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

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Table of contents

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Collaborating Centres – Feasibility phase
(1) University Hospitals Coventry and Warwickshire NHS Trust, University Hospital
(2) University Hospitals Birmingham NHS Foundation Trust, Queen Elizabeth Hospital
(3) Oxford Radcliffe Hospitals NHS Trust, John Radcliffe Hospital
(4) North Bristol NHS Trust, Frenchay Hospital
(5) The Newcastle upon Tyne Hospitals NHS foundation Trust, Royal Victoria Hospital

Additional collaborating centres – Main phase
(6) Royal London Hospital (RLH)
(7) Poole Hospital (POH)
(8) Aintree University Hospital (AUH)
(9) Leeds General Infirmary (LGI)
(10) Addenbrookes Hospital, Cambridge (ADH)
(11) University Hospital Southampton (UHS)
(12) Northern General Hospital Sheffield (STH)
(13) Queen Alexandra Hospital (QAH)
(14) Royal Berkshire Hospital (RBH)
(15) Kings College Hospital (KCH)
(16) University Hospital of North Staffordshire (UNS)
(17) Plymouth Hospitals (PLY)
(18) Norfolk and Norwich University Hospital (NNH)
(19) Royal Derby Hospital (RDH)
(20) Hull Royal Infirmary (HRI)
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Trial Management Group

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Trial Steering Committee

Professor Amar Rangan	Consultant Orthopaedic Surgeon (Chair)
Mr Mike Read	Consultant Orthopaedic Surgeon (Independent member)
Mr Matthew Costa	Chief Investigator
Sonia Davis	Trial co-ordinator
Dr Nick Parsons	Trial Statistician
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Professor Lee Shepstone	Professor of Medical Statistics (Chair)
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2. Background

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

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

3. Trial design

3.1 Trial summary

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

Feasibility

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

Main RCT

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

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

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

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.

The secondary outcome measures in this trial are:

(1) Deep Infection; Patients will be asked to self-report any medical intervention related to infection associated with their open fracture at each of the follow-up points. Any infection that requires ongoing medical intervention or has already led to amputation at or after the routine six week outpatient appointment will therefore be considered a deep infection. In addition, we will use photographs of the wound at each clinical follow-up until the wound is healed in order to provide an objective assessment of wound healing and infection up to 12 months after the injury. The photographs will be reviewed by two experienced investigators who are blind to the treatment allocation.

(2) EuroQol EQ-5D; The EuroQol EQ-5D is a validated measure of health-related quality of life, consisting of a five dimension health status classification system and a separate visual analogue scale.

(3) SF-12; The Short-Form 12 is a validated and widely-used health-related quality of life measure. Each permutation of response to the SF-12 will be converted into a MAU score using a published utility algorithm. These data will be combined with survival data to generate QALY profiles for the purposes of the economic evaluation.

(4) Complications; All complications and subsequent medical interventions related to the trial interventions will be recorded.

(5) Resource use; This will be monitored for the economic analysis. Unit cost data will be obtained from national databases such as the BNF and PSSRU Costs of Health and Social Care. The cost consequences following discharge, including NHS costs and patients' out-of-pocket expenses will be recorded via a short questionnaire which will be administered at 3, 6, 9 and 12 months post surgery. Patient self-reported information on service use has been shown to be accurate in terms of the intensity of use of different services.

4. Data management and security

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

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

5. Statistical analysis

5.1 Software

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

5.2 Data validation

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

5.3 Missing data

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

5.4 Interim analyses

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

5.5 Final statistical analyses

5.5.1 Feasibility Study

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

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

5.5.2 Main RCT

Primary Outcome

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

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

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

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

Secondary Outcomes and Complications

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

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

5.5.3 Analysis plan

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

5.6 Reporting

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