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UK WOLLF: UK Wound management of Open Lower Limb Fractures

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

Statistical Analysis Plan version 2

8th December 2015

Ethical approval

MREC approval was obtained on 6th February 2012 under reference number 12/WM/0001

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Ref number 10/57/20

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Registration

The study is registered with the current controlled trials database under reference number ISRCTN33756652

Dates

Study start date: March 2012
Study end date: February 2017

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59 **1. Contact details**

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86 **Collaborating Centres – Feasibility phase**

87 (1) University Hospitals Coventry and Warwickshire NHS Trust, University Hospital

88 (2) University Hospitals Birmingham NHS Foundation Trust, Queen Elizabeth Hospital

89 (3) Oxford Radcliffe Hospitals NHS Trust, John Radcliffe Hospital

90 (4) North Bristol NHS Trust, Frenchay Hospital

91 (5) The Newcastle upon Tyne Hospitals NHS foundation Trust, Royal Victoria Hospital

92

93 **Additional collaborating centres – Main phase**

94 (6) Royal London Hospital (RLH)

95 (7) Poole Hospital (POH)

96 (8) Aintree University Hospital (AUH)

97 (9) Leeds General Infirmary (LGI)

98 (10) Addenbrookes Hospital, Cambridge (ADH)

99 (11) University Hospital Southampton (UHS)

100 (12) Northern General Hospital Sheffield (STH)

101 (13) Queen Alexandra Hospital (QAH)

102 (14) Royal Berkshire Hospital (RBH)

103 (15) Kings College Hospital (KCH)

104 (16) University Hospital of North Staffordshire (UNS)

105 (17) Plymouth Hospitals (PLY)

106 (18) Norfolk and Norwich University Hospital (NNH)

107 (19) Royal Derby Hospital (RDH)

108 (20) Hull Royal Infirmary (HRI)

109 (21) University Hospital Leicester (UHL)

110 (22) Nottingham University Hospital (NUH)

111 (23) Morriston Hospital Swansea (MHS)
112 (24) Royal Sussex County Hospital, Brighton (RSC)

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116 **Trial Management Group**

117 Professor Matthew Costa
118 Professor Sallie Lamb
119 Dr Juul Achten
120 Dr Nick Parsons
121 Sonia Davis
122 Susie Hennings

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125 **Trial Steering Committee**

126 Professor Amar Rangan	Consultant Orthopaedic Surgeon (Chair)
127 Mr Mike Read	Consultant Orthopaedic Surgeon (Independent member)
128 Mr Matthew Costa	Chief Investigator
129 Sonia Davis	Trial co-ordinator
130 Dr Nick Parsons	Trial Statistician
131 Prof Stavros Petrou	Trial health economist
132 Mrs Ceri Jones	Sponsor representative (manager R&D UHCW)
133 Mrs Carole Beamish	Lay Member

134

135 **Data monitoring committee**

136 Professor Lee Shepstone	Professor of Medical Statistics (Chair)
137 Prof Simon Donell	Consultant Orthopaedic Surgeon
138 Mr Phillip Johnston	Consultant Orthopaedic Surgeon

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141 **2. Background**

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143 A full summary of the background to the trial can be found in the WOLLF protocol.
144 Fractures of the lower limb are extremely common injuries in both the civilian and
145 military populations. Fortunately, the majority of these injuries are 'closed' i.e. the skin
146 around the fracture is intact. In such cases, the risk of infection is low. However, if the
147 fracture is 'open' such that the barrier provided by the skin is breached, then the
148 broken bone is exposed to contamination from the environment. *Traditionally a non-*
149 *adhesive dressing/sterile gauze is applied to the exposed area. This is then wrapped*
150 *up in a bandage to protect the open fracture from further contamination. The*
151 *wound is covered in this way until a second look and further debridement is*
152 *performed in the operating theatre, usually 48 hours after the initial injury. This*
153 *method has been used throughout the NHS and in military practice for many years.*
154 *However, any bleeding or ooze from the open fracture will soak into the dressings;*
155 *this may be uncomfortable for the patient and, if the blood soaks through the*
156 *dressings, may pose an infection risk. Negative-pressure wound therapy (NPWT) is an*
157 *alternative form of dressing which may be applied to open fractures. In this*
158 *treatment, an 'open-cell', solid foam is laid onto the wound followed by an*
159 *adherent, waterproof dressing. A hole is made in the dressing overlying the foam*
160 *and a sealed tube is used to connect the foam to a pump which creates a partial*
161 *vacuum over the wound. This negative-pressure therapy removes blood and ooze*
162 *from the area of the wound, may also remove any bacteria left in the wound and*

163 encourages the formation of 'granulation' (healing) tissue. NPWT is considerably
164 more expensive than traditional wound dressings, both for the dressing itself and the
165 associated machinery which generates the partial vacuum. There is a pressing need
166 to evaluate this relatively expensive technology. Therefore a multi-centre
167 randomised clinical trial is proposed to compare **negative-pressure wound therapy**
168 with **standard dressings** for patients with wounds associated with open fractures of
169 the lower limb.

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172 **3. Trial design**

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175 **3.1 Trial summary**

176 The proposed project is a two-phased study. Phase 1 (Feasibility phase) will assess the
177 feasibility of running a large-scale multi-centre randomised controlled trial in this
178 complicated area of trauma research. Phase 2 (Main phase) will undertake the
179 proposed randomised controlled trial in a minimum of 18 trauma centres across the
180 UK.

181

182 *Feasibility*

183 The feasibility phase will take place in 5 centres over a period of 6 months. The trial
184 will run as described below for the main trial, with the addition of a qualitative sub-
185 study assessing patients' experience of giving consent for the trial and the
186 acceptability of the trial procedures to patients and staff. Screening logs will be kept
187 at each site to determine the number of patients assessed for eligibility and reasons
188 for any exclusion. In addition, the number of eligible and recruited patients will be
189 recorded.

190

191 *Main RCT*

192 All adult patients presenting at the trial centres within 72 hours of sustaining an open
193 fracture of the lower limb are potentially eligible to take part in the trial. Inclusion
194 within the trial depends on the severity the wound associated with the fracture.
195 Gustilo and Anderson Grade 2 and 3 injuries will be included. A randomisation
196 sequence, stratified by trial centre and Gustilo and Anderson grade, will be
197 produced and administered by a secure web-based service. The random allocation
198 will be to either standard wound management or negative pressure wound therapy.

199

200 The patients will have clinical follow-up in the local fracture clinic up to a minimum of
201 12 months as per standard NHS practice after this injury. Functional and quality of life
202 outcome data will be collected using the DRI, SF12 and EQ-5D questionnaires at 3
203 months, 6 months, 9 months and 12 months post-operatively. These postal
204 questionnaires will be administered centrally by a data administrator. In addition, at
205 the same time-points, information will be requested with regards to resource use and
206 any late complications or interventions related to their injury with specific note of
207 ongoing treatment for deep infection.

208

209 The full trial details, including eligibility, inclusions and exclusion criteria, withdrawal
210 protocols, blinding, randomisation, sample size calculations and methods for the
211 management of adverse events are fully described in the WOLFF protocol. With an
212 allowance for a conservative 10% loss to follow-up, the trial plans to recruit **460**
213 **patients** in total.

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3.2 Objectives

This pragmatic randomised controlled trial will compare standard dressings with negative-pressure wound therapy in the treatment of wounds associated with open fractures of the lower limb.

Feasibility

The specific objectives for the feasibility phase of this study are:

- (1) A qualitative assessment of patients' experience of giving consent for the trial and the acceptability of the trial procedures to patients and staff
- (2) To determine the number of eligible, recruited and withdrawn patients in the 5 feasibility trauma centres over the course of 6 months

At the end of the feasibility phase, the Trial Management Group will provide a report to the Trial Steering Committee. The report will show the actual rate of recruitment at the five centres involved in the feasibility phase compared with the target rate of recruitment (one patient per month per centre), in the context of the results of the qualitative study. If the patients are willing to give their consent and the rate of recruitment achieves the target rate by the end of the feasibility phase, we would anticipate proceeding to the main trial.

Main RCT

The primary objective for the full RCT is:

- (1) To quantify and draw inferences on observed differences in the Disability Rating Index at 12 months after the open fracture.

The secondary objectives are:

- (2) To quantify and draw inferences on patient-reported differences in the rate of wound healing and deep infection of the limb, in the 12 months after the open fracture. Photographs will be used to assess wound healing. Any infection that requires ongoing medical intervention or has already led to amputation at or after the six week review will be considered a 'deep' infection.
- (3) To quantify and draw inferences on observed differences in general quality of life (SF-12 and EQ-5D) of patients with an open fracture of the lower limb in the 12 months after the injury.
- (4) To determine the rate of complications and any further medical intervention related to these, of negative pressure wound therapy versus standard dressing during the first 12 months after the open fracture.
- (5) To investigate, using appropriate statistical and economic analysis methods, the resource use, and thereby the cost effectiveness, of negative pressure wound therapy versus standard dressing for wounds associated with open fractures of the lower limb.

3.3 Outcome measures

Primary outcome measure:

The primary outcome measure for this study is the **Disability Rating Index (DRI)** a self-administered, 12-item Visual Analogue Scale questionnaire assessing the patients' own rating of their disability. This measure was chosen as it addresses "gross body movements" rather than specific joints or body segments. Therefore, it will facilitate the assessment of patients with different fractures of the lower limb.

267 The secondary outcome measures in this trial are:
268 (1) Deep Infection; Patients will be asked to self-report any medical intervention
269 related to infection associated with their open fracture at each of the follow-up
270 points. Any infection that requires ongoing medical intervention or has already
271 led to amputation at or after the routine six week outpatient appointment will
272 therefore be considered a deep infection. In addition, we will use photographs
273 of the wound at each clinical follow-up until the wound is healed in order to
274 provide an objective assessment of wound healing and infection up to 12
275 months after the injury. The photographs will be reviewed by two experienced
276 investigators who are blind to the treatment allocation.
277 (2) EuroQol EQ-5D; The EuroQol EQ-5D is a validated measure of health-related
278 quality of life, consisting of a five dimension health status classification system
279 and a separate visual analogue scale.
280 (3) SF-12; The Short-Form 12 is a validated and widely-used health-related quality
281 of life measure. Each permutation of response to the SF-12 will be converted into
282 a MAU score using a published utility algorithm. These data will be combined
283 with survival data to generate QALY profiles for the purposes of the economic
284 evaluation.
285 (4) Complications; All complications and subsequent medical interventions
286 related to the trial interventions will be recorded.
287 (5) Resource use; This will be monitored for the economic analysis. Unit cost data
288 will be obtained from national databases such as the BNF and PSSRU Costs of
289 Health and Social Care. The cost consequences following discharge, including
290 NHS costs and patients' out-of-pocket expenses will be recorded via a short
291 questionnaire which will be administered at 3, 6, 9 and 12 months post surgery.
292 Patient self-reported information on service use has been shown to be accurate
293 in terms of the intensity of use of different services.
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296 **4. Data management and security**

297 The Case Report Forms (CRFs) will be designed by the trial coordinator in conjunction
298 with the trial management team. All electronic patient-identifiable information will
299 be held on a secure, password-protected database accessible only to essential
300 personnel. Paper forms with patient-identifiable information will be held in secure,
301 locked filing cabinets within a restricted area of Warwick Medical School. Patients will
302 be identified by a code number only. Direct access to source data/documents will
303 be required for trial-related monitoring. All paper and electronic data will be
304 retained for at least five years after completion of the trial.
305

306 Full details of management and checking of CRFs, x-rays, participant postal
307 questionnaires and SAE forms are given in the WOLLF Data Management Plan. For
308 newly employed data administrators entering data the trial coordinator will perform
309 a 100% data check of a minimum of 30 CRFs and questionnaires entered or until the
310 error rate is less than 1%. A routine 10% check will be performed every month; the
311 sample will be generated from the forms entered that month. If an error rate of over
312 1% is found, then an additional sample will be taken. If a further 1% error rate is found,
313 then a 100% check will be performed of the particular forms concerned.
314

315 **5. Statistical analysis**

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319 **5.1 Software**

320 When any analyses are required, data will be retrieved from the trial database by
321 the trial statistician. The statistician will import data directly into the statistical
322 package R for analysis and reporting (<http://www.r-project.org/>) using an ODBC
323 (Open DataBase Connectivity) link; the version numbers of all software used, data
324 files and all R scripts will be made available to the Data Monitoring Committee (DMC)
325 on request at any stage of the trial. Statistical results will be reported in accordance
326 with CONSORT guidelines (<http://www.consort-statement.org/>).
327

328
329 **5.2 Data validation**

330 Prior to formal analysis, data will be checked for outliers, missing values and
331 validated using the defined score ranges for all outcome measures. Queries will be
332 reported to the trial coordinator and investigated. Standard statistical summaries
333 (e.g. medians and ranges or means and variances, dependent on the distribution of
334 the outcome) and graphical plots showing correlations will be presented for the
335 primary outcome measure and all secondary outcome measures. Baseline data will
336 be summarized to check comparability between treatment arms, and to highlight
337 any characteristic differences between those individuals in the study, those ineligible,
338 and those eligible but withholding consent.
339

340
341 **5.3 Missing data**

342 It seems likely that some data may not be available due to voluntary withdrawal of
343 patients, lack of completion of individual data items or general loss to follow-up.
344 Where possible the reasons for data 'missingness' will be ascertained and reported.
345 Although missing data are not expected to be a problem for this study, the nature
346 and pattern of the missingness will be carefully considered — including in particular
347 whether data can be treated as missing completely at random (MCAR). If judged
348 appropriate, missing data will be imputed using the multiple imputation facilities
349 (mice package) available in R (<http://www.r-project.org/>). Any imputation methods
350 used for scores and other derived variables will be carefully considered and justified.
351 If the degree of missingness is relatively low, as expected, the primary analysis will be
352 based on complete cases only (*complete case analysis*), with analysis of imputed
353 datasets used to assess the sensitivity of the analysis to the missing data. Reasons for
354 ineligibility, non-compliance, withdrawal or other protocol violations will be stated
355 and any patterns summarized. More formal analysis, for example using logistic
356 regression with 'protocol violation' as a response, may also be appropriate and aid
357 interpretation.
358

359
360 **5.4 Interim analyses**

361 Interim analyses will be performed only where directed by the DMC. Interim analyses
362 will follow the same procedure as the final analyses.
363

364
365 **5.5 Final statistical analyses**

366
367 **5.5.1 Feasibility Study**

368 At the end of the feasibility phase, the overall mean recruitment rates at the five
369 selected centres for this phase of the study will be estimated (with a 95% confidence
370 interval based on a normal approximation) and compared to the target rate of one

371 patient per month per centre. The estimated recruitment rate in the feasibility phase
372 will inform both the design and the decision to proceed to the main RCT. Additionally
373 the nature and pattern of trial withdrawals and the likely impact of this on the main
374 RCT will also be carefully considered.

375

376 **5.5.2 Main RCT**

377

378 *Primary Outcome*

379 The null hypothesis for WOLLF is that, *there is no difference in the Disability Rating*
380 *Index score (DRI) one year post-injury between adult patients with an open fracture*
381 *to the lower limb treated with standard wound dressings versus negative pressure*
382 *wound therapy.*

383

384 The main analysis will investigate differences in the primary outcome measure, the
385 Disability Rating Index (DRI) score at one year after injury, between the two
386 treatment groups (standard wound dressings and negative pressure wound therapy)
387 on an intention-to-treat basis. In addition, early functional status will also be assessed
388 and reported at 3, 6 and 9 months. Differences between groups will be assessed,
389 based on a normal approximation for the DRI score at 12 months post-injury, and at
390 interim occasions. Tests will be two-sided and considered to provide evidence for a
391 significant difference if p-values are less than 0.05 (5% significance level).

392

393 The stratified randomisation procedure should ensure a balance in Gustilo and
394 Anderson grade and the recruiting centre between test treatments. Although
395 generally we have no reason to expect that clustering effects will be important for
396 this study, in reality the data will be hierarchical in nature, with patients naturally
397 clustered into groups by recruiting centre. Therefore we will account for this by
398 generalizing the conventional linear (fixed-effects) regression approach to a mixed-
399 effects modelling approach; where patients are naturally grouped by recruiting
400 centres (random-effects). This model will formally incorporate terms that allow for
401 possible heterogeneity in responses for patients due to the recruiting centre, in
402 addition to the fixed effects of the treatment groups, Gustilo and Anderson grade
403 and other patient characteristics that may prove to be important moderators of the
404 treatment effect such as age and gender.

405

406 The main analyses will be conducted using specialist mixed-effects modelling
407 functions available in the software package R (<http://www.r-project.org/>) where DRI
408 data will be assumed to be normally distributed; possibly after appropriate variance-
409 stabilising transformation. The primary focus will be the comparison of the two
410 treatment groups of patients, and this will be reflected in the analysis which will be
411 reported together with appropriate diagnostic plots that check the underlying
412 model assumptions. Results will be presented as mean differences between the trial
413 groups, with 95% confidence intervals.

414

415 *Secondary Outcomes and Complications*

416 Secondary analyses will be undertaken using the above strategy for approximately
417 normally distributed outcome measures SF-12 and EQ5D. For dichotomous outcome
418 variables, such as indicators of deep infection and other complications related to
419 the trial interventions, mixed effects logistic regression analysis will be undertaken with
420 results presented as odds ratios (and 95% confidence intervals) between the trial
421 groups. The temporal patterns of any complications will be presented graphically
422 and if appropriate a time-to-event analysis (Kaplan-Meier survival analysis) will be

423 used to assess the overall risk and risk within individual classes of complications (e.g.
424 infection). About 1-2% of patients are expected to die during follow-up, so this is
425 unlikely to be a serious cause of bias. However, we will also if appropriate conduct a
426 secondary analysis taking account of the competing risk of death, based on
427 cumulative incidence functions. If multiple complications prove to be widely
428 reported, then a secondary analysis will use a Poisson regression model (or zero-
429 inflated Poisson regression model) to assess overall differences in counts of events
430 between groups, adjusting for potential confounding factors such as age and
431 gender. Multiple complications are defined as two or more independent events, i.e.
432 not continuations of a previous complication, for the same patient and will be
433 identified only after discussion with the clinical team.

434

435 **5.5.3 Analysis plan**

436 The statistical analysis plan (SAP) will be agreed with the Data management
437 Committee (DMC) at the start of the study. Any subsequent amendments to this
438 initial SAP will be clearly stated and justified. Interim analyses will be performed only
439 where directed by the DMC. The routine statistical analysis will mainly be carried out
440 using R (<http://www.r-project.org/>) and S-PLUS (<http://www.insightful.com/>).

441

442 **5.6 Reporting**

443 Wherever possible, the results of all analyses will be presented in a simple and easy to
444 follow manner and relate any observed differences to their clinical importance, such
445 that they could be clearly understood by those with only rudimentary statistical
446 knowledge. Open and confidential reports of the statistical analyses will be
447 produced, as required, by the trial statistician and where appropriate results will be
448 disseminated through peer-reviewed journals, conference presentations and through
449 local mechanisms.

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