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1 **Effect of Negative Pressure Wound Therapy vs Standard Wound Management on**
2 **12-month Disability Among Adults with Severe Open Fracture of the Lower Limb:**
3 **The WOLLF Randomized Clinical Trial**
4 **ISRCTN33756652**

5

6

7 Matthew L Costa PhD, ^{1,2,3}, Juul Achten PhD², Julie Bruce PhD¹, Elizabeth Tutton

8 PhD^{1,2}, Stavros Petrou PhD ¹, Sarah E Lamb PhD^{1,2}, Nick R Parsons PhD⁴ for the UK

9 WOLLF collaboration.

10

11 1. *Warwick Clinical Trials Unit, Warwick Medical School, The University of Warwick, Gibbet*
12 *Hill Campus, Coventry CV4 7AL*

13 2. *Oxford Trauma, Nuffield Department of Orthopaedics, Rheumatology & Musculoskeletal*
14 *Sciences, University of Oxford, Oxford, OX3 9DU, UK*

15 3. *University Hospitals Coventry and Warwickshire NHS Trust, Clifford Bridge Road,*
16 *Coventry, CV2 2DX, UK*

17 4. *Statistics and Epidemiology Unit, Warwick Medical School, The University of Warwick,*
18 *Gibbet Hill Campus, Coventry, CV4 7AL, UK*

19 *Word count: 2765 words*

20 *Corresponding Author:*

21 *Professor Matthew Costa*

22 *Oxford Trauma, Nuffield Department of Orthopaedics, Rheumatology & Musculoskeletal*
23 *Sciences, University of Oxford, Oxford, OX3 9DU, UK*

24 *Matthew.costa@ndorms.ox.ac.uk*

25

26 **Key points**

27 Question: Does either negative pressure wound therapy or standard wound dressing result in less
28 disability 12 months after sustaining an open fracture of the lower limb.

29

30 Findings: In this randomized clinical trial that included 460 adults, there was no statistically
31 significant difference in self-rated disability between negative pressure wound therapy or
32 standard wound dressing at 12 months (45.5 vs 42.4 points out of a possible 100).

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34 Meaning: Negative pressure wound therapy did not improve 12-month disability for
35 patients with severe open fracture of the lower limb compared with standard wound
36 dressing

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51 ABSTRACT

52 **Importance**

53 Open fractures of the lower limb occur when a broken bone penetrates the skin. These are life-
54 changing injuries where wound healing complications are common.

55 **Objectives**

56 To assess the disability, rate of deep infection and quality of life in patients with severe open
57 fracture of the lower limb treated with negative pressure wound therapy (NPWT) versus standard
58 wound management after the first surgical debridement of the wound.

59 **Design, Setting and Participants**

60 Multi-center, randomized trial, embedded in the UK Major Trauma Network, recruiting 460 patients
61 ≥ 16 years with a severe open fracture of the lower limb from July 2012 through December 2015.

62 Final outcome collected November 2016. Exclusions: presentation > 72 hours after injury; inability to
63 complete questionnaires.

64 **Interventions**

65 NPWT (n=226) where an open cell solid foam or gauze was placed over the surface of the wound
66 and connected to a suction pump which created a partial vacuum over the dressing vs standard
67 dressings not involving negative pressure (n=234).

68 **Main outcomes and Measures**

69 Disability Rating Index (DRI); score 0 [no disability] to 100 [completely disabled] at 12 months was
70 the primary outcome measure, with a minimal clinically important difference (MCID) of 8 points.

71 Secondary outcomes were complications including deep infection, and quality of life (QOL; score
72 ranged from 1 (best possible) to -0.59 (worst possible), MCID 0.08) collected at 3, 6, 9 and 12
73 months.

74 **Results**

75 Among 460 patients who were randomized (mean age, 45.3 years; 74% men), 88% (374/427) of
76 available study participants completed the trial. There was no statistically significant difference in
77 the patients' DRI at 12 months (mean score 45.5 (sd=28.0) in the NPWT group vs 42.4 (24.2) in the
78 standard dressing group; mean difference of -3.9 (95%CI; -8.9 to 1.2; p=0.13). There was no
79 statistically significant difference in the number of deep surgical site infections (16 (7.1%) in the
80 NPWT group vs 19 (8.1%) in the standard dressing group; difference 1.0% (95% CI; -4.2% to 6.3%;
81 p=0.64). There was no statistically significant difference in QOL between groups; difference in EQ-5D
82 0.02 (95% CI; -0.05 to 0.08), SF-12 PCS 0.5 (95% CI; -3.1 to 4.1) and SF-12 MCS -0.4 (95% CI; -2.2 to
83 1.4).

84 **Conclusions and relevance**

85 Among patients with severe open fracture of the lower limb, use of negative pressure wound
86 therapy compared with standard wound dressing did not improve self-rated disability at 12 months.
87 The findings do not support this treatment for severe open fractures.

88

89 Word count: 399 words

90 **Trial registration:** Current Clinical Trials [ISRCTN33756652](#)

91

92 **Background**

93 Fractures of the lower limb are common injuries in civilian and military populations.^{1,2} Most fractures
94 are 'closed'; the skin overlying the fracture is intact. However, if the fracture is 'open', the broken
95 bone is exposed to contamination and the risk of healing complications is greatly increased.³ In
96 severe, open fractures of the lower limb, infection rates up to 27% are reported, even in specialist
97 trauma centres.⁴ The costs of treating wound complications is extremely high for both patients and
98 healthcare systems.⁵

99 The initial management of open fractures involves surgical debridement with excision of damaged
100 tissue and contamination, and the administration of antibiotics.^{6,7} The fracture is usually
101 immobilized with fixation of the bone and a dressing is applied to the surface of the wound.
102 Traditionally, a sealed, non-adhesive layer is applied to protect the open fracture from further
103 contamination. Reassessment and further debridement of the wound typically performed 48-72
104 hours later.

105 Negative-pressure wound therapy (NPWT) is an alternative form of dressing. This device creates a
106 vacuum using suction which removes blood and fluid that may collect in the wound. The vacuum
107 may also encourage the formation of granulation (healing) tissue.^{4,8} However, NPWT dressings and
108 the vacuum machines are considerably more expensive than traditional wound dressings.

109 Before this study, there was only one randomized clinical trial comparing standard wound dressing
110 with NPWT for patients with open fractures of the lower limb.¹¹ That trial suggested improved
111 outcomes in patients treated with NPWT but included only 59 patients at a single trauma center.
112 Despite the lack of strong evidence, clinical guidelines around the world incorporated the use of
113 NPWT for open fracture wounds.^{6,7,12}

114 The aim of this pragmatic, multicenter RCT was to compare standard wound dressings with negative
115 pressure wound therapy for adults with an open fracture of the lower limb.

116 **Methods**

117 **Study design and eligibility criteria**

118 The National Research Ethics Service approved the study, the approved protocol and statistical
119 analysis plan are available as an online supplement. The trial was overseen by independent steering
120 and data and safety monitoring committees.

121 The trial took place in 24 major trauma hospitals representing the UK Major Trauma Network; in the
122 UK, patients with serious injuries such as open fractures are transported directly to a specialist
123 trauma center with joint orthopedic and plastic surgery facilities. Eligible patients were aged 16
124 years or older and had a severe open fracture of the lower limb graded as Gustilo and Anderson II or
125 III; type II is an open fracture with a laceration more than one centimeter long without extensive
126 soft-tissue damage, flaps, or avulsions and type III either an open segmental fracture or an
127 open fracture with extensive soft-tissue damage.¹⁴ Since surface NPWT can only be applied to
128 wounds which are left open, the surgeons could only include the most severe injuries i.e. where it
129 was not possible to safely suture the wound edges the end of the first surgical debridement.

130 Patients had to present to the trial hospital within 72 hours of their injury, including those who were
131 transferred from other hospitals. Patients were excluded if they had known contra-indications to
132 anesthesia or were deemed unable to adhere to trial procedures or complete questionnaires, for
133 example those with a pre-existing diagnosis of dementia. For patients with acute confusional states
134 or temporary impairment of consciousness, we approached a Consultee to provide agreement on
135 behalf of the patient, as per the UK Mental Capacity Act 2005. All participants randomized under this
136 provision, were subsequently approached for consent once capacity was restored, with the option
137 to continue or discontinue involvement in the trial. For this reason, we anticipated higher levels of
138 post-randomization withdrawal than might be expected in most clinical trials.

139 **RANDOMISATION AND MASKING**

140 A computer-generated randomization algorithm was created by the trial statistician and delivered by
141 an accredited Clinical Trials Unit to ensure that the allocation sequence was concealed. The
142 individual patient was allocated treatment on a 1:1 basis, stratified by trial center and Gustilo and
143 Anderson grade; the Gustilo and Anderson grade. When a patient entered the trial, non-identifiable
144 details were logged on the secure, encrypted, web-based system.

145 Participants were assigned to their treatment allocation intraoperatively at the end of initial surgery,
146 but before any wound dressing was applied.

147 It was not possible to blind trial participants to treatment allocation as wound dressings were clearly
148 visible. In addition, the treating surgeons could not be blind to the intervention, but the surgical and
149 healthcare team were not involved in any trial assessments. Wound photographs taken at six weeks
150 and standard radiographs were used to look for signs of delayed wound healing and non-union of
151 the bone respectively. These were reviewed by independent clinicians who were blind to the
152 treatment allocation.

153 INTERVENTIONS

154 At presentation, all patients were listed for the next available trauma operating list. In the operating
155 theatre, all patients received a general or regional anesthetic. The wound associated with the
156 fracture was surgically debrided and the fracture immobilized with either internal (under the skin) or
157 external fixation. At the end of the initial operation, if the wound could not be closed primarily i.e.
158 direct suture of the wound edges was not possible, the patient was randomized to either standard
159 dressings or NPWT. All other elements of postoperative care remained the same for all patients.

160 *Standard Dressing Group.* All hospitals used a sterile dressing sealed from external contamination.

161 However, the details of the materials used were left to the discretion of the treating healthcare
162 team as per routine care at their center. Details of each dressing applied in the trial were recorded
163 and classified according to British National Formulary (BNF) classification.

164 *NPWT group*. The NPWT dressing used an 'open-cell' solid foam or gauze laid onto the wound
165 followed by an adherent, sealed dressing. A sealed tube was connected from the dressing to a
166 suction pump which created a partial vacuum over the wound. The basic features of the NPWT are
167 universal, but the exact details of the dressing and pressure (mmHg) were left to the discretion of
168 the treating healthcare team. Details of the NPWT were recorded in trial documentation.

169 Patients with an open fracture of the lower limb that could not be closed primarily, had a second
170 operation at 48-72 hours, where a further wound assessment and debridement was performed and
171 the wound closed either primarily with sutures or by soft-tissue reconstruction as necessary.

172 DATA COLLECTION AND OUTCOME MEASURES

173 The primary outcome was the patient-reported Disability Rating Index (DRI) at 12 months after
174 randomisation.¹⁵ The DRI provides a 100-point score, where zero represents normal function and
175 100 complete disability, with a minimum clinically important difference of 8 points.

176 Secondary outcomes were health-related quality of life using EuroQol (EQ-5D-3L)^{16,17} and Short form
177 12 (SF-12)^{18,19} deep surgical site infection (SSI) at 30 days as per CDC definition²⁰ and other
178 complications. EQ-5D-3L responses were converted into an overall utility score¹⁷, that ranged from 1
179 (best possible) to -0.59 (worst possible), where zero represents the quality of life associated with
180 death; the minimum clinically important difference is 0.08 points. Physical and mental health
181 Composite Scores (PCS and MCS) were computed from SF-12 responses²¹; these scores range from 0
182 to 100, where a 0 score indicates the lowest level of health. Infection outcomes and complications
183 were extracted from the patients' medical records by independent research staff in each trial center.
184 Wound photographs and radiographs were reviewed independently and blind to treatment
185 allocation.

186 Deep infection following an open fracture is a key driver of subsequent disability. However, a deep
187 infection which is treated early and definitively may resolve completely with no disability. Similarly,
188 wounds which are not infected may still heal with excess scar-tissue or require extensive tissue

189 grafts which can lead to reduced mobility and chronic pain. Therefore, the DRI was considered to be
190 more important as a primary outcome measure than the rate of deep infection or size of the wound
191 per se. Patient-reported outcomes (DRI, EQ-5D-3L, SF-12) and self-reported complications were
192 collected by questionnaire. Pre-injury baseline scores were collected retrospectively at the time of
193 consent and again by postal questionnaire at three, six, nine, and twelve months.

194

195 STATISTICAL ANALYSIS

196 A minimum clinically important difference for the Disability Rating Index of 8 points was selected to
197 power the study;¹³ for an individual patient, at the lower level this represents the ability to climb
198 stairs or run, with 'some difficulty' versus, at the higher level with 'great difficulty' and at a
199 population level, eight points represents the difference between a 'healthy patient' (score=1
200 points) and a 'patient with a minor disability' (score=9 points). The standard deviation (SD) of the DRI
201 used in the sample size calculation was 25 points. Allowing a margin of 10% loss during follow-up,
202 including the small number of patients who die in the first year following their injury, gave a total
203 sample size of 460 patients. Therefore, 230 patients consented to each intervention group would
204 provide 90% power to detect a difference of eight points in DRI at 12 months at the 5% significance
205 level.

206 When calculating summary statistics for assessing treatment efficacy, NPWT data were subtracted
207 from control group data; such that a positive difference indicated that a score or outcome measure
208 was larger in the control group. We investigated differences in the primary outcome measure, the
209 DRI score at one year after injury, between the two treatment groups on an intention-to-treat basis.
210 Early and mid-term disability was assessed and reported at three, six and nine months. A secondary
211 per-treatment analysis was also performed. Mixed-effects regression analysis, with recruiting center
212 as a random effect, and fixed terms to adjust for age group, sex, baseline pre-injury score and
213 Gustilo and Anderson grade was used to test for treatment group differences using complete case

214 data. Secondary endpoints were not adjusted for multiple comparisons, and should be interpreted
215 as exploratory. In a post hoc sensitivity analysis for the primary outcome, missing data were imputed
216 using the chained equation methodology²² and models fitted to give a pooled estimate of the
217 treatment effect.

218 All tests were two-sided and significance was assessed at the 5% level. Analyses of primary and
219 secondary outcomes used complete-case data and all analyses were implemented in R version 3.3.0
220²³, using packages base, graphics, mice, lme4 and nlme (see <https://cran.r-project.org/>).

221

222 **Results**

223 A total of 625 patients were randomized between July 2012 and December 2015. Some patients
224 who did not have mental capacity before surgery, were unable or not willing to provide informed
225 consent after randomization. The majority of the 165 patients who did not provide consent were
226 found to be ineligible after randomization; for example, due to primary closure of the wound or
227 permanent cognitive impairment which could not be predicted before surgery/randomization. Only
228 29 potentially eligible patients declined to participate in the trial; 14 in the NPWT group and 15 in
229 the standard dressing group (Figure 1).

230 A total of 460 patients consented to take part in the WOLLF trial: 85% were grade III injuries and 82%
231 involved the tibia. The characteristics of the two groups were well balanced after randomization
232 (Table 1).

233 ****Figure 1****

234 ****Table 1****

235 On an intention-to-treat basis, there was no significant difference in the DRI at 12 months between
236 those patients treated with NPWT versus those treated with standard wound dressings (Figure 2).
237 The mean DRI in the NPWT group was 45.5 versus 42.4 in the standard dressing group, giving a
238 difference of -3.9 (95%CI; -8.9 to 1.2) in favor of standard dressings, p-value=0.13; from adjusted
239 mixed-effect regression analysis (Table 2). Therefore, the results of this trial are consistent with a -
240 8.9 worse disability rating attributable to the use of NPWT which, based on the minimal clinically
241 important difference, would be clinically important but also ranging to a non-clinically important
242 benefit of these dressings of 1.2 points on the DRI scale. Similarly, there was no significant difference
243 in disability rating at three months, six months or nine months (Figure 2).

244 The secondary per-protocol (per treatment) analysis of the DRI did not significantly differ from the
245 primary intention-to-treat analysis; the difference between groups being -4.0 (95% CI; -9.1 to 1.0) in
246 favour of the standard dressings (p-value 0.12).

247 ****Table 2****

248 Secondary exploratory analysis showed that there was no significant difference in the health-related
249 quality of life scores between the treatment groups at any point in the 12 months following the
250 injury. The mean SF-12 Physical Component Score at 12 months in the NPWT group was 32.2 (17.4)
251 versus 32.7 (15.5) in the standard dressing group, giving an adjusted difference of 0.4 (-3.0 to 3.8) in
252 favor of standard dressings (p-value=0.82; from adjusted mixed-effect regression analysis). The
253 mean EQ-5D score in the NPWT group was 0.55 (0.33) versus 0.56 (0.32) in the standard dressing
254 group, giving a difference of 0.01 (-0.06 to 0.07) in favor of standard dressing (p-value=0.82).

255 There was no significant difference in the number of deep surgical site infections between the
256 treatment groups (Table 3). In total 35 of the 460 participants (7.6%) had a deep SSI at 30 days; 16
257 (7.1%) in the NPWT treatment group and 19 (8.1%) in the standard dressing group, giving an
258 estimated odds ratio 0.85 (95% CI; 0.42 to 1.70) and percentage difference in rates 1.0% (95% CI; -
259 4.2% to 6.3%) in favor of NPWT (p-value=0.64 from adjusted mixed-effect logistic regression
260 analysis). There was no significant difference in the proportion of wounds found to be fully healed
261 on the six-week photographs; 52.0% (91/175) in the NPWT group and 51.7% (93/180) in the
262 standard dressing group, giving an odds ratio of 1.0 (95%CI; 0.6 to 1.6, p-value=0.99) and difference
263 in rates -0.3% (95% CI; -11.1% to 10.4%). There was no significant difference in the proportion of
264 patients with complete bone union on the radiographs at 12-months; 69.6% (112/161) in the NPWT
265 group and 71.9% (110/153) in the standard dressing group, giving an odds ratio of 1.1 (95%CI;0.7 to
266 1.9, p-value=0.68) and difference in rates 2.3% (95% CI; -8.4% to 13.0%).

267 The primary outcome data were 88% complete (374 of 427 available study participants provided
268 final outcome data) and there was no evidence for non-random patterns of missingness. Imputing

269 missing data gave pooled estimates of the treatment effect for DRI at 12 months as - 4.5 (95% CI; -
270 9.3 to 0.4), with the percentage of the variability attributable to the uncertainty caused by the
271 missing data estimated at 12.8%.

272 **Table 3**

273 **Discussion**

274 This multi-center trial of patients with severe open fractures of the lower limb, found no significant
275 difference in the Disability Rating Index between those patients treated with NPWT versus those
276 treated with standard wound dressings at 12 months post-injury. There was no significant difference
277 in the rate of deep surgical site infection, or other healing complications. Nor was there a significant
278 difference in health-related quality of life at any point in the first 12 months after the injury.

279 Before this trial, a review of the literature ²⁴ showed only one RCT comparing standard wound
280 dressing with NPWT for the initial management of patients with severe open fractures of the lower
281 limb. Stannard et al ¹¹ demonstrated a difference in health-related quality of life and a reduction in
282 the rate of deep wound infection in patients treated with NPWT compared with control (5.4% versus
283 20%; RR 0.199, 95% CI 0.05, 0.87). However, this was a small trial (59 patients, 63 fractures), and
284 there were only 7 deep infections in the control group and 2 in the NPWT group. It is possible that
285 this difference in the rate of deep infection was due to systematic differences in the patients and/or
286 treatment pathway in a single center in the US, compared with the WOLLF trial which took place in
287 the much broader setting of 24 major trauma centers. However, given the relatively small number of
288 cases in the Stannard et al trial, it is possible that the result represents a lack of precision in the
289 estimate of the incidence of deep infection. A trial published in 2016 also comparing NPWT with
290 standard dressings in the context of open fractures. This study took place in Pakistan and used
291 negative pressure dressings over a prolonged period of time (weeks) to reduce the size of the
292 wound.²⁵ This is a very different use of NPWT than advocated by current guidance for the
293 management of open fractures, where early definitive wound closure - within 72 hours - is

294 recommended.^{6,7} Therefore, it is not clear whether the results of that trial are pertinent to other
295 healthcare systems.

296 Limitations

297 This study has several limitations. Firstly, patients with an open fracture of the lower limb have
298 usually experienced severe trauma and present to hospital with variable states of consciousness and
299 cognition. For emergency interventions, it was anticipated that some patients who were randomized
300 would subsequently found not to be eligible or not able to provide informed consent; for example
301 patients who had significant head injury or who died of their injuries in the early post-operative
302 period. Some patients were also found to be ineligible after randomization due to the surgeon
303 deciding that the wound could be closed by direct suturing, which may reflect the difficulties of
304 classifying these injuries at the time of the initial debridement of the wound; only patients where
305 the surgeon felt that the wound had to be left open were included in the trial ²⁶. However, 460 of
306 the 485 (95%) patients who were randomized and eligible for the trial agreed to participate,
307 suggesting that participants were representative of the overall population with severe open
308 fractures of the lower limb. Second, after randomization some patients crossed over from one
309 treatment group to another. However, 95% percent of patients received the treatment to which
310 they were allocated. Third, there was loss to follow-up, with study completion by only 88% of the
311 original participants. However, multiple imputation analysis resulted in consistent findings. Finally,
312 although patients were only eligible to enter the study if they presented to the treating hospital
313 within 72 hours of their injury, we were not able to adjust for the exact time of the open fracture
314 which is a possible confounder in the analysis.

315 **Conclusion**

316 Among patients with severe open fracture of the lower limb, use of negative pressure wound
317 therapy compared with standard wound dressing did not improve self-rated disability at 12 months.

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320

321 **Author contributions**

322 MC, NP, JB, SL, LT, SP and JA were responsible for the trial design. MC and JA were responsible for
323 acquisition of data. NP was responsible for the statistical analysis.

324 All authors were responsible for the interpretation of the data and for drafting and approving the
325 final submitted manuscript.

326 **UK WOLLF Collaborators**

327 Keith Willett, Damian Griffin, Steven Jeffery, Jill Arrowsmith, Gorav Datta, Mick Dennison, Mark
328 Farrar, Peter Giannoudis, Andrew Gray, Philip Henman, Peter Hull, Umraz Khan, Charlotte Lewis,
329 David Loveday, Jitendra Mangwani, Andrew McAndrew, Damian McClelland, Mike McNicholas,
330 David Noyes, Ben Ollivere, Ian Pallister, Keith Porter, Manoj Ramachandran, Rory Rickard, Benedict
331 Rogers, Hemant Sharma, Adel Tavakkolizadeh, Jonathan Young.

332 **Conflicts of interest**

333 M Costa is a member of the UK NIHR HTA General Board; S Lamb is a member of the UK NIHR HTA
334 Additional Capacity Funding Board, HTA end of life care and add-on studies, HTA Prioritisation Group
335 and HTA Trauma Board.

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346 reporting of the trial.

347 Prof Matthew Costa and Dr Nick Parsons have full access to all of the data in the study and take
348 responsibility for the integrity of the data and the accuracy of the data analysis

349

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358

359

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430 **Figure 2**

431 Temporal trends in main study outcomes. Disability Rating Index (DRI), the primary outcome
432 (Panel A), EQ-5D quality of life (Panel B) and SF-12 physical component score (PCS) and
433 mental component score (MCS) (Panel C). Shown are means, with 95% confidence
434 intervals, at each study follow-up time point (3, 6, 9 and 12 months) and at baseline (Base).
435 Pre-injury assessments were made retrospectively by all study participants and immediately
436 post-injury for EQ-5D. Minimum clinically important differences (MCID) are shown for DRI
437 and EQ-5D.
438

Head	14 (6.2)	11 (4.7)
Pelvis	8 (3.5)	15 (6.4)
Ipsilateral lower limb	6 (2.7)	16 (6.8)
Contralateral lower limb	4 (1.8)	14 (6.0)
Abdomen	3 (1.3)	12 (5.1)
Gustilo & Anderson grade; n (%)		
Grade 2	34 (15.0)	30 (12.8)
Grade 3	171 (75.7)	180 (76.9)
Grade 3 + VI	21 (9.3)	24 (10.3)
Fracture fixation; n (%)		
External fixator-half-pin	107 (47.3)	111 (47.4)
Nail	49 (21.7)	56 (23.9)
Plate and screws	38 (16.8)	32 (13.7)
Other	21 (9.3)	21 (9.0)
External fixator-fine-wire	3 (1.3)	11 (4.7)
Wires/tension band wires	7 (3.1)	3 (1.3)
Unknown	1 (0.4)	0 (0.0)
IQR = interquartile range; sd = standard deviation; † Some study participants had multiple injuries associated with the open fracture		

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Table 2. Primary and secondary outcomes							
	NPWT		Standard		Difference (95% CI)		P value for adjusted analysis
	Mean (sd)	n	Mean (sd)	n	Raw [†]	Adjusted [‡]	
<i>Primary outcome</i>							
DRI (12 m)	45.5 (28.0)	179	42.4 (24.2)	195	-3.1 (-8.5 - 2.2)	-3.9 (-8.9 - 1.2)	0.13
<i>Secondary outcomes</i>							
<i>Disability scores over time</i>							
DRI (3 m)	64.3 (22.3)	166	65.6 (20.1)	188	1.3 (-3.1 - 5.8)	0.7 (-3.7 - 5.0)	0.76
DRI (6 m)	53.2 (23.8)	154	50.3 (24.1)	175	-2.8 (-8.0 - 2.4)	-3.5 (-8.4 - 1.5)	0.17
DRI (9 m)	49.2 (25.9)	153	45.4 (25.2)	161	-3.8 (-9.5 - 1.9)	-4.4 (-10.0 - 1.3)	0.13
<i>Quality of life</i>							
EQ-5D (12 m)	0.55 (0.33)	172	0.56 (0.32)	192	0.02 (-0.05 - 0.08)	0.01 (-0.06 - 0.07)	0.82
SF-12 PCS (12 m)	32.2 (17.4)	154	32.7 (15.5)	175	0.5 (-3.1 - 4.1)	0.4 (-3.0 - 3.8)	0.82
SF-12 MCS (12 m)	44.7 (8.4)	154	44.3 (8.2)	175	-0.4 (-2.2 - 1.4)	-0.2 (-2.1 - 1.6)	0.80
[†] Mean of Standard group minus mean of NPWT (Negative Pressure Wound Therapy) group; for DRI a negative value is in favor of the Standard treatment, as a lower score indicates less disability [‡] Mixed effects regression based on a complete case analysis with, treatment group, age group, gender, baseline pre-injury score and wound grade as covariates (fixed effects) and recruiting center as a random effect; p-values are from analysis of variance (ANOVA) F-test sd = standard deviation Disability Rating Index (DRI) is assessed on a 100-point score scale, where zero represents normal function and 100 complete disability, with a minimum clinically important difference of 8 points							

EuroQol EQ-5D-3L (EQ-5D) is a measure of health-related quality of life, in the range -0.59 (worst possible state) to 1 (perfect health), anchored at 0 (death), with a minimum clinically important difference 0.08 points
SF-12 Physical and Mental health Composite Scores (PCS and MCS) are computed from the short form health survey and range from 0 to 100, where a 0 score indicates the lowest level of health

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Table 3: Post-operative complications reported as secondary outcomes during 12 months follow-up

Complication	NPWT (n = 226)	Standard (n = 234)	Difference (%)	Odds ratio [‡]	P value [‡]
Wound complications at 30 days					
Red and inflamed; n (%)	13 (5.8)	19 (8.1)	2.4 (-2.7 - 7.4)	0.64 (0.28 - 1.42)	0.27
Swollen; n (%)	38 (16.8)	49 (20.9)	4.1 (-3.4 - 11.7)	0.70 (0.42 - 1.16)	0.15
Painful/tender; n (%)	35 (15.5)	33 (14.1)	-1.4 (-8.3 - 5.5)	1.01 (0.58 - 1.77)	0.99
Fluid leaking; n (%)	28 (12.4)	27 (11.5)	-0.9 (-7.2 - 5.5)	1.01 (0.55 - 1.86)	0.99
Fluid (pus) cloudy; n (%)	11 (4.9)	10 (4.3)	-0.6 (-4.8 - 3.7)	1.21 (0.43 - 3.46)	0.81
Gaping open; n (%)	6 (2.7)	4 (1.7)	-0.9 (-4.1 - 2.2)	1.48 (0.34 - 7.22)	0.75
Surgeon opened; n (%)	2 (0.9)	0 (0.0)	-	-	-
Fever > 38°C; n (%)	0 (0.0)	0 (0.0)	-	-	-
Abscess/infection; n (%)	3 (1.3)	5 (2.1)	0.8 (-2.0 - 3.6)	0.57 (0.09 - 2.95)	0.49
Deep surgical site infection at 30 days					
Deep SSI [†] ; n (%)	16 (7.1)	19 (8.1)	1.0 (-4.2 - 6.3)	0.85 (0.42 - 1.70)	0.64
Other postoperative complications related to the index wound / injury reported during follow-up					
Soft Tissue [^] ; n (%)	20 (8.8)	17 (7.3)	-1.6 (-7.0 - 3.8)	1.24 (0.60 - 2.59)	0.61
Neurovascular; n (%)	5 (2.2)	8 (3.4)	1.2 (-2.2 - 4.7)	0.64 (0.16 - 2.26)	0.58
Persistent pain; n (%)	8 (3.5)	11 (4.7)	1.2 (-2.9 - 5.2)	0.74 (0.25 - 2.08)	0.64
DVT/PE ^{^^} ; n (%)	6 (2.7)	4 (1.7)	-0.9 (-4.1 - 2.2)	1.57 (0.37 - 7.65)	0.54
Further surgery related to the open fracture reported during follow-up					
Revision fixation; n (%)	18 (8.0)	15 (6.4)	-1.6 (-6.7 - 3.6)	1.26 (0.58 - 2.77)	0.59
Wound management; n (%)	19 (8.4)	21 (9.0)	0.6 (-5.0 - 6.1)	0.93 (0.46 - 1.88)	0.87
Bone graft; n (%)	10 (4.4)	18 (7.7)	3.3 (-1.5 - 8.0)	0.56 (0.22 - 1.31)	0.17
Amputation; n (%)	4 (1.8)	6 (2.6)	0.8 (-2.3 - 3.9)	0.69 (0.14 - 2.93)	0.75

[‡] Unless stated otherwise, odds ratio, 95% confidence interval and p-value from Fisher's exact test; a value > 1 indicates a greater risk in the NPWT group; where testing was not possible or sensible, then these are marked as '-'

[†] Deep SSI was recorded according to CDC criteria: involvement of deep tissues with purulent drainage from the incision, or spontaneous dehiscence or incision deliberately opened by a surgeon and there was fever or localized pain or tenderness, or confirmation of abscess, or deep SSI diagnosed by a surgeon/attending physician.

[^] Complications that are not related to the bone and not included under wound infection, for example problems caused by scar tissue or tendon irritation.

^{^^} Deep vein thrombosis/Pulmonary Embolism