

Supplementary Appendix S1. PRISMA-S Compliant Search Reporting

Final search date: 30 June 2024

Databases: PubMed and Scopus

Registries: ClinicalTrials.gov and WHO ICTRP

Other sources: Hand-searching of reference lists of included RCTs and key reviews

These strategies correspond exactly to the description in the main manuscript (Methods: *Information sources and search strategy*). Queries are presented verbatim and copy-pasteable per PRISMA-S guidance. Registry searches identified no additional eligible completed RCTs, consistent with the Results.

Table S1. PRISMA-S compliant search strategies and registry parameters (final run: 30 June 2024); n = 371)

Platform/interface: pubmed.ncbi.nlm.nih.gov

Exact search string (copy/paste):

("Diabetic Foot"[Mesh] OR ("diabetic foot"[tiab] OR "diabetic feet"[tiab] OR "foot ulcer*"[tiab] OR "diabetic ulcer*"[tiab]))
AND ("Negative-Pressure Wound Therapy"[Mesh] OR ("negative pressure wound therap*"[tiab] OR NPWT[tiab] OR "vacuum-assisted closure"[tiab] OR VAC[tiab] OR "vacuum therapy"[tiab] OR "subatmospheric pressure"[tiab]))
AND (randomized controlled trial[pt] OR controlled clinical trial[pt] OR randomi?ed[tiab] OR randomly[tiab] OR trial[ti] OR "clinical trial"[tiab])
NOT (animals[mh] NOT humans[mh])
AND English[lang]

Filters/limits: Humans; English; no date limits (screened through 30 June 2024)

Results: 371

Notes: 'Search details' export not retained contemporaneously during dissertation→manuscript transition; full query, run date, and hit count recorded here.

Scopus (Final search, 30 June 2024; n = 366)

Platform/interface: www.scopus.com (TITLE-ABS-KEY)

Exact search string (copy/paste):

TITLE-ABS-KEY("diabetic foot" OR "foot ulcer*" OR "diabetic ulcer*")
AND TITLE-ABS-KEY("negative pressure wound therap*" OR NPWT OR "vacuum-assisted closure" OR "vacuum therapy" OR "subatmospheric pressure")
AND (TITLE-ABS-KEY(random*) OR TITLE-ABS-KEY(trial))
AND DOCTYPE(ar)
AND LANGUAGE(english)

Filters/limits: Document type = Article; English language; no date limits (screened through 30 June 2024)

Results: 366

Notes: Scopus Query History identifier not available retrospectively; full TITLE-ABS-KEY strategy, run date, and hit count recorded here.

ClinicalTrials.gov (Final search, 30 June 2024)

Platform/interface: clinicaltrials.gov (Advanced Search)

Parameters:

- Condition: “diabetic foot ulcer”
- Intervention: (“negative pressure wound therapy” OR NPWT OR “vacuum-assisted closure” OR “vacuum therapy”)
- Study type: Interventional (Clinical Trial)
- Status: All

Results: No additional eligible completed RCTs identified.

Notes: Registry search performed to capture ongoing/unpublished RCTs. Export links/screenshots not archived contemporaneously; parameter set and run date recorded.

WHO ICTRP (Final search, 30 June 2024)

Platform/interface: trialsearch.who.int (ICTRP)

Parameters:

- Condition: (diabetic foot OR foot ulcer)
- Intervention: (“negative pressure wound therapy” OR NPWT OR “vacuum-assisted closure” OR “vacuum therapy”)
- Status: All

Results: No additional eligible completed RCTs identified.

Notes: CSV export not archived contemporaneously; parameter set and run date recorded.

Hand-searching

Source: Reference lists of included RCTs and key reviews

Results: No additional unique RCTs identified.

Footnote: This manuscript extends prior graduate work; some platform export IDs were not retained contemporaneously. To maximise transparency, we provide verbatim strategies, run dates, and hit counts per PRISMA-S guidance. These data are consistent with the PRISMA flow diagram (Figure 1 in the main manuscript).

Table S1b. Full-text articles excluded (n = 76) with grouped reasons.

Grouped reasons for exclusion (aligned with Study Selection criteria in the main manuscript):

Reason for exclusion	Number of studies (n)
Not randomized controlled trial	28
Population not eligible (non-DFU or mixed, not separable)	14
Intervention/comparator not eligible (not NPWT vs. standard care)	12
Duplicate / overlapping report	8
Insufficient outcome data or follow-up	7
Conference abstract only (no full article)	4
Other reason (methodological)	3

Total excluded: 76 full-text articles

Note: Exclusions listed here map directly to the PRISMA flow diagram (Figure 1 in the main manuscript).

References

Page, M.J.; McKenzie, J.E.; Bossuyt, P.M.; Boutron, I.; Hoffmann, T.C.; Mulrow, C.D.; Shamseer, L.; Tetzlaff, J.M.; Akl, E.A.; Brennan, S.E.; et al. The PRISMA 2020 statement: An updated guideline for reporting systematic reviews. *Br. Med. J.* **2021**, *372*, n71. <https://doi.org/10.1136/bmj.n71>.

Supplementary Appendix Table S2. Cochrane RoB 2 — Domain-Level Judgments with Expanded Justifications

Notes:

- Judgments are based only on information reported in the published articles (no author queries).
- Where reporting was insufficient, the domain is rated *Some concerns* (as prespecified).
- Downgrades for *risk of bias* in the GRADE framework (see Supplementary Appendix S3) map directly to the judgments here.
- The DiaFu cohort appears in two publications (Seidel 2020 – clinical outcomes; Seidel 2022 – economic/resource outcomes). The cohort is counted once in participant totals and meta-analyses (see Methods and Table 1 of the main manuscript).

Study ID (Author– Year)	Randomization process	Deviations from intended interventions	Missing outcome data	Measurement of outcomes	Selection of reported results	Overall RoB	Expanded justification (linked to GRADE)
Blume 2008	Some concerns	Some concerns	Low risk	Some concerns	Some concerns	Some concerns	Randomization described but allocation concealment not fully detailed; unblinded care likely; outcome data largely complete; assessor blinding unclear; no accessible preregistered protocol. → Contributed to <i>risk of bias</i> downgrade in GRADE.
Apelqvist 2008	Some concerns	Some concerns	Low risk	Some concerns	Some concerns	Some concerns	Allocation concealment unclear; management unblinded; completeness acceptable; assessor blinding not explicit; selective reporting cannot be excluded. → Downgraded for <i>risk of bias</i> .
Sepúlveda 2009	Some concerns	Some concerns	Some concerns	Some concerns	Some concerns	Some concerns	Small RCT; sequence/concealment insufficiently reported; possible care deviations; some attrition; assessor

Study ID (Author– Year)	Randomization process	Deviations from intended interventions	Missing outcome data	Measurement of outcomes	Selection of reported results	Overall RoB	Expanded justification (linked to GRADE)
Karatepe 2011	Some concerns	Some concerns	Some concerns	Some concerns	Some concerns	Some concerns	blinding unclear; no registered protocol. → Downgraded for <i>risk of bias</i> . Allocation concealment not detailed; performance bias possible; incomplete details on attrition handling/ITT; assessor blinding unclear; outcome selection not prespecified. → Downgraded for <i>risk of bias</i> .
Armstrong 2012 (mechanically powered vs. VAC)	Low risk	Some concerns	Low risk	Some concerns	Some concerns	Some concerns	Multicentre RCT with clearer randomization/concealment; unblinded device use; outcome data largely complete; assessor blinding unclear; protocol access limited. → Some concerns only; contributed less to downgrading.
Seidel 2020 (DiaFu clinical)	Some concerns	Some concerns	Some concerns	Some concerns	Some concerns	Some concerns	Large multicentre RCT; randomization described but concealment details limited; unblinded care; missing data handling not fully explicit; assessor blinding unclear; selective reporting cannot be ruled out. → Downgraded for <i>risk of bias</i> .
Seidel 2022 (DiaFu economic)	Some concerns	Some concerns	Low risk	Some concerns	Some concerns	Some concerns	Same cohort as Seidel 2020; economic/resource outcomes; reporting solid for costs/resources; blinding not feasible; preregistration not clearly linked to outcomes. → Downgraded

Study ID (Author– Year)	Randomization process	Deviations from intended interventions	Missing outcome data	Measurement of outcomes	Selection of reported results	Overall RoB	Expanded justification (linked to GRADE)
Maranna 2021	Some concerns	Some concerns	Some concerns	Some concerns	Some concerns	Some concerns	for <i>risk of bias</i> in economic outcomes. Single-centre RCT; allocation concealment unclear; unblinded management; small sample with some attrition; assessor blinding not stated; selective reporting possible. → Downgraded for <i>risk of bias</i> .
Alamdari 2021	Some concerns	Some concerns	Low risk	Some concerns	Some concerns	Some concerns	Randomization mentioned; concealment unclear; unblinded care; outcome completeness acceptable; assessor blinding not described; protocol not available. → Downgraded for <i>risk of bias</i> .
Campitiello 2021 (NPWT+ vs. standard NPWT)	Some concerns	High risk	Some concerns	Some concerns	Some concerns	High risk	Device-modification trial; deviations from intended interventions likely with limited mitigation; some attrition detail; assessor blinding unclear; protocol linkage not explicit. → <i>High risk of bias</i> , major contributor to GRADE downgrades.
Kirsner 2021 (single-use NPWT vs. traditional NPWT)	Low risk	Some concerns	Low risk	Some concerns	Some concerns	Some concerns	Multicentre RCT with clearer randomization; device use unblinded; outcome completeness good; assessor blinding unclear; selective reporting risk not fully excludable. → Minor contributor to downgrading.

Legend:

- RoB 2 domains: Randomization process; Deviations from intended interventions; Missing outcome data; Measurement of outcomes; Selection of reported results.
- Overall judgment follows Cochrane RoB 2 (*Low risk; Some concerns; High risk*).
- *Expanded justifications explicitly indicate where downgrades were applied in the GRADE Summary of Findings (Supplementary Appendix S3).*

References

1. Sterne, J.A.C.; Savović, J.; Page, M.J.; Elbers, R.G.; Blencowe, N.S.; Boutron, I.; Cates, C.J.; Cheng, H.Y.; Corbett, M.S.; Eldridge, S.M.; et al. RoB 2: A revised tool for assessing risk of bias in randomised trials. *Br. Med. J.* **2019**, *366*, 14898. <https://doi.org/10.1136/bmj.14898>.
2. Guyatt, G.H.; Oxman, A.D.; Vist, G.E.; Kunz, R.; Falck-Ytter, Y.; Alonso-Coello, P.; Schünemann, H.J.; for the GRADE Working Group. GRADE: An emerging consensus on rating quality of evidence and strength of recommendations. *Br. Med. J.* **2008**, *336*, 924–926. <https://doi.org/10.1136/bmj.39489.470347.AD>.

Supplementary Appendix S3. GRADE Summary of Findings

This table presents pooled effect estimates with certainty ratings and explicit downgrade reasons. Outcome labels, trial counts, and effect estimates are identical to those in Table 2 of the main manuscript. Each downgrade reason corresponds to specific RoB 2 domain judgments in Supplementary Appendix S2.

Cost outcomes are explicitly framed as **exploratory** due to sparse evidence and heterogeneity, consistent with the Discussion.

Outcome	No. trials (n)	Effect estimate (random effects)	Certainty	Notes (explicit downgrade reasons)
Time to complete healing	6 (1,038)	MD -18 days (-28 to -8)	Moderate	-1 inconsistency ($I^2 = 55\%$); no downgrade for imprecision (CI excludes null).
≥95% granulation tissue	5 (873)	RR 1.32 (1.10–1.59)	Low	-1 risk of bias (some concerns across multiple domains in S2); -1 inconsistency (direction consistent but magnitude varies across small trials).
Minor amputation	7 (1,212)	RR 0.71 (0.50–1.00)	Low	-1 imprecision (upper CI includes minimal/no effect); -1 risk of bias (allocation concealment/blinding concerns, see S2).
Adverse events (any)	6 (917)	RR 1.09 (0.93–1.29)	Moderate	-1 risk of bias (unblinded management, variable ascertainment); no downgrade for inconsistency (point estimates similar).
Length of hospital stay	4 (622)	MD -3.8 days (-6.2 to -1.4)	Low	-1 inconsistency ($I^2 = 68\%$); -1 imprecision (few trials; wide CIs).
Direct treatment cost	2 (504)	MD -USD 8,400 (-13,900 to -2,900)	Low	-1 inconsistency (heterogeneous cost components/price years); -1 imprecision (only two trials; wide CIs). → <i>Exploratory evidence only; further contemporary studies needed.</i>

Legend:

- GRADE certainty levels: High, Moderate, Low, Very low.
- Downgrade domains considered: risk of bias, inconsistency, indirectness, imprecision, publication bias.
- Rows correspond to outcomes reported in Table 2 of the main manuscript.
- All downgrades map directly to RoB 2 judgments in Supplementary Appendix S2.

References

3. Sterne, J.A.C.; Savović, J.; Page, M.J.; Elbers, R.G.; Blencowe, N.S.; Boutron, I.; Cates, C.J.; Cheng, H.Y.; Corbett, M.S.; Eldridge, S.M.; et al. RoB 2: A revised tool for assessing risk of bias in randomised trials. *Br. Med. J.* **2019**, *366*, 14898. <https://doi.org/10.1136/bmj.14898>.
4. Guyatt, G.H.; Oxman, A.D.; Vist, G.E.; Kunz, R.; Falck-Ytter, Y.; Alonso-Coello, P.; Schünemann, H.J.; for the GRADE Working Group. GRADE: An emerging consensus on rating quality of evidence and strength of recommendations. *Br. Med. J.* **2008**, *336*, 924–926. <https://doi.org/10.1136/bmj.39489.470347.AD>.