

Traditional wound dressing (N = 50)

Characteristics

Study-level characteristics

Characteristic	Study (N = 100)
Tibia No of events	% = 91
Femur No of events	% = 9

Arm-level characteristics

Characteristic	Vacuum assisted dressing (N = 50)	Traditional wound dressing (N = 50)
% Female No of events	n = 2 ; % = 4	n = 3 ; % = –

Critical appraisal Cochrane Risk of Bias to–l (RoB 2.0) Normal RCT - objective measure (length of hospitalisation)

Question	Answer
Risk of bias judgement	Moderate *(Some concerns around randomisation as there was no information about allocation concealment or the method of randomisation. There were also some concerns around bias in the selection of the reported result as there was no information on whether a pre-specified trial plan was finalised before analysis.)*
Overall Directness	Directly applicable

Critical appraisal - Cochrane Risk of Bias to–l (RoB 2.0) Normal RCT - subjective measure (post hoc - time to 100% granulation)

Question	Answer
Risk of bias judgement	High *(Some concerns around randomisation as there was no information about allocation concealment or the method of randomisation. There were also some concerns around measurement of the outcome as this was likely assessed by unblinded assessors. There were also some concerns around bias in the selection of the reported result as there was no information on whether a pre-specified trial plan was finalised before analysis.)*
Overall Directness	Indirectly applicable *(Post hoc outcome not in review protocol)*

D.1.1.9 Sibin, 2017

Bibliographic Reference	Sibin, J; Pullatttu, BR; Jose, FC; Vacuum assisted closure in grade III open tibial fractures; Indian J Appl Res; 2017; vol. 7

Study details

Trial registration number and/or trial name	Not reported
Study type	Randomised controlled trial (RCT)
Study location	India
Study setting	Government Medical College Hospital
Study dates	January 1st 2015 to July 31st 2015
Sources of funding	Not reported
Inclusion criteria	Age: Older than 18 years Fracture type: Type III tibia fractures Treated by external fixation
Exclusion criteria	Fracture type: Type IIIC Fracture site in contact with exposed blood vessels, anastomotic sites or nerve Associated neurovascular injuries
Intervention(s)	VAC: • A polyurethane open celled sponge (having pore size approximately between 400-600 mm) obtained from upholstery shop, was cut to match the shape of the wound and autoclaved. • The suction tube of a standard negative suction apparatus was placed on the sponge and allowed to exit the dressing parallel to the surface of the sponge. • The dressing was covered by an adherent clear plastic film. • The apparatus operated cyclically 20 minutes every 2 hours to get cyclical negative pressure at the wound site. [All patients treated with wound debridement and external fixation followed by application of VAC or sterile dressing. Infected wounds were treated with wound care and parenteral antibiotics based on pus culture and sensitivity report.]
Comparator	Sterile dressings (no further information reported)

Outcome measures	• Infection • Length of hospitalisation • Primary wound coverage • Wound healing by 6 weeks
Number of participants	30 patients
Duration of follow-up	Not reported
Loss to follow-up	Not reported
Methods of analysis	• Analysis type (eg. ITT, per-protocol): not reported • Continuous measurements are presented as Mean ± SD. • Results of categorical measurements are presented in Number (%). • Chi-square/Fisher Exact test was used to find the significance of study parameters on categorical scale between the two groups.
Additional comments	No information was given around treatment following NPWT or sterile dressings.

Study arms

VAC (N = 15)

Sterile dressing (N = 15)

Characteristics

Study-level characteristics

Characteristic	**Study (N = 30)**
% Female No of events	n = 4 ; % = 13.3
Mean age (SD) M86oad(SD)	46.73 (14.67)
Road traffic accident No of events	n = 18 ; % = 66
Fall from height No of events	n = 8 ; % = 26.7
Machine injury No of events	n = 4 ; % = 13.3

Characteristic	Study (N = 30)
Type IIIA tibia fracture No of events	n = 9 ; % = 30
Type IIIB tibia fracture No of events	n = 21 ; % = 7–

Critical appraisal - Cochrane Risk of Bias to–l (RoB 2.0) Normal RCT - objective measure (length of hospitalisation)

Question	Answer
Risk of bias judgement	Moderate *(There were concerns around bias arising from the randomisation process as there was no information about allocation concealment, baseline characteristics were not reported at arm-level, and there was no information about the method of randomisation. There were also concerns about bias in selection of the reported result as there was no information about whether the trial was analysed in accordance with a pre-specified plan.)*
Overall Directness	Directly applicable

Critical appraisal - Cochrane Risk of Bias to–l (RoB 2.0) Normal RCT - subjective measure (infection, and wound healing by 6 weeks)

Question	Answer
Risk of bias judgement	High *(There were concerns around bias arising from the randomisation process as there was no information about allocation concealment, baseline characteristics were not reported at arm-level, and there was no information about the method of randomisation. There were concerns around measurement of the outcome, as subjective measures were reported by non-blinded assessors. There were also concerns about bias in selection of the reported result as there was no information about whether the trial was analysed in accordance with a pre-specified plan.)*
Overall Directness	Directly applicable

D.1.1.10 Stannard, 2009

Bibliographic Reference	Stannard JP; Volgas DA; Stewart R; McGwin G; Alonso JE; Negative pressure wound therapy after severe open fractures: a prospective randomized study.; Journal of orthopaedic trauma; 2009; vol. 23 (no. 8)

Study details

Trial registration number and/or trial name	Not reported
Study type	Randomised controlled trial (RCT)
Study location	USA
Study setting	Academic level I trauma centre
Study dates	Between June 2001 and August 2006
Sources of funding	Kinetics Concepts
Inclusion criteria	• Age: greater than 18 years • Severe open fracture that required serial surgical debridements • Willingness to complete the treatment protocol and follow-up
Exclusion criteria	• Patients whose wounds could be closed at the index surgery • Patients not willing to give consent • Or family members • Patients with wounds on which it would not be possible to use NPWT • Prisoners • Pregnant women • Anyone unable to complete the treatment protocol including NPWT
Intervention(s)	NPTW - VAC dressing over the open fracture [All patients underwent the same treatment protocols with the exception of the dressing. This included irrigation and debridement followed by skeletal stabilisation as soon as they were cleared to go to the operating room. All patients had their initial surgical irrigation and debridement within 24 hours of the injury. Patients then had a second surgery including irrigation and debridement within 37-72 hours of the initial procedure. Wounds were graded by the surgeon based on readiness for closure. Open wounds were closed when they were graded as having abundant granulation tissue ready for closure, and all other had the assigned dressing replaced and underwent surgical irrigation and debridement 36-72 hours later. All patients had prophylactic intravenous antibiotics given until 24 hours after closure or coverage of the wound.]
Comparator	Saline wet to moist dressings over the open fracture
Outcome measures	• Infection • Health-related quality of life (SF-36) • Deep infection • Wound dehiscence • Fracture unions • Acute infection • Amputation

Number of participants	59 patients were enrolled, one patient underwent an amputation, meaning that the patient was omitted from the study to give 58 patients with 62 open fractures.
Duration of follow-up	Mean follow-up is 28 months, with a range of 14–67 months
Loss to follow-up	Data from one patient who underwent amputation were omitted.
Methods of analysis	• Continuous variables were summarized using arithmetic averages, standard deviations, 95% exact confidence intervals (CIs), and the range. • Differences between treatment groups for continuous variables were compared using a 1-factor analysis of variance test. • Proportions were summarized using counts, percentages, and 95% exact binomial CIs. • The relative risk of specific events was presented with 95% CIs. • The differences in proportions between treatment groups were compared using a 2-tailed Fisher exact test based on the hypergeometric distribution. • Probability values <0.05 were considered significant • Analysis (–g ITT or per-protocol) - not reported • Sample size calculations were based on proportion of patients requiring ≥3 surgical debridements vs <3 surgical debridements, and the study was powered to detect a ≥20% difference between treatment groups assuming that 25% of control patients and 55 of NPWT patients require ≥3 surgical debridements. Type II error rate would be 1% with 100 patients enrolled and balanced by treatment assignment. 29 patients would be needed per treatment arm to detect a difference at the alpha = 0.05 level based on a power of 80%.
Additional comments	None

Study arms

NPWT (N = 35) - 35 patients with 37 fra–tures

Control (N = 23) - 23 patients with 25 fractures

Characteristics

Arm-level characteristics

Characteristic	NPWT (N = 35)	Control (N = 23)
% Female % calculated by reviewer from n No of events	n = 9 ; % = 25.7	n = 10 ; % = 43.5
Smoking status	n = 18 ; % = 51	n = 7 ; % = 30

Characteristic	NPWT (N = 35)	Control (N = 23)
No of events		
Tibia No of events	n = 14 ; % = 38	n = 12 ; % = 48
Pilon No of events	n = 5 ; % = 14	n = 3 ; % = 12
Femur No of events	n = 7 ; % = 19	n = 3 ; % = 12
Radius No of events	n = 1 ; % = 3	n = 1 ; % = 4
Humerus No of events	n = 2 ; % = 5	n = 1 ; % = 4
Calcaneus No of events	n = 0 ; % = 0	n = 1 ; % = 4
Talus No of events	n = 0 ; % = 0	n = 1 ; % = 4
Ankle No of events	n = 5 ; % = 14	*empty data*
Both bone forearm No of events	n = 1 ; % = 3	n = 1 ; % = 4
Olecranon No of events	n = 1 ; % = 3	n = 0 ; % = 0
Foot No of events	n = 1 ; % = 3	n = 1 ; % = 4
Type II No of events	n = 3 ; % = 8.1	n = 2 ; % = 8
Type IIIA No of events	n = 15 ; % = 40.5	n = 12 ; % = 48
Type IIIB No of events	n = 18 ; % = 48.6	n = 9 ; % = 36
Type IIIC No of events	n = 1 ; % = 2.7	n = 2 ; % = 8–

Critical appraisal - Cochrane Risk of Bias to–l (RoB 2.0) Normal RCT - objective measure (acute infection, deep infection, amputation)

Question	Answer
Risk of bias judgement	Moderate *(Some concerns due to a lack of information around allocation concealment and no information reported about the trial protocol. No concerns around measurement of infection and deep infection outcomes as it appears that tissue culture was used to confirm presence of infection in most cases.)*
Overall Directness	Indirectly applicable *(Some concerns as not all fractures in the study were long bone fractures*)

Critical appraisal - Cochrane Risk of Bias to–l (RoB 2.0) Normal RCT - subjective measure (quality of life)

Question	Answer
Risk of bias judgement	High *(Very serious concerns due to lack of information around allocation concealment, self-reported outcome measures where blinding was not possible, and bias in selection of the reported result, as no information was provided about a study protocol, and data were only presented for participants who had been infected, and no data were presented for participants at 12 months and follow up.)*
Overall Directness	Indirectly applicable *(Some concerns as not all fractures in the study were long bone fractures)*

D.1.1.11 Virani, 2016

Bibliographic Reference	Virani, S.R.; Dahapute, A.A.; Bava, S.S.; Muni, S.R.; Impact of negative pressure wound therapy on open diaphyseal tibial fractures: A prospective randomized trial; Journal of Clinical Orthopaedics and Trauma; 2016; vol. 7 (no. 4); 256-259

Study details

Trial registration number and/or trial name	Not reported
Study type	Randomised controlled trial (RCT)
Study location	India

Study setting	Not reported
Study dates	Not reported
Sources of funding	Not reported
Inclusion criteria	Age: Greater than 18 years Fracture type: Open tibial fracture
Exclusion criteria	• Patients whose wounds could be closed at the index surgery • Patients not needing repeated debridement and dressing • Aged less than 18 years • Patients not willing to give consent
Intervention(s)	NPWT: • Dressing consisted of a custom cut open cell foam and gauze that was put over the wound under an adhesive occlusive dressing. • Negative pressure of 125 mmHg [Prior to NPWT or control conditions, all patients underwent debridement, stabilization of the fractures (commonly external fixator), and perioperative antibiotic coverage (as per the institutional protocol which included a third generation cephalosporin, an amino glycoside and a clindamycin) which was continued post-operatively. The wound was opened every 4th day for reapplication of dressing and swab sent for culture. Once the wound had sufficient granulation tissue to undergo skin grafting, or the wound had contracted to a size that could be surgically closed, it was either closed or covered with skin graft. Serial irrigation and debridement was continued till the wounds were ready for closure or coverage.]
Comparator	Daily cleaning, dressing and debridement
Outcome measures	**Infection**: Signs included raised total leucocyte count and local signs like pus discharge from the wound with erythema of skin edges within 1 week of primary debridement **Deep infection:** Deep infections included cases developing features of chronic osteomyelitis like a discharging sinus, fixed puckered overlying soft tissue and radiological changes consistent with chronic osteomyelitis. A case was considered to be culture positive if even a single culture out of the serial analysis showed quantitative bacterial growth.
Number of participants	95 patients were enrolled. Two patients were excluded as they required amputation as primary mode of treatment. 93 patients were randomised
Duration of follow-up	Mean follow-up around 23 ± 6 weeks
Loss to follow-up	Not reported
Methods of analysis	• Continuous variables were analysed using arithmetic mean, standard deviations and range.

	• An unpaired t-test was used to determine whether there was a significant differences in the occurrence of various confounding factors. • The relative risk was calculated using 95% confidence intervals. • Fischer exact test was used to measure differences in incidences of infection in the two groups. A p-value less than 0.05 was considered significant. • Type of analysis (eg ITT, per-protocol) was not reported
Additional comments	None

Study arms

NPWT (N = 43)

Control (N = 50)

Characteristics

Arm-level characteristics

Characteristic	NPWT (N = 43)	Control (N = 50)
% Female % calculated by reviewer No of events	n = 15 ; % = 34.9	n = 18 ; % = 36
Mean age (SD) Mean (SD)	34.8 (*empty data*)	37.4 (*empty data*)
Smoking status No of events	n = 11 ; % = 25.5	n = 14 ; % = 28
Grade I No of events	n = 0 ; % = 0	n = 0 ; % = 0
grade II No of events	n = 5 ; % = 11	n = 8 ; % = 16
Grade IIIA No of events	n = 15 ; % = 34.8	n = 14 ; % = 28
Grade IIIB No of events	n = 22 ; % = 51.1	n = 27 ; % = 54
Grade IIIC No of events	n = 1 ; % = 2.3	n = 1 ; % = 2–

Critical appraisal - Cochrane Risk of Bias tool (RoB 2.0) Normal RCT – subjective measure (infection, and deep infection)

Question	Answer
Risk of bias judgement	High *(Some concerns due to lack of information around allocation concealment and lack of information concerning the study protocol. Also some concerns around measurement of the outcome, as subjective methods were used to assess infection in addition to objective measures, and these subjective measures were conducted by non-blinded assessors.)*
Overall Directness	Directly applicable

Appendix E – Forest plots

Negative pressure wound therapy vs. conventional therapy

Figure 2: Outcome: wound healing by 6 weeks

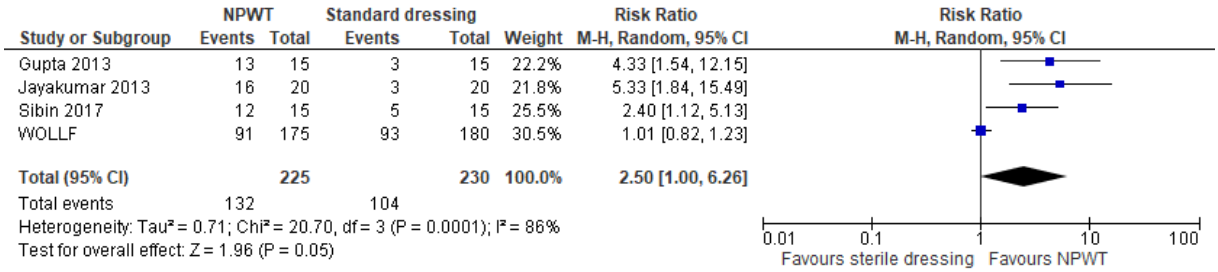


Figure 3: Outcome: wound infection

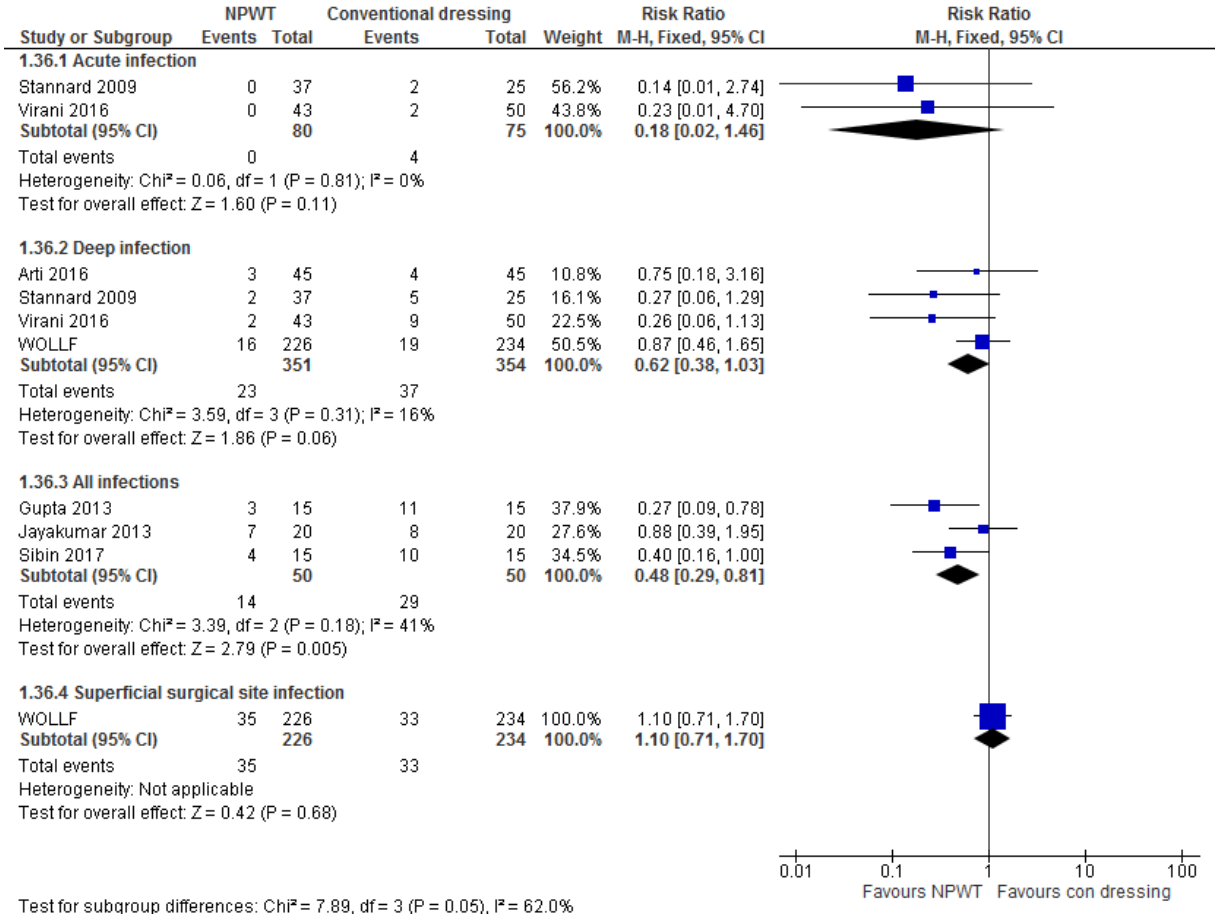


Figure 4: Outcome: Hospital stay less than 1 month

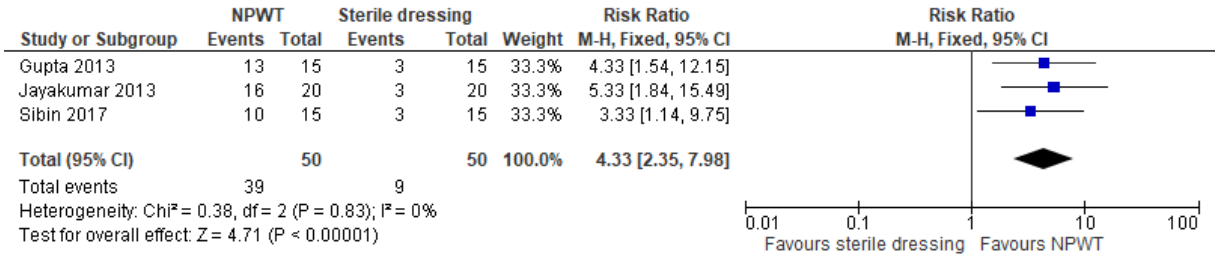
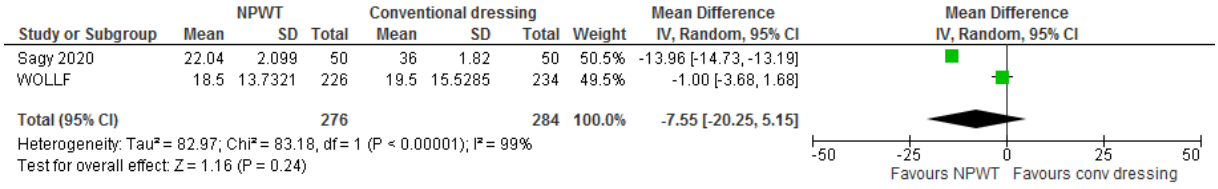


Figure 5: Outcome: Hospital stay less than 1 month



Appendix F – GRADE tables

Table 9: Wound healing by 6 weeks

Certainty assessment							№ of patients		Effect		Certainty
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	NPWT	Standard dressing	Relative (95% CI)	Absolute (95% CI)	
Wound healing by 6 weeks											
4[a]	randomised trials	very serious[b]	very serious[c]	not serious	serious[d]	none	132/225 (58.7%)	104/230 (45.2%)	**RR 2.50** (1.00 to 6.26)	**678 more per 1,000** (from 0 fewer to 1,000 more)	⨁◯◯◯ Very low

CI: confidence interval; **MD:** mean difference; **RR:** risk ratio

Explanations

a. WOLLF, Jayakumar 2013, Sibin 2017, Gupta 2013

b. greater than 33.3% of studies at high risk of bias

c. I^2 greater than 66.7%

d. 95% CI crosses one MID

Table 10: Wound infection

Certainty assessment							№ of patients		Effect		Certainty
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	NPWT	Standard dressing	Relative (95% CI)	Absolute (95%–CI)	
Wound infection - Acute infection											
2[c]	randomised trials	very serious[d]	not serious	serious[e]	very serious[b]	none	0/80 (0.0%)	4/75 (5.3%)	**RR 0.18** (0.02 to 1.46)	**44 fewer per 1,000** (from 52 fewer to 25 more)	⨁◯◯◯ Very low
Wound infection - Deep infection											
4[g]	randomised trials	serious[a]	not serious	not serious	serious[f]	none	23/351 (6.6%)	37/354 (10.5%)	**RR 0.62** (0.38 to 1.03)	**40 fewer per 1,000** (from 65 fewer to 3 more)	⨁⨁◯◯ Low
Wound infection - All infections											

Certainty assessment							№ of patients		Effect		Certainty
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	NPWT	Standard dressing	Relative (95% CI)	Absolute (95%–CI)	
3[h]	randomised trials	very serious[d]	serious[i]	not serious	serious[f]	none	14/50 (28.0%)	29/50 (58.0%)	**RR 0.48** (0.29 to 0.81)	**302 fewer per 1,000** (from 412 fewer to 110 fewer)	⨁◯◯◯ Very low

Wound infection - Superficial surgical site infection

1[j]	randomised trials	serious[k]	NA[l]	not serious	very serious[b]	none	35/226 (15.5%)	33/234 (14.1%)	**RR 1.10** (0.71 to 1.70)	**14 more per 1,000** (from 41 fewer to 99 more)	⨁◯◯◯ Very low

CI: confidence interval; **MD**: mean difference; **RR**: risk ratio

Explanations

a. greater than 33.3% of studies at moderate or high risk of bias

b. 95% CI crosses both MIDs

c. Stannard 2009, Virani 2016

d. greater than 33% of studies at high risk of bias

e. Stannard 2009 indirectly applicable as not all fractures were long bone.

f. 95% CI crosses one MID

g. Arti 2016, WOLLF, Stannard 2009, Virani 2016

h. Gupta 2013, Jayakumar 2013, Sibin 2017

i. I^2 greater than 33.3% but less than 66.7%

j. WOLLF

k. Some concerns due to attrition and subjective outcome

l. Single study analysis

Table 11: Deep infection by Gustilo and Anderson grade

Certainty assessment							№ of patients		Effect		Certainty
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	NPWT	Standard dressing	Relative (95% CI)	Absolute (95– CI)	
Deep infection – G&A subgroup analysis - II											
1[e]	randomised trials	very serious[f]	NA[d]	serious[c]	very serious[g]	none	0/3 (0.0%)	0/2 (0.0%)	not estimable	not estimable	⨁◯◯◯ Very low
Deep infection – G&A subgroup analysis - IIIA											

Certainty assessment							№ of patients		Effect		Certainty
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	NPWT	Standard dressing	Relative (95% CI)	Absolute (95– CI)	
1[e]	randomised trials	very serious[f]	NA[d]	serious[c]	serious[b]	none	1/15 (6.7%)	5/12 (41.7%)	**RR 0.16** (0.02 to 1.19)	**350 fewer per 1,000** (from 408 fewer to 79 more)	⊕◯◯◯ Very low

Deep infection – G&A subgroup analysis - IIIB

1[e]	randomised trials	very serious[f]	NA[d]	serious[c]	very serious[a]	none	1/18 (5.6%)	3/9 (33.3%)	**RR 0.17** (0.02 to 1.38)	**277 fewer per 1,000** (from 327 fewer to 127 more)	⊕◯◯◯ Very low

Deep infection – G&A subgroup analysis - IIIC

1[e]	randomised trials	very serious[f]	NA[d]	serious[c]	very serious[a]	none	0/1 (0.0%)	1/2 (50.0%)	**RR 0.50** (0.04 to 7.10)	**250 fewer per 1,000** (from 480 fewer to 1,000 more)	⊕◯◯◯ Very low

CI: confidence interval; **MD:** mean difference; **RR:** risk ratio

Explanation

a. 95% CI crosses both MIDs

b. 95% CI crosses one MID

c. Stannard 2009 indirectly applicable as not all fractures were long bone.

d. Single study analysis

e. Stannard 2009

f. Very serious concerns due to lack of information around allocation concealment, self-reported outcome measures where blinding was not possible, and bias in selection of the reported result,

g. No effect size estimable

Table 12: Hospital stay

Certainty assessment							№ of patients		Effect		Certainty
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	NPWT	Standard dressing	Relative (95% CI)	Absolute (95% CI)	
Duration of hospital stay [days] [MID 8.7] (Better indicated by lower values)											
2[e]	randomised trials	serious[f]	very serious[d]	not serious	serious[b]	none	276	284	-	MD **7.55 lower** (20.25 lower to 5.15 higher)	⨁◯◯◯ Very low
Hospital stay less than 1 month											

Certainty assessment							№ of patients		Effect		Certainty
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	NPWT	Standard dressing	Relative (95% CI)	Absolute (95% CI)	
3[c]	randomised trials	serious[a]	not serious	not serious	not serious	none	39/50 (78.0%)	9/50 (18.0%)	**RR 4.33** (2.35 to 7.98)	**599 more per 1,000** (from 243 more to 1,000 more)	⨁⨁⨁◯ Moderate

CI: confidence interval; **MD**: mean difference; **RR**: risk ratio

Explanations

a. greater than 33.3% of studies at moderate or high risk of bias

b. 95% CI crosses one of the MIDs

c. Gupta 2013, Jayakumar 2013, Sibin 2017

d. I^2 greater than 66.7%

e. Sagy 2020, WOLLF trial

f. Some concerns around randomisation as there was no information about allocation concealment or the method of randomisation and attrition

Table 13: Postoperative pain

Certainty assessment							№ of patients		Effect		Certainty
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	NPWT	Standard dressing	Relative (95% CI)	Absolute (95% CI)	
Postoperative pain											
1[c]	randomised trials	very serious[d]	NA[b]	not serious	very serious[a]	none	8/226 (3.5%)	11/234 (4.7%)	**RR 0.75** (0.31 to 1.84)	**12 fewer per 1,000** (from 32 fewer to 39 more)	⨁◯◯◯ Very low

CI: confidence interval; **MD:** mean difference; **RR:** risk ratio

Explanation

a. 95% CI crosses both MIDs

b. Single study analysis

c. WOLLF trial (Costa 2018, 2018b, 2022)

d. very serious concerns due to self-reported outcomes without blinding, and attrition.

Table 14: Post hoc analyses of tissue granulation

Certainty assessment							№ of patients		Effect		Certainty
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	NPWT	Standard dressing	Relative (95% CI)	Absolu–e (95% CI)	
Post-hoc - Time for appearance of 100% granulation tissue [MID 1] Better indicated by lower values											
1[b]	randomised trials	very serious[c]	NA[a]	serious[f]	not serious	none	50	50	-	MD **9.04 lower** (9.83 lower to 8.25 lower)	⨁◯◯◯ Very low
Post-hoc - appearance of 100% granulation tissue in less than 21 days											
1[d]	randomised trials	very serious[e]	NA[a]	serious[f]	not serious	none	21/25 (84.0%)	1/25 (4.0%)	**RR 21.00** (3.05 to 144.39)	**800 more per 1,000** (from 82 more to 1,000 more)	⨁◯◯◯ Very low

CI: confidence interval; **MD:** mean difference; **RR:** risk ratio

Explanation

a

a. Single study analysis

b. Sagy 2020

c. Some concerns around randomisation as there was no information about allocation concealment or the method of randomisation. There were also concerns around measurement of the outcome as this was likely assessed by unblinded assessors.

d. Rasool 2013

e. Very serious concerns as alternation was used, and it is likely that allocation was not concealed until all participants were enrolled and assigned to interventions. There were also concerns around measurement of the outcome as subjective assessment was likely carried out by an unblinded assessor. There are also no details about a trial protocol,

f. Outcome measure not in PICO for this review

Table 15: Function

Certainty assessment							№ of patients		Effect		Certainty
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	NPWT	Standard dressing	Relative (95% CI)	Absolu–e (95– CI)	
Function - DRI - 3 months (assessed with: Disability Rating Index [MID 8] Better indicated by lower values)											
1[b]	randomised trials	serious[c]	NA[a]	not serious	not serious	none	166	188	-	MD **1.3 lower** (5.75 lower to 3.15 higher)	⨁⨁⨁◯ Moderate
Function - DRI- 6 months (assessed with: Disability Rating Index [MID 8] Better indicated by lower values)											

Certainty assessment							№ of patients		Effect		Certainty
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	NPWT	Standard dressing	Relative (95% CI)	Absolu–e (95– CI)	
1[b]	randomised trials	serious[c]	NA[a]	not serious	serious[d]	none	154	175	-	MD **2.9 higher** (2.28 lower to 8.08 high–r)	⊕⊕◯◯ Low

Function - DRI - 9 months (assessed with: Disability Rating Index [MID 8] Better indicated by lower values)

1[b]	randomised trials	serious[c]	NA[a]	not serious	serious[d]	none	153	161	-	MD **3.8 higher** (1.86 lower to 9.46 high–r)	⊕⊕◯◯ Low

Function - DRI - 12 months (assessed with: Disability Rating Index [MID 8] Better indicated by lower values)

1[b]	randomised trials	serious[c]	NA[a]	not serious	serious[d]	none	179	195	-	MD **3.1 higher** (2.23 lower to 8.43 high–r)	⊕⊕◯◯ Low

Certainty assessment							№ of patients		Effect		Certainty
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	NPWT	Standard dressing	Relative (95% CI)	Absolu–e (95– CI)	
Function - DRI - 2 years (assessed with: Disability Rating Index [MID 8] Better indicated by lower values)											
1[b]	randomised trials	serious[c]	NA[a]	not serious	serious[d]	none	59	66	-	MD **2.52 lower** (11.76 lower to 6.72 high–r)	⊕⊕◯◯ Low
Function - DRI - 3 years (assessed with: Disability Rating Index [MID 8] Better indicated by lower values)											
1[b]	randomised trials	serious[c]	NA[a]	not serious	very serious[e]	none	39	49	-	MD **0.27 higher** (10.6 lower to 11.14 higher)	⊕◯◯◯ Very low
Function - DRI - 4 years (assessed with: Disability Rating Index [MID 8] Better indicated by lower values)											

Certainty assessment							№ of patients		Effect		Certainty
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	NPWT	Standard dressing	Relative (95% CI)	Absolu–e (95– CI)	
1[b]	randomised trials	serious[c]	NA[a]	not serious	serious[d]	none	61	61	-	MD **1.56 lower** (10.85 lower to 7.73 high–r)	⨁⨁◯◯ Low

Function - DRI - 5 years (assessed with: Disability Rating Index [MID 8] Better indicated by lower values)

1[b]	randomised trials	serious[c]	NA[a]	not serious	serious[d]	none	62	69	-	MD **3.52 lower** (11.71 lower to 4.67 higher)	⨁⨁◯◯ Low

CI: confidence interval; **MD:** mean difference; **RR:** risk ratio

Explanation

a. Single study analysis

b. WOLLF trial (Costa 2018, 2018b, 2022)

c. Some concerns due to self-reported outcomes without blinding

d. 95% CI crosses one the MID of 8 points [taken from Costa 2018]

e. 95% confidence interval crosses both MIDs (set at 8 points by Costa 2018)

Table 16: Quality of life

Certainty assessment							№ of patients		Effect		Certainty
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	NPWT	Standard dressing	Relative (95% CI)	Absolute (95% CI)	
HR–oL- EQ-5D-3L (utility) - post-injury [MID 0.15] Better indicated by higher values											
1[c]	randomised trials	serious[d]	NA[b]	not serious	not serious	none	210	226	-	MD **0** (0.06 lower to 0.06 higher–	⨁⨁⨁◯ Moderate
HRQ–L - EQ-5D-3L (utility) - 3 months [MID 0.16] Better indicated by higher values											
1[c]	randomised trials	serious[d]	NA[b]	not serious	not serious	none	152	175	-	MD **0** (0.07 lower to 0.07 higher–	⨁⨁⨁◯ Moderate
HRQoL - EQ-5D-3L (utility)- 6 months [MID 0.16] Better indicated by higher values											

Certainty assessment							№ of patients		Effect		Certainty
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	NPWT	Standard dressing	Relative (95% CI)	Absolute (95% CI)	
1[c]	randomised trials	serious[d]	NA[b]	not serious	not serious	none	146	166	-	MD **0** (0.07 lower to 0.07 higher–	⊕⊕⊕◯ Moderate

HRQoL - EQ-5D-3L (utility)- 9 months [MID 0.15] Better indicated by higher values

1[c]	randomised trials	serious[d]	NA[b]	not serious	not serious	none	144	154	-	MD **0.03 higher** (0.04 lower to 0.1 higher–	⊕⊕⊕◯ Moderate

HRQ–L - EQ-5D-3L (utility) - 12 months [MID 0.16] Better indicated by higher values

1[c]	randomised trials	serious[d]	NA[b]	not serious	not serious	none	172	192	-	MD **0.01 higher** (0.06 lower to 0.08 higher–	⊕⊕⊕◯ Moderate

HRQ–L - EQ-5D-3L (utility) - 2 years [MID 0.13] Better indicated by higher values

Certainty assessment							№ of patients		Effect		Certainty
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	NPWT	Standard dressing	Relative (95% CI)	Absolute (95% CI)	
1[c]	randomised trials	serious[d]	NA[b]	not serious	not serious	none	58	65	-	MD **0.03 lower** (0.12 lower to 0.06 higher–	⊕⊕⊕◯ Moderate

HRQ–L - EQ-5D-3L (utility) - 3 years [MID 0.16] Better indicated by higher values

1[c]	randomised trials	serious[d]	NA[b]	not serious	serious[a]	none	38	49	-	MD **0.04 lower** (0.17 lower to 0.08 h– gher)	⊕⊕◯◯ Low

HRQ–L - EQ-5D-3L (utility) - 4 years [MID 0.14] Better indicated by higher values

1[c]	randomised trials	serious[d]	NA[b]	not serious	serious[a]	none	56	63	-	MD **0.06 lower** (0.16 lower to 0.05 h– gher)	⊕⊕◯◯ Low

Certainty assessment							№ of patients		Effect		Certainty
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	NPWT	Standard dressing	Relative (95% CI)	Absolute (95% CI)	
HRQ–L - EQ-5D-3L (utility) - 5 years [MID 0.14] Better indicated by higher values											
1[c]	randomised trials	serious[d]	NA[b]	not serious	not serious	none	63	69	-	MD **0.03 lower** (0.13 lower to 0.07 higher–	⨁⨁⨁◯ Moderate
HRQoL - EQ-5D VAS - post-injury [MID 12] Better indicated by higher values											
1[c]	randomised trials	serious[d]	NA[b]	not serious	not serious	none	210	223	-	MD **0.91 lower** (5.36 lower to 3.54 higher–	⨁⨁⨁◯ Moderate
HRQoL - EQ-5D VAS - 3 months [MID 12] Better indicated by higher values											

Certainty assessment							№ of patients		Effect		Certainty
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	NPWT	Standard dressing	Relative (95% CI)	Absolute (95% CI)	
1[c]	randomised trials	serious[d]	NA[b]	not serious	not serious	none	151	175	-	MD **3.28 higher** (1.55 lower to 8.11 higher–	⨁⨁⨁◯ Moderate

HRQoL - EQ-5D VAS - 6 months [MID 12] Better indicated by higher values

1[c]	randomised trials	serious[d]	NA[b]	not serious	not serious	none	144	165	-	MD **0.5 higher** (4.62 lower to 5.62 higher–	⨁⨁⨁◯ Moderate

HRQoL - EQ-5D VAS - 9 months [MID 12] Better indicated by higher values

1[c]	randomised trials	serious[d]	NA[b]	not serious	not serious	none	144	151	-	MD **1.7 higher** (3.56 lower to 6.96 higher–	⨁⨁⨁◯ Moderate

Certainty assessment							№ of patients		Effect		Certainty
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	NPWT	Standard dressing	Relative (95% CI)	Absolute (95% CI)	
HRQoL - EQ-5D VAS - 12 months [MID 12] Better indicated by higher values											
1[c]	randomised trials	serious[d]	NA[b]	not serious	not serious	none	174	190	-	MD **0.6 higher** (4.22 lower to 5.42 higher–	⨁⨁⨁◯ Moderate
HRQoL - EQ-5D VAS - 2 years [MID 11] Better indicated by higher values											
1[c]	randomised trials	serious[d]	NA[b]	not serious	not serious	none	59	66	-	MD **2.91 lower** (10.42 lower to 4.6 higher–	⨁⨁⨁◯ Moderate
HRQoL - EQ-5D VAS - 3 years [MID 10] Better indicated by higher values											

Certainty assessment							№ of patients		Effect		Certainty
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	NPWT	Standard dressing	Relative (95% CI)	Absolute (95% CI)	
1[c]	randomised trials	serious[d]	NA[b]	not serious	not serious	none	39	48	-	MD **0.07 lower** (9.04 lower to 8.9 higher–	⊕⊕⊕◯ Moderate

HRQoL - EQ-5D VAS - 4 years [MID 11] Better indicated by higher values

1[c]	randomised trials	serious[d]	NA[b]	not serious	serious[a]	none	56	62	-	MD **6.49 lower** (14.18 lower to 1.2 h– gher)	⊕⊕◯◯ Low

HRQoL - EQ-5D VAS - 5 years [MID 10] Better indicated by higher values

1[c]	randomised trials	serious[d]	NA[b]	not serious	not serious	none	63	69	-	MD **0.89 lower** (7.88 lower to 6.1 higher–	⊕⊕⊕◯ Moderate

HRQoL - SF-12 - PCS - 3 months [MID 6] Better indicated by higher values

Certainty assessment							№ of patients		Effect		Certainty
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	NPWT	Standard dressing	Relative (95% CI)	Absolute (95% CI)	
1[c]	randomised trials	serious[d]	NA[b]	not serious	not serious	none	138	164	-	MD **0.5 higher** (2.23 lower to 3.23 higher–	⨁⨁⨁◯ Moderate

HRQoL - SF-12 - PCS - 6 months [MID 8] Better indicated by higher values

1[c]	randomised trials	serious[d]	NA[b]	not serious	not serious	none	132	156	-	MD **0.1 higher** (3.33 lower to 3.53 higher–	⨁⨁⨁◯ Moderate

HRQoL - SF-12 - PCS - 9 months [MID 8] Better indicated by higher values

1[c]	randomised trials	serious[d]	NA[b]	not serious	not serious	none	130	137	-	MD **0.2 higher** (3.75 lower to 4.15 higher–	⨁⨁⨁◯ Moderate

Certainty assessment							№ of patients		Effect		Certainty
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	NPWT	Standard dressing	Relative (95% CI)	Absolute (95% CI)	
HRQoL - SF-12 - PCS - 12 months [MID 8] Better indicated by higher values											
1[c]	randomised trials	serious[d]	NA[b]	not serious	not serious	none	154	175	-	MD **0.5 higher** (3.08 lower to 4.08 higher–	⊕⊕⊕◯ Moderate
HRQoL - SF-12 - MCS - 3 months [MID 5] Better indicated by higher values											
1[c]	randomised trials	serious[d]	NA[b]	not serious	not serious	none	138	164	-	MD **0.4 higher** (1.64 lower to 2.44 higher–	⊕⊕⊕◯ Moderate
HRQoL - SF-12 - MCS - 6 months [MID 5] Better indicated by higher values											

Certainty assessment							№ of patients		Effect		Certainty
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	NPWT	Standard dressing	Relative (95% CI)	Absolute (95% CI)	
1[c]	randomised trials	serious[d]	NA[b]	not serious	not serious	none	132	156	-	MD **0.4 lower** (2.57 lower to 1.77 higher–	⨁⨁⨁◯ Moderate

HRQoL - SF-12 - MCS - 9 months [MID 4] Better indicated by higher values

1[c]	randomised trials	serious[d]	NA[b]	not serious	not serious	none	130	137	-	MD **1.5 higher** (0.56 lower to 3.56 higher–	⨁⨁⨁◯ Moderate

HRQoL - SF-12 - MCS - 12 months [MID 4] Better indicated by higher values

1[c]	randomised trials	serious[d]	NA[b]	not serious	not serious	none	154	175	-	MD **0.4 lower** (2.2 lower to 1.4 higher)	⨁⨁⨁◯ Moderate

CI: confidence interval; **MD:** mean difference; **RR:** risk ratio

Explanation

a. 95% CI crosses one MID

b. Single study analysis

c. WOLLF trial (Costa 2018, 2018b, 2022)

d. Some concerns due to self-reported outcomes without blinding

Table 17: Re-operation or amputation

Certainty assessment							№ of patients		Effect		Certainty
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	NPWT	Standard dressing	Relative (95% CI)	Absolute (95% CI)	
Re-operation/amputation within 12 months - Revision fixation											
1[d]	randomised trials	serious[e]	not serious[c]	not serious	very serious[a]	none	18/226 (8.0%)	15/234 (6.4%)	RR 1.24 (0.64 to 2.40)	**15 more per 1,000** (from 23 fewer to 90 more)	⨁◯◯◯ Very low
Re-operation/amputation within 12 months - Wound management											

Certainty assessment							№ of patients		Effect		Certainty
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	NPWT	Standard dressing	Relative (95% CI)	Absolute (95% CI)	
1[d]	randomised trials	serious[e]	not serious[c]	not serious	very serious[a]	none	19/226 (8.4%)	21/234 (9.0%)	RR 0.94 (0.52 to 1.70)	**5 fewer per 1,000** (from 43 fewer to 63 more)	⊕◯◯◯ Very low

Re-operation/amputation within 12 months - Bone graft

1[d]	randomised trials	serious[e]	not serious[c]	not serious	serious[b]	none	10/226 (4.4%)	18/234 (7.7%)	RR 0.58 (0.27 to 1.22)	**32 fewer per 1,000** (from 56 fewer to 17 more)	⊕⊕◯◯ Low

Re-operation/amputation within 12 months - Amputation

1[d]	randomised trials	serious[e]	not serious[c]	not serious	very serious[a]	none	4/226 (1.8%)	6/234 (2.6%)	RR 0.69 (0.20 to 2.41)	**8 fewer per 1,000** (from 21 fewer to 36 more)	⊕◯◯◯ Very low

Re-operation/amputation - 2-year follow-up - Metalwork removal

Certainty assessment							№ of patients		Effect		Certainty
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	NPWT	Standard dressing	Relative (95% CI)	Absolute (95% CI)	
1[d]	randomised trials	serious[e]	not serious[c]	not serious	very serious[a]	none	14/59 (23.7%)	10/66 (15.2%)	RR 1.57 (0.75 to 3.25)	**86 more per 1,000** (from 38 fewer to 341 more)	⨁◯◯◯ Very low

Re-operation/amputation - 2-year follow-up - Surgery for nonunion

1[d]	randomised trials	serious[e]	not serious[c]	not serious	very serious[a]	none	6/59 (10.2%)	9/66 (13.6%)	RR 0.75 (0.28 to 1.97)	**34 fewer per 1,000** (from 98 fewer to 132 more)	⨁◯◯◯ Very low

Re-operation/amputation - 2-year follow-up - Surgery to revise/augment fixation

1[d]	randomised trials	serious[e]	not serious[c]	not serious	very serious[a]	none	2/59 (3.4%)	6/66 (9.1%)	RR 0.37 (0.08 to 1.78)	**57 fewer per 1,000** (from 84 fewer to 71 more)	⨁◯◯◯ Very low

Certainty assessment							№ of patients		Effect		Certainty
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	NPWT	Standard dressing	Relative (95% CI)	Absolute (95% CI)	
Re-operation/amputation - 2-year follow-up - Amputation											
1[d]	randomised trials	serious[e]	not serious[c]	not serious	very serious[a]	none	2/59 (3.4%)	0/66 (0.0%)	RR 5.58 (0.27 to 113.99)	**0 fewer per 1,000** (from 0 fewer to 0 fewer)	⨁◯◯◯ Very low
Re-operation/amputation - 2-year follow-up - Other treatment											
1[d]	randomised trials	serious[e]	not serious[c]	not serious	very serious[a]	none	6/59 (10.2%)	7/66 (10.6%)	RR 0.96 (0.34 to 2.69)	**4 fewer per 1,000** (from 70 fewer to 179 more)	⨁◯◯◯ Very low
Re-operation/amputation - 3-year follow-up - Metalwork removal											

Certainty assessment							№ of patients		Effect		Certainty
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	NPWT	Standard dressing	Relative (95% CI)	Absolute (95% CI)	
1[d]	randomised trials	serious[e]	not serious[c]	not serious	very serious[a]	none	4/39 (10.3%)	5/49 (10.2%)	RR 1.01 (0.29 to 3.49)	**1 more per 1,000** (from 72 fewer to 254 more)	⨁◯◯◯ Very low

Re-operation/amputation - 3-year follow-up - Surgery for nonunion

1[d]	randomised trials	serious[e]	not serious[c]	not serious	very serious[a]	none	0/39 (0.0%)	3/49 (6.1%)	RR 0.18 (0.01 to 3.36)	**50 fewer per 1,000** (from 61 fewer to 144 more)	⨁◯◯◯ Very low

Re-operation/amputation - 3-year follow-up - Surgery to revise/augment fixation

Certainty assessment							№ of patients		Effect		Certainty
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	NPWT	Standard dressing	Relative (95% CI)	Absolute (95% CI)	
1[d]	randomised trials	serious[e]	not serious[c]	not serious	very serious[a]	none	2/39 (5.1%)	2/49 (4.1%)	RR 1.26 (0.19 to 8.52)	**11 more per 1,000** (from 33 fewer to 307 more)	⨁◯◯◯ Very low

Re-operation/amputation - 3-year follow-up - Amputation

1[d]	randomised trials	serious[e]	not serious[c]	not serious	very serious[a]	none	1/39 (2.6%)	0/49 (0.0%)	RR 3.75 (0.16 to 89.59)	**0 fewer per 1,000** (from 0 fewer to 0 fewer)	⨁◯◯◯ Very low

Re-operation/amputation - 3-year follow-up - Other treatment

1[d]	randomised trials	serious[e]	not serious[c]	not serious	very serious[a]	none	1/39 (2.6%)	1/49 (2.0%)	RR 1.26 (0.08 to 19.45)	**5 more per 1,000** (from 19 fewer to 377 more)	⨁◯◯◯ Very low

Certainty assessment							№ of patients		Effect		Certainty
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	NPWT	Standard dressing	Relative (95% CI)	Absolute (95% CI)	
Re-operation/amputation - 4-year follow-up - Metalwork removal											
1[d]	randomised trials	serious[e]	not serious[c]	not serious	very serious[a]	none	5/56 (8.9%)	1/64 (1.6%)	RR 5.71 (0.69 to 47.46)	**74 more per 1,000** (from 5 fewer to 726 more)	⨁◯◯◯ Very low
Re-operation/amputation - 4-year follow-up - Surgery for nonunion											
1[d]	randomised trials	serious[e]	not serious[c]	not serious	very serious[a]	none	4/56 (7.1%)	3/64 (4.7%)	RR 1.52 (0.36 to 6.52)	**24 more per 1,000** (from 30 fewer to 259 more)	⨁◯◯◯ Very low
Re-operation/amputation - 4-year follow-up - Surgery to revise/augment fixation											

Certainty assessment							№ of patients		Effect		Certainty
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	NPWT	Standard dressing	Relative (95% CI)	Absolute (95% CI)	
1[d]	randomised trials	serious[e]	not serious[c]	not serious	very serious[a]	none	4/56 (7.1%)	0/64 (0.0%)	RR 10.26 (0.56 to 186.53)	**0 fewer per 1,000** (from 0 fewer to 0 fewer)	⨁◯◯◯ Very low

Re-operation/amputation - 4-year follow-up - Amputation

1[d]	randomised trials	serious[e]	not serious[c]	not serious	very serious[a]	none	0/56 (0.0%)	1/64 (1.6%)	RR 0.38 (0.02 to 9.15)	**10 fewer per 1,000** (from 15 fewer to 127 more)	⨁◯◯◯ Very low

Re-operation/amputation - 4-year follow-up - Other treatment

1[d]	randomised trials	serious[e]	not serious[c]	not serious	very serious[a]	none	4/56 (7.1%)	5/64 (7.8%)	RR 0.91 (0.26 to 3.24)	**7 fewer per 1,000** (from 58 fewer to 175 more)	⨁◯◯◯ Very low

Certainty assessment							№ of patients		Effect		Certainty
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	NPWT	Standard dressing	Relative (95% CI)	Absolute (95% CI)	
Re-operation/amputation - 5-year follow-up - Metalwork removal											
1[d]	randomised trials	serious[e]	not serious[c]	not serious	very serious[a]	none	3/64 (4.7%)	5/72 (6.9%)	RR 0.68 (0.17 to 2.71)	**22 fewer per 1,000** (from 58 fewer to 119 more)	⨁◯◯◯ Very low
Re-operation/amputation - 5-year follow-up - Surgery for nonunion											
1[d]	randomised trials	serious[e]	not serious[c]	not serious	very serious[a]	none	0/64 (0.0%)	3/72 (4.2%)	RR 0.16 (0.01 to 3.05)	**35 fewer per 1,000** (from 41 fewer to 85 more)	⨁◯◯◯ Very low
Re-operation/amputation - 5-year follow-up - Surgery to revise/augment fixation											

Certainty assessment							№ of patients		Effect		Certainty
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	NPWT	Standard dressing	Relative (95% CI)	Absolute (95% CI)	
1[d]	randomised trials	serious[e]	not serious[c]	not serious	very serious[a]	none	0/64 (0.0%)	2/72 (2.8%)	RR 0.22 (0.01 to 4.59)	**22 fewer per 1,000** (from 27 fewer to 100 more)	⊕◯◯◯ Very low

Re-operation/amputation - 5-year follow-up - Amputation

1[d]	randomised trials	serious[e]	not serious[c]	not serious	very serious[a]	none	1/64 (1.6%)	0/72 (0.0%)	RR 3.37 (0.14 to 81.27)	**0 fewer per 1,000** (from 0 fewer to 0 fewer)	⊕◯◯◯ Very low

Re-operation/amputation - 5-year follow-up - Other treatment

1[d]	randomised trials	serious[e]	not serious[c]	not serious	very serious[a]	none	4/64 (6.3%)	5/72 (6.9%)	RR 0.90 (0.25 to 3.21)	**7 fewer per 1,000** (from 52 fewer to 153 more)	⊕◯◯◯ Very low

Certainty assessment							№ of patients		Effect		Certainty
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	NPWT	Standard dressing	Relative (95% CI)	Absolute (95% CI)	
Re-operation/amputation - any year - Metalwork removal											
1[d]	randomised trials	serious[e]	not serious[c]	not serious	very serious[a]	none	20/81 (24.7%)	17/89 (19.1%)	RR 1.29 (0.73 to 2.29)	**55 more per 1,000** (from 52 fewer to 246 more)	⨁◯◯◯ Very low
Re-operation/amputation - any year - Surgery for nonunion											
1[d]	randomised trials	serious[e]	not serious[c]	not serious	serious[b]	none	9/81 (11.1%)	17/89 (19.1%)	RR 0.58 (0.27 to 1.23)	**80 fewer per 1,000** (from 139 fewer to 44 more)	⨁⨁◯◯ Low
Re-operation/amputation - any year - Surgery to revise/augment fixation											

Certainty assessment							№ of patients		Effect		Certainty
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	NPWT	Standard dressing	Relative (95% CI)	Absolute (95% CI)	
1[d]	randomised trials	serious[d]	not serious[c]	not serious	very serious[a]	none	8/81 (9.9%)	10/89 (11.2%)	RR 0.88 (0.36 to 2.12)	**13 fewer per 1,000** (from 72 fewer to 126 more)	⨁◯◯◯ Very low

Re-operation/amputation - any year - Amputation

1[d]	randomised trials	serious[e]	not serious[c]	not serious	very serious[a]	none	2/81 (2.5%)	3/89 (3.4%)	RR 0.73 (0.13 to 4.27)	**9 fewer per 1,000** (from 29 fewer to 110 more)	⨁◯◯◯ Very low

Re-operation/amputation - any year - Other treatment

Certainty assessment							№ of patients		Effect		Certainty
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	NPWT	Standard dressing	Relative (95% CI)	Absolute (95% CI)	
1[d]	randomised trials	serious[e]	not serious[c]	not serious	very serious[a]	none	13/81 (16.0%)	17/89 (19.1%)	RR 0.84 (0.44 to 1.62)	**31 fewer per 1,000** (from 107 fewer to 118 more)	⨁◯◯◯ Very low

CI: confidence interval; **MD**: mean difference; **RR**: risk ratio

Explanations

a. 95% CI crosses both MIDs

b. 95% CI crosses one MID

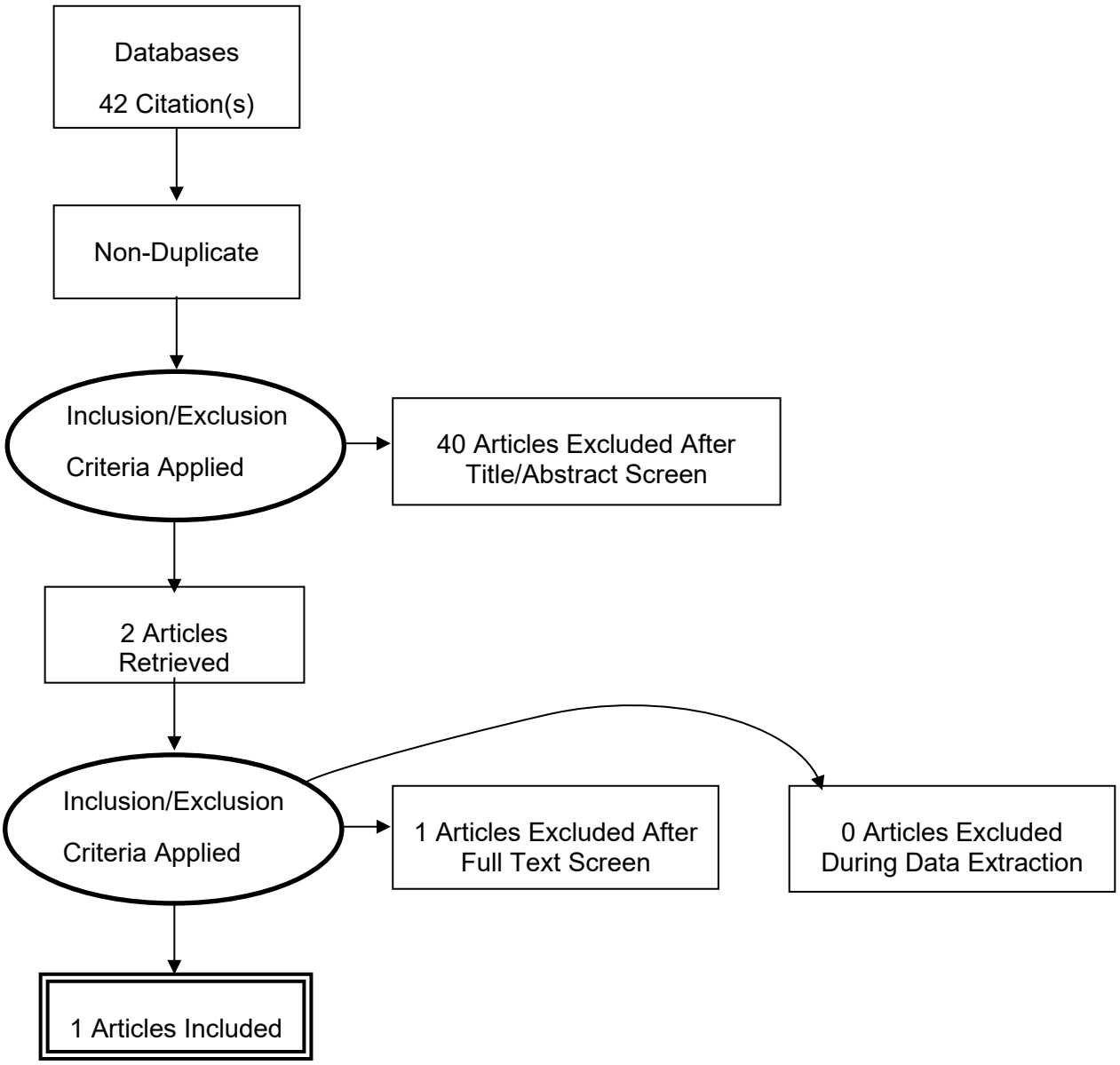
c. Single study analysis

d. WOLLF trial (Costa 2018, 2018b, 2022)

e. Some concerns due to attrition

Appendix G – Economic evidence study selection

Figure 4: Economic evidence study selection flowchart



Appendix H – Economic evidence tables

Study	Study type	Setting	Interventions	Population	Methods of analysis	Base-case results	Sensitivity analyses	Additional comments
Petrou et al 2019	Cost-utility study alongside the WOLLF study Time horizon: 12 months	UK NHS and PSS perspective Based in a hospital setting	Negative Pressure Wound Therapy (NPWT) Standard wound dressing Both sets of patients received surgical debridement before NPWT or the standard wound dressing	NPWT (n=226): Mean age 46.1, 78.8% male, 6.2% had diabetes, 31% were smokers Standard wound dressing (n=234): Mean age 44.5, 70.1% male, 5.6% had diabetes, 33.8% were smokers	QALY: WOLLF participants used the EQ-5D-3L at baseline, 3, 6, 9 and, 12 months. The York A1 tariff set was applied to obtain a utility score. Multiple imputation was used to account for missing data and obtain a full data set. Costs: Staff and consumable resource use was obtained from a sample of 38 WOLLF participants (NPWT n=20, Standard n=18) and were obtained from the finance department at University Hospital Coventry and Warwickshire. Readmission costs were obtained from NHS reference costs 2014/15. Further costs (aids and adaptions, community care costs) were obtained from PSSRU 2015. Medications were sourced from the NHS Prescription cost Analysis database 2014	Incremental costs: £678[(a)] (95% CI: -£1,082 to £2,438) Incremental QALYs: 0.002 (95% CI: -0.054 to 0.059) ICER: £267,910[(a)] NMB (£20,000 per QALY threshold): -£606 (95% CI: -£2,210 to £938) Absolute costs and QALYs were not reported	Deterministic: None Probabilistic: Probability that NPWT is cost effective at £20,000 threshold was 24.4%. Probability that NPWT is cost effective does not exceed 27% at any threshold. Scenario: Adopting a broader societal perspective increases the ICER to £282,858. Restricting the analysis to patients with full data resulted in NPWT being the dominant treatment (NPWT is less costly and more effective).	Source of funding: NIHR and HTA Limitation: Full health economic data over the study follow up period was only available for 31% of the participants. Authors conclusion: NPWT is unlikely to be cost effective for improving outcomes in adult patients with severe open fractures of the lower limb.

These values were directly reported in the paper and not inflated

Table 2: Economic evaluation checklist [for appendix]

Study identification Include author, title, reference, year of publication		
Category	**Rating**	**Comments**
Applicability		
1.1 Is the study population appropriate for the review question?	Yes	
1.2 Are the interventions appropriate for the review question?	Yes	

Study identification Include author, title, reference, year of publication		
Category	**Rating**	**Comments**
1.3 Is the system in which the study was conducted sufficiently similar to the current UK context?	Yes	
1.4 Is the perspective for costs appropriate for the review question?	Yes	
1.5 Is the perspective for outcomes appropriate for the review question?	Yes	
1.6 Are all future costs and outcomes discounted appropriately?	Yes	No discounting is necessary as the time horizon was 12 months.
1.7 Are QALYs, derived using NICE's preferred methods, or an appropriate social care-related equivalent used as an outcome? If not, describe rationale and outcomes used in line with analytical perspectives taken (item 1.5 above).	Yes	
1.8 OVERALL JUDGEMENT	**DIRECTLY APPLICABLE**	
Limitations		
2.1 Does the model structure adequately reflect the nature of the topic under evaluation?	Yes	
2.2 Is the time horizon sufficiently long to reflect all important differences in costs and outcomes?	Yes	12 months
2.3 Are all important and relevant outcomes included?	Yes	
2.4 Are the estimates of baseline outcomes from the best available source?	Yes	
2.5 Are the estimates of relative intervention effects from the best available source?	Yes	
2.6 Are all important and relevant costs included?	Yes	
2.7 Are the estimates of resource use from the best available source?	Yes	
2.8 Are the unit costs of resources from the best available source?	Yes	
2.9 Is an appropriate incremental analysis presented or can it be calculated from the data?	Yes	The absolute data was not presented, only the incremental data.

Study identification Include author, title, reference, year of publication		
Category	**Rating**	**Comments**
2.10 Are all important parameters whose values are uncertain subjected to appropriate sensitivity analysis?	Yes	
2.11 Has no potential financial conflict of interest been declared?	Yes	
2.12 OVERALL ASSESSMENT	**MINOR LIMITATIONS**	

Appendix I – Excluded studies

I.1 Studies excluded at full text from the effectiveness review

Study	Reason for exclusion
Achten, J.; Parsons, N.R.; Bruce, J. (2016) Correction: Protocol for a randomised controlled trial of standard wound management versus negative pressure wound therapy in the treatment of adult patients with an open fracture of the lower limb: UK Wound management of Lower Limb Fractures (UK WOLLF). BMJ Open 6(5): 009087corr1	- Correction only
Achten, Juul, Parsons, Nick R, Bruce, Julie et al. (2015) Protocol for a randomised controlled trial of standard wound management versus negative pressure wound therapy in the treatment of adult patients with an open fracture of the lower limb: UK Wound management of Lower Limb Fractures (UK WOLLF). BMJ open 5(9): e009087	- Protocol only
Achten, Juul, Vadher, Karan, Bruce, Julie et al. (2018) Standard wound management versus negative-pressure wound therapy in the treatment of adult patients having surgical incisions for major trauma to the lower limb-a two-arm parallel group superiority randomised controlled trial: protocol for Wound Healing in Surgery for Trauma (WHIST). BMJ open 8(6): e022115	- Does not contain a population of people with open fracture
Ali, E and Raghuvanshi, M (2017) Treatment of open upper limb injuries with infection prevention and negative pressure wound therapy: a systematic review. Journal of wound care 26(12): 712-719	- Systematic review used as source of primary studies
Arundel, Catherine, Buckley, Hannah, Clarke, Emma et al. (2016) Negative pressure wound therapy versus usual care for Surgical Wounds Healing by Secondary Intention (SWHSI trial): study protocol for a randomised controlled pilot trial. Trials 17: 1-7	- Does not contain a population of people with open fracture
Atwan, Y, Sprague, S, Slobogean, GP et al. (2022) Does negative pressure wound therapy reduce the odds of infection and improve health-related quality of life in patients with open fractures?. Bone & joint open 3(3): 189-195	- Comparator in study does not match that specified in protocol
Bruce, J., Verdun, A., Davis, S. et al. (2017) Using photographic images to aid wound assessment within a randomised controlled trial of standard wound management versus negative pressure wound therapy: UK WOLLF trial. Trials 18(supplement1)	- Conference abstract
Cook, Rob, Thomas, Vaughan, Martin, Rosie et al. (2019) Negative pressure dressings are no better than standard dressings for open fractures. BMJ (Clinical research ed.) 364: k4411	- Editorial, opinion piece or letter
Costa, Matthew L. (2018) Negative Pressure Wound Therapy for Open Fractures-Reply...Costa ML, Achten J, Bruce J, et al; UK WOLLF Collaboration. Effect of negative pressure wound therapy vs standard wound management on 12-month disability among adults with severe open fracture of the lower limb: the WOLLF randomized clinical trial.	- Editorial, opinion piece or letter

Study	Reason for exclusion
JAMA . 2018;319(22):2280-2288. JAMA: Journal of the American Medical Association 320(16): 1709-1710	
Grant-Freemantle, M.C., Ryan, E.J., Moloney, D.P. et al. (2019) The effectiveness of negative pressure wound therapy versus conventional dressing in the treatment of open fractures: A systematic review and meta analysis. Irish Journal of Medical Science 188(supplement8): 1866	- Conference abstract
Grant-Freemantle, Marc C, Ryan, Eanna J, Flynn, Sean O et al. (2020) The Effectiveness of Negative Pressure Wound Therapy Versus Conventional Dressing in the Treatment of Open Fractures: A Systematic Review and Meta-Analysis. Journal of orthopaedic trauma 34(5): 223-230	- Systematic review used as source of primary studies
Iheozor-Ejiofor, Zipporah, Newton, Katy, Dumville, Jo C et al. (2018) Negative pressure wound therapy for open traumatic wounds. The Cochrane database of systematic reviews 7: cd012522	- Systematic review used as source of primary studies
Kim, Jun-Ho and Lee, Dae-Hee (2019) Negative pressure wound therapy vs. conventional management in open tibia fractures: Systematic review and meta-analysis. Injury 50(10): 1764-1772	- Systematic review used as source of primary studies
Liu, Xi, Zhang, Hui, Cen, Shiqiang et al. (2018) Negative pressure wound therapy versus conventional wound dressings in treatment of open fractures: A systematic review and meta-analysis. International journal of surgery (London, England) 53: 72-79	- Systematic review used as source of primary studies
Myatt, A., Saleeb, H., Robertson, G.A.J. et al. (2021) Management of Gustilo-Anderson IIIB open tibial fractures in adults - A systematic review. British Medical Bulletin 139(1): 48-58	- Systematic review used as source of primary studies
Newton, K., Wordsworth, M., Allan, A.Y. et al. (2017) Negative pressure wound therapy for traumatic wounds. Cochrane Database of Systematic Reviews 2017(1): cd012522	- Protocol only
Papes, Dino (2018) Negative Pressure Wound Therapy for Open Fractures...Costa ML, Achten J, Bruce J, et al; UK WOLLF Collaboration. Effect of negative pressure wound therapy vs standard wound management on 12-month disability among adults with severe open fracture of the lower limb: the WOLLF randomized clinical trial. JAMA. 2018;319(22):2280-2288. JAMA: Journal of the American Medical Association 320(16): 1709-1709	- Editorial, opinion piece or letter
Petrou, S, Parker, B, Masters, J et al. (2019) Cost-effectiveness of negative-pressure wound therapy in adults with severe open fractures of the lower limb: evidence from the WOLLF randomized controlled trial. The bone & joint journal 101b(11): 1392-1401	- Secondary publication of an included study that does not provide any additional relevant information

Study	Reason for exclusion
Qian, H.; Lei, T.; Hu, Y. (2022) Negative pressure wound therapy versus gauze dressings in managing open fracture wound of lower limbs: A meta-analysis of randomized controlled trials. Foot and Ankle Surgery	- Systematic review used as source of primary studies
Schlatterer, Daniel R; Hirschfeld, Adam G; Webb, Lawrence X (2015) Negative pressure wound therapy in grade IIIB tibial fractures: fewer infections and fewer flap procedures?. Clinical orthopaedics and related research 473(5): 1802-11	- Systematic review used as source of primary studies
Sinha K, Chauhan VD, Maheshwari R et al. (2013) Vacuum Assisted Closure Therapy versus Standard Wound Therapy for Open Musculoskeletal Injuries. Advances in orthopedics 2013: 245940	- Does not contain an outcome of interest
Tahir, M., Chaudhry, E.A., Zimri, F.K. et al. (2020) Negative pressure wound therapy versus conventional dressing for open fractures in lower extremity trauma: A multicentre randomized controlled trial. Bone and Joint Journal 102(7): 912-917	- Publication has been retracted
Tahir, Muhammad, Chaudhry, Ejaz A, Zimri, Faridullah K et al. (2020) [RETRACTED] Negative pressure wound therapy versus conventional dressing for open fractures in lower extremity trauma. The bone & joint journal 102b(7): 912-917	- Publication has been retracted

I.2 Studies excluded at full text from the economic review

Study	Reason for exclusion
Iheozor-Ejiofor Z, Newton K, Dumville JC, Costa ML, Norman G, Bruce J. Negative pressure wound therapy for open traumatic wounds. Cochrane Database of Systematic Reviews 2018, Issue 7. Art. No.: CD012522. DOI: 10.1002/14651858.CD012522.pub2.	Study is based on the same data as Petrou et al. 2019 with the same results. Therefore the more recent study was used.

Appendix J – Research recommendation – full details

J.1 Research recommendation

What is the most clinically and cost effective temporary (up to 72 hours) dressing (including negative pressure dressings) for open fractures after wound excision for:

- minimising the number of dressing changes or supplementary dressings
- minimising the number of associated bedding changes
- acceptability to patients, for example minimising patient pain
- minimising nursing time.

J.2 Why this is important

Dressing of open fractures between wound excision and definitive closure (before 72 hours) has little impact on medium- and long-term outcomes, however it is important to minimise the number of dressing changes during this time to reduce the risks associated with dressing changes (for example, pain, misapplication of dressing, risk of infection), to minimise the amount of nursing time taken with redressing and with bed-linen changes, and to maximise patient comfort and acceptability. Further research is required to establish what method of temporary wound dressing is most effective for this purpose.

J.3 Rationale for research recommendation

Importance to 'patients' or the population	Patient comfort and autonomy is dependent on the type of wound dressing used. Inappropriate dressings will mean that the dressing will need to be changed much more regularly which may be uncomfortable or painful for the patient.
Relevance to NICE guidance	Previous versions of the guideline recommended considering negative pressure wound therapy (NPWT) for this, but more recent research has shown this is unlikely to be effective or cost-effective. Future iterations of the guideline will benefit from more evidence about alternative dressings and their effectiveness.
Relevance to the NHS	Reduction of dressing changes and bed changes will lead to more efficient use of nursing time and less resource use in terms of number of dressings and clinical waste.
National priorities	Low
Current evidence base	Some UK and international data on NPWT
Equality considerations	None known

J.4 Modified PICO table

Population	Children, young people, and adults with an open long bone fracture who have had wound

	excision, but definitive soft tissue cover has not been performed
Intervention	Temporary dressing (including negative pressure dressings) until definitive coverage
Comparator	Other dressing
Outcome	• Number of dressing changes • Number of dressing supplementations • Number of bed-linen changes due to exudate • Acceptability to patient, including patient pain and discomfort (measured using a validated scale) • • Nursing time
Study design	Randomised Controlled Trial Cost-utility study
Timeframe	72 hours (time to definitive coverage)
Additional information	None

Appendix K – Methods

Development of the guideline

What this guideline covers

This guideline covers the use of negative pressure wound therapy for temporary cover of open fractures after surgical debridement (including wound excision) where immediate definitive soft tissue cover has not been performed.

What this guideline does not cover

For all other areas of the guideline:

- There will be no evidence review.
- We may make changes to ensure consistency.

Methods

This guideline was developed using the methods described in the 2022 NICE guidelines manual.

Declarations of interest were recorded according to NICE's conflicts of interest policy.

Developing the review questions and outcomes

The review questions developed for this guideline was based on the key areas identified in the guideline scope. They were drafted by the NICE guideline updates team and refined and validated by the guideline committee.

The review question was based on the Population, Intervention, Comparator and Outcome [and Study type] (PICO[S]) framework for reviews of interventions. See section 1.1.2.

Reviewing research evidence

Review protocol

The review protocol was developed with the guideline committee to outline the inclusion and exclusion criteria used to select studies for the evidence review. The review was not prospectively registered in the PROSPERO register of systematic reviews due to time constraints.

Searching for evidence

Evidence was searched for each review question using the methods specified in the 2022 NICE guidelines manual. For details of the search methods see section 1.1.3.1 and appendix B.

Selecting studies for inclusion

All references identified by the literature searches and from other sources (for example, previous versions of the guideline or studies identified by committee members) were uploaded into EPPI reviewer software (version 5) and de-duplicated. Titles and abstracts were assessed for possible inclusion using the criteria specified in the review protocol. 10% of the abstracts were reviewed by two reviewers, with any disagreements resolved by discussion or, if necessary, a third independent reviewer.

The evidence reviews did not make use of the priority screening functionality within the EPPI-reviewer software because the number of studies to be assessed was small and therefore prioritisation was not necessary.

As an additional check to ensure that relevant studies were not missed, systematic reviews were included in the review protocol and search strategy. Relevant systematic reviews were used to identify any papers not found through the primary search.

The full text of potentially eligible studies was retrieved and assessed according to the criteria specified in the review protocol. A standardised form was used to extract data from included studies and full evidence tables are presented in appendix D.

Methods of combining evidence

Data synthesis

Where possible, pairwise meta-analyses were conducted to combine the results of RCTs for each outcome. Pairwise meta-analyses were performed in Cochrane Review Manager V5.3. A pooled relative risk was calculated for dichotomous outcomes (using the Mantel–Haenszel method) reporting numbers of people having an event, and a pooled incidence rate ratio was calculated for dichotomous outcomes reporting total numbers of events. Both relative and absolute risks were presented, with absolute risks calculated by applying the relative risk to the risk in the comparator arm of the meta-analysis (calculated as the total number events in the comparator arms of studies in the meta-analysis divided by the total number of participants in the comparator arms of studies in the meta-analysis).

A pooled mean difference was calculated for continuous outcomes (using the inverse variance method) when the same scale was used to measure an outcome across different studies. Where different studies presented continuous data measuring the same outcome but using different numerical scales (e.g. a 0-10 and a 0-100 visual analogue scale), these outcomes were all converted to the same scale before meta-analysis was conducted on the mean differences. Where outcomes measured the same underlying construct but used different instruments/metrics, data were analysed using standardised mean differences (SMDs, Hedges' g).

For continuous outcomes analysed as mean differences, change from baseline values were used in the meta-analysis if they were accompanied by a measure of spread (for example standard deviation). Where change from baseline (accompanied by a measure of spread) were not reported, the corresponding values at the timepoint of interest were used. If only a subset of trials reported change from baseline data, final timepoint values were combined with change from baseline values to produce summary estimates of effect. For continuous outcomes analysed as standardised mean differences this was not possible. In this case, if all studies reported final timepoint data, this was used in the analysis. If some studies only reported data as a change from baseline, analysis was done on these data, and for studies where only baseline and final time point values were available, change from baseline standard deviations were estimated, assuming a correlation coefficient derived from studies reporting both baseline and endpoint data, or if no such studies were available, assuming a correlation of 0.5 as a conservative estimate (Follman et al., 1992; Fu et al., 2013).. In cases where SMDs were used they were back converted to a single scale to aid interpretation by the committee where possible.

Random effects models were fitted when significant between-study heterogeneity in methodology, population, intervention or comparator was identified by the reviewer in advance of data analysis. This decision was made and recorded before any data analysis was undertaken. For all other syntheses, fixed- and random-effects models were fitted, with the presented analysis dependent on the degree of heterogeneity in the assembled evidence. Fixed-effects models were the preferred choice to report, but in situations where the assumption of a shared mean for fixed-effects model were clearly not met, even after

appropriate pre-specified subgroup analyses were conducted, random-effects results are presented. Fixed-effects models were deemed to be inappropriate if there was significant statistical heterogeneity in the meta-analysis, defined as $I^2 \geq 50\%$.

However, in cases where the results from individual pre-specified subgroup analyses were less heterogeneous (with $I^2 < 50\%$) the results from these subgroups were reported using fixed effects models. This may have led to situations where pooled results were reported from random-effects models and subgroup results were reported from fixed-effects models.

Appraising the quality of evidence

RCTs were quality assessed using the Cochrane Risk of Bias Tool (version 2.0). Evidence on each outcome for each individual study was classified into one of the following groups:

1. Low risk of bias – The true effect size for the study is likely to be close to the estimated effect size.
2. Moderate risk of bias – There is a possibility the true effect size for the study is substantially different to the estimated effect size.
3. High risk of bias – It is likely the true effect size for the study is substantially different to the estimated effect size.

Each individual study was also classified into one of three groups for directness, based on if there were concerns about the population, intervention, comparator and/or outcomes in the study and how directly these variables could address the specified review question. Studies were rated as follows:

4. Direct – No important deviations from the protocol in population, intervention, comparator and/or outcomes.
5. Partially indirect – Important deviations from the protocol in one of the following areas: population, intervention, comparator and/or outcomes.
6. Indirect – Important deviations from the protocol in at least two of the following areas: population, intervention, comparator and/or outcomes.

Minimally important differences (MIDs) and clinical decision thresholds

The Core Outcome Measures in Effectiveness Trials (COMET) database was searched to identify published minimal clinically important difference thresholds relevant to this guideline that might aid the committee in identifying clinical decision thresholds for the purpose of GRADE. In addition, the Guideline Committee were asked to prospectively specify any outcomes where they felt a consensus clinical decision threshold could be defined from their experience.

Clinical decision thresholds were used to assess imprecision using GRADE and aid interpretation of the size of effects for different outcomes.

For this review, no clinical decision thresholds were identified and therefore default decision thresholds were used as described below.

For continuous outcomes expressed as a mean difference where no other clinical decision threshold was available, a clinical decision threshold of 0.5 of the median standard deviations of the comparison group arms was used (Norman et al. 2003). For one outcome (Disability rating Index [DRI]) an MID of 8 was suggested by the authors of the paper and this was used in the analysis.

For relative risks and hazard ratios, where no other clinical decision threshold was available, a default clinical decision threshold for dichotomous outcomes of 0.8 to 1.25 was used.

Odds ratios were converted to risk ratios before presentation to the committee to aid interpretation.

GRADE for intervention studies analysed using pairwise analysis

GRADE was used to assess the quality of evidence for the outcomes specified in the review protocol. Data from randomised controlled trials (which were quality assessed using the Cochrane risk of bias tool) were initially rated as high quality. The quality of the evidence for each outcome was downgraded or not from this initial point, based on the criteria given in Table 1.

Table 1: Rationale for downgrading quality of evidence for intervention studies

GRADE criteria	Reasons for downgrading quality
Risk of bias	**Not serious:** If less than 33.3% of the weight in a meta-analysis came from studies at moderate or high risk of bias, the overall outcome was not downgraded. **Serious**: If greater than 33.3% of the weight in a meta-analysis came from studies at moderate or high risk of bias, the outcome was downgraded one level. **Very serious**: If greater than 33.3% of the weight in a meta-analysis came from studies at high risk of bias, the outcome was downgraded two levels.
Indirectness	**Not serious:** If less than 33.3% of the weight in a meta-analysis came from partially indirect or indirect studies, the overall outcome was not downgraded. **Serious:** If greater than 33.3% of the weight in a meta-analysis came from partially indirect or indirect studies, the outcome was downgraded one level. **Very serious:** If greater than 33.3% of the weight in a meta-analysis came from indirect studies, the outcome was downgraded two levels.
Inconsistency	Concerns about inconsistency of effects across studies, occurring when there is unexplained variability in the treatment effect demonstrated across studies (heterogeneity), after appropriate pre-specified subgroup analyses have been conducted. This was assessed using the I^2 statistic. **N/A:** Inconsistency was marked as not applicable if data on the outcome was only available from one study. **Not serious:** If the I^2 was less than 33.3%, the outcome was not downgraded. **Serious**: If the I^2 was between 33.3% and 66.7%, the outcome was downgraded one level. **Very serious**: If the I^2 was greater than 66.7%, the outcome was downgraded two levels.
Imprecision	The outcome was downgraded once if the 95% confidence interval for the effect size crossed one line of the MID, and twice if it crosses both lines of the MID.

GRADE criteria	Reasons for downgrading quality
	Outcomes meeting the criteria for downgrading above were not downgraded if the confidence interval was sufficiently narrow that the upper and lower bounds would correspond to clinically equivalent scenarios.
Publication bias	Where 10 or more studies were included as part of a single meta-analysis, a funnel plot was produced to graphically assess the potential for publication bias. When a funnel plot showed convincing evidence of publication bias, or the review team became aware of other evidence of publication bias (for example, evidence of unpublished trials where there was evidence that the effect estimate differed in published and unpublished data), the outcome was downgraded once. If no evidence of publication bias was found for any outcomes in a review (as was often the case), this domain was excluded from GRADE profiles to improve readability.

Reviewing economic evidence

Inclusion and exclusion of economic studies

Literature reviews seeking to identify published cost–utility analyses of relevance to the issues under consideration were conducted for all questions. In each case, the search undertaken for the clinical review was modified, retaining population and intervention descriptors, but removing any study-design filter and adding a filter designed to identify relevant health economic analyses. In assessing studies for inclusion, population, intervention and comparator, criteria were always identical to those used in the parallel clinical search; only cost–utility analyses were included. Economic evidence profiles, including critical appraisal according to the Guidelines manual, were completed for included studies.

Appraising the quality of economic evidence

Economic studies identified through a systematic search of the literature were appraised using a methodology checklist designed for economic evaluations (NICE guidelines manual; 2014). This checklist is not intended to judge the quality of a study per se, but to determine whether an existing economic evaluation is useful to inform the decision-making of the committee for a specific topic within the guideline.

There are 2 parts of the appraisal process. The first step is to assess applicability (that is, the relevance of the study to the specific guideline topic and the NICE reference case); evaluations are categorised according to the criteria in Table 2.

Table 3 Applicability criteria

Level	Explanation
Directly applicable	The study meets all applicability criteria, or fails to meet one or more applicability criteria but this is unlikely to change the conclusions about cost effectiveness

Level	Explanation
Partially applicable	The study fails to meet one or more applicability criteria, and this could change the conclusions about cost effectiveness
Not applicable	The study fails to meet one or more applicability criteria, and this is likely to change the conclusions about cost effectiveness. These studies are excluded from further consideration

In the second step, only those studies deemed directly or partially applicable are further assessed for limitations (that is, methodological quality); see categorisation criteria in Table 3.

Table 4 Methodological criteria

Level	Explanation
Minor limitations	Meets all quality criteria, or fails to meet one or more quality criteria but this is unlikely to change the conclusions about cost effectiveness
Potentially serious limitations	Fails to meet one or more quality criteria and this could change the conclusions about cost effectiveness
Very serious limitations	Fails to meet one or more quality criteria and this is highly likely to change the conclusions about cost effectiveness. Such studies should usually be excluded from further consideration

Where relevant, a summary of the main findings from the systematic search, review and appraisal of economic evidence is presented in an economic evidence profile alongside the clinical evidence.

References

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Norman G., Sloan JA., Wyrwich KW. (2003) Interpretation of changes in health-related quality of life: the remarkable universality of half a standard deviation. Med Care 41(5):582-92.