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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)

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Abstract

Introduction

Patients with closed high-energy injuries associated with major trauma, have surprisingly high rates of surgical site infection in incisions created during fracture fixation. One factor which may reduce the risk of surgical site infection is the type of dressing applied over the closed surgical incision. In this multi-centre randomised clinical trial, negative-pressure wound therapy will be compared with standard dressings with outcomes of deep infection, quality of life, pain and disability.

Methods and analysis

Adult patients presenting to hospital within 72 hours of sustaining major trauma, requiring a surgical incision to treat a fractured lower limb are eligible for inclusion. Randomisation, stratified by trial centre, open/closed fracture at presentation, and Injury Severity Score ≤15 vs ISS ≥16 will be administered via a secure web-based service using minimisation. The random allocation will be to either standard wound management or negative pressure wound therapy.

Trial participants will usually have clinical follow-up at the local fracture clinic for a minimum of 6 months, as per standard NHS practice. Diagnosis of deep infection will be recorded at 30 days. Functional, pain and quality of life outcome data will be collected using the Disability Rating Index, Douleur Neuropathique Questionnaire and EQ-5D-5L questionnaires at 3 months and 6 months post-injury. Further data will be captured on resource use and any late post-operative complications.

Longer term outcomes will be assessed annually for five years and reported separately.

Ethics and Dissemination

National Research Ethic Committee approved this study on 16/02/2016 16/WM/0006

The NIHR Health Technology Assessment monograph and a manuscript to a peer-reviewed journal will be submitted upon completion of this trial. The results of this trial will inform clinical practice on the clinical and cost effectiveness of the treatment of this injury.

This study has been registered on the ISRCTN registry with reference number ISRCTN12702354

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Strength and limitations of this study

- Broad eligibility criteria to ensure generalisability.
- Deep infection data will be supplemented with patient-reported outcomes.
- Assessment of outcomes at multiple time points will allow for information on recovery profile.
- In addition to a comparison of clinical outcomes, a full cost-effectiveness evaluation will be performed.
- It will not be possible to blind patients to their allocated treatment, as the type of wound dressing will be clearly visible.

Background

Major trauma is the leading cause of death in people aged under 45 years and a significant cause of short- and long-term morbidity. The National Audit Office (NAO) estimates that there are at least 20,000 cases of Major Trauma each year in England, resulting in 5,400 deaths and many survivors suffer permanent disabilities requiring long-term care. The NAO estimate that trauma costs the NHS between £0.3 and £0.4 billion a year for immediate treatment. This does not include the cost of subsequent hospital treatments, rehabilitation, home care support, or informal carers. The NAO estimate that the annual lost economic output from traumatic injury is between £3.3 billion and £3.7 billion.

Fractures of the limbs are extremely common injuries, with 85% of major trauma patients sustaining serious limb injuries. [1] In open fractures of the lower limb, where the broken bone is exposed to the environment by a breach in the skin, the risk of infection is particularly high.[1] However, even in closed high-energy injuries associated with major trauma, the rate of infection remains high. For example, tibial plateau fractures are associated with average infection rates of up to 27%,[2-6] while pilon fractures have an incidence of deep infections ranging from 5% to 40%[7-10]. If surgical site infection does occur, treatment frequently continues for years after the initial injury. This often involves prolonged courses of antibiotics, with attendant risk of antibiotic resistance in chronic wounds, and a huge health care cost associated with such injuries. A US study found that the average cost associated with infection was $163,000 if the limb could be salvaged and $500,000+ where amputation was necessary, and these only represent a fraction of the subsequent personal and societal costs[11].

Major trauma patients are at greater risk of infection due to several factors, including the presence of antibiotic resistant organisms in the ITU and high-dependency environment. Furthermore, the presence of a wound haematoma or postoperative wound leak oozing may predispose to infection in wounds created by surgical incisions. One of the factors which may reduce the risk of surgical site infection is the type of dressing applied over the closed incision at completion of the operative procedure. Dressings may reduce bacterial ingress into the wound. The published literature suggests that the type of dressing applied to the wound influences the healing process itself[12]. This trial concerns the type of dressing that is applied to the closed surgical incision at the end of the operation.

Traditionally, the surgical incision is covered with an adhesive dressing or gauze maintained in place with a bandage to protect the wound from contamination from the outside environment. These 'standard dressings' have been used throughout the NHS and in military practice for many years. Negative-pressure wound therapy (NPWT) or topical negative pressure is an alternative form of

dressing which may be applied to closed surgical incisions. In this treatment, an 'open-cell', solid foam overlies the incision and is covered with a semipermeable membrane which is only permeable to gas. A sealed tube is used to connect the foam to a pump, which creates a partial vacuum over the wound. This negative-pressure therapy provides a sealed environment, preventing bacterial ingress and removes blood and serous fluid exuding from the wound. The application of negative pressure to the foam leads to the application of positive pressure to the wound bed and has been shown to reduce the incidence of wound haematoma[13]. Recent laboratory studies suggest that NPWT shifts the cytokine profile to being less inflammatory, potentially promoting the production of pro-angiogenic growth factors and enzymes responsible for matrix remodelling, leading to improved wound healing.[12] However, NPWT for closed wounds is considerably more expensive than traditional wound dressings. There has been only one randomised trial comparing standard wound dressing with NPWT for patients with closed surgical wounds following major trauma to the lower limb.[13] This trial demonstrated a reduction in the rate of late/deep wound infection in the group of patients treated with NPWT (9%) versus the standard dressing group (15%). However, the reduction was of borderline statistical significance (p=0.049) and the study has been criticised in the subsequent Cochrane review for methodological flaws. [14]

The recent Cochrane review for surgical wounds concluded *that "it is still not clear whether NPWT promotes faster healing and reduces complications associated with clean surgery". "Given the cost and widespread use of NPWT, there is an urgent need for suitably powered, high-quality trials to evaluate the effects of the newer NPWT products that are designed for use on clean, closed surgical incisions. Such trials should focus initially on wounds that may be difficult to heal".* [14] The WHIST Trial aims to address this evidence gap.

Good Clinical Practice

The trial will be carried out in accordance with Medical Research council (MRC) Good Clinical Practice and applicable UK legislation using the following protocol.

CONSORT

The trial will be reported in line with the CONSORT statement using the non-pharmacological treatment interventions extension.

Trial design

Aim

The aim of this pragmatic randomised controlled trial is to compare negative-pressure wound therapy with standard wound dressings for the treatment of surgical incisions associated with major trauma to the lower limb on outcomes of deep infection, quality of life, pain and disability.

The primary objective for the RCT is:

To quantify and draw inferences on differences in the rate of 'deep surgical site infection (SSI)' of the lower limb in the 30 days after randomisation between treatment arms of standard wound dressing versus NPWT. Any wound infection that requires continuing medical intervention or has already led to amputation at the 30-day review will be considered a 'deep' infection.

The secondary objectives are:

i) To quantify and draw inferences on observed differences in the disability rating index (DRI) in the 6 months after the major trauma.

ii) To quantify and draw inferences on observed differences in general health-related quality of life in the 6 months after the major trauma.

iii) To quantify and draw inferences on the quality of wound healing, using a validated, patient-reported assessment of the scar. The patient-reported assessment will be supplemented with photographs taken at 6 weeks to objectively assess wound healing and apparent signs of infection.

iv) To determine the number and nature of complications in the first 6 months after the major trauma: including chronic pain, deep SSI at 90 days and further surgical interventions related to the injury.

v) To investigate the cost effectiveness, of negative pressure wound therapy versus standard dressing for wounds associated with major trauma to the lower limbs.

Outcome measures

The primary outcome measure for this study is **Deep Surgical Site Infection**; We will use the Centers for Disease Control and Prevention (CDC) definition of a "deep surgical site infection", that is a wound infection involving the tissues deep to the skin that occurs within 30 days of injury. [15]

The treating clinical team will make the diagnosis of 'infection', as per routine clinical practice. The treating clinicians will not be part of the research team. As the prompt diagnosis and treatment of

infection is fundamental to the patient's routine clinical care, the treating surgeon/clinician will always document such a change in management in the patient's medical record. The medical records will be reviewed by an independent research associate who will complete the Clinical Reporting Forms, which will include the specific criteria used by the CDC to define a "deep surgical site infection". Any infection that requires continuing medical intervention or has already led to amputation at or after the 30-day review will be considered a deep infection.

The secondary outcome measures in this trial are:

Disability Rating Index measured using a self-administered, 12-item Visual Analogue Scale questionnaire assessing the patients' own rating of their disability.[16] This measure was chosen as it addresses gross body movements rather than specific joints or body segments. Therefore, it will capture function and disability associated with different fractures and injuries of the lower limbs.

EuroQol EQ-5D-5L: 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. [17] An updated version of the EQ-5D with 5 response levels, the EQ-5D-5L, has recently been developed to enhance the responsiveness of the instrument to changes in patient health.[18] Responses to the health status classification system will be converted into multi-attribute utility (MAU) scores using tariffs currently under development for England.[19] These MAU scores will be combined with survival data to generate QALY profiles for the purposes of the economic evaluation. The EQ-5D has been validated to be completed by a patient's proxy in case of continued impaired capacity.

Wound Healing: A patient-reported scar assessment will be collected using the patient scale from the Patient and Observer Scar Assessment Scale22 consisting of six questions regarding different aspects of the scar, as well as an overall assessment of the scar. This will be used to provide a subjective patient-assessment of wound healing. An objective assessment of wound healing using a standardised photograph of the wound from the 30-day review will be evaluated by two independent experienced assessors who are blind to the treatment allocation. Patients will also be asked to self-report any treatment for infection will be cross-referenced with the participant's medical record. This will allow us to report deep infection at later time-points, for example at 90 days.

Complications: Chronic pain: The proportion of patients reporting chronic pain post-injury with neuropathic characteristics will be measured using the Douleur Neuropathique Questionnaire

(DN420). Chronic pain after surgery and trauma is common and disabling but no previous studies have assessed the prevalence of persistent painful neuropathic characteristics after lower limb fracture. The interview versions of the DN4 is a short validated neuropathic pain screening tool comprising seven questions. This screening tool is recommended for use by the International Association for the Study of Pain (IASP 21). Scores of 3 or greater are likely to be indicative of neuropathic pain. Patients will also be asked to self-report (or a consultee on their behalf, in case of continued impaired capacity) at each of the follow-up points on wound healing complications, any treatment for infection and any medical/surgical intervention related to infection associated with their surgical wound. Any self-report of treatment for infection will be cross-referenced with the participant's medical record. This will allow us to report deep infection at later time-points, for example at 90 days. All other post-operative complications and surgical interventions related to the index wound will be recorded.

Resource use 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.[23] Where these are not available the unit cost will be estimated in consultation with the hospital finance department. 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 three and six months post major trauma. Patient self-reported (or consultee reported) information on service use has been shown to be accurate in terms of the intensity of use of different services.[24]

Data collection

Table 1 displays the time points when outcome measures are being collected.

TIME POINT	DATA COLLECTION
Baseline	DRI *and* EQ-5D *pre-injury and contemporary*,
30 days	Deep infection, complication records, scar assessment, operative record, photograph of limb wound
3 months	DRI, EQ-5D, DN4, scar assessment, record of complications/rehabilitation or other interventions and economics questionnaire
6 months	DRI, EQ-5D, DN4, scar assessment, record of complications/rehabilitation or other interventions and economics questionnaire
12 months	DRI, EQ-5D, DN4, record of complications/ further interventions
2,3,4,5 years	DRI, EQ-5D, DN4, record of complications/ further interventions

Table 1: outcome collection

For the purposes of long-term follow-up, patients will subsequently be contacted on an annual basis for 5 years to complete the EQ-5D-5L, DRI and DN4 questionnaires. Longer-term follow-up will be reported separately.

Sample size

There has only been one previous randomised trial to compare negative pressure wound therapy to standard dressings for surgical incisions associated with major trauma to the lower limb. This trial indicated that the rate of 'late' (deep) infection was 15% in the standard dressing group versus 9% in the NPWT group. [13]

In the absence of a 'Minimum Clinically Important Difference' for deep wound infection, we surveyed surgeons in the UK Orthopaedic Trauma Society who perform surgery for major trauma to the limbs (unpublished data 2015). The survey showed that those who responded to the survey considered that a 6% reduction in the rate of 'deep infection' would, universally, be sufficient to change clinical practice with regard to the choice of wound dressing.

Therefore, assuming a reduction in the proportion of patients having a deep infection from 15% to 9%, 615 patients would be required in each group to provide 90% power at the 5% level. Our previous experience in clinical trials of lower limb fracture surgery for major trauma indicates that up to 20% of primary outcome data may be lost during the follow-up period; due to death and loss to follow-up. Therefore, we aim to recruit **1540 patients** in total for this trial.

Methodology

Screening

Patients will be screened from the Emergency Department or Trauma Unit from participating trial centres. Throughout the study, screening logs will be kept at each site to determine the number of patients assessed for eligibility and any reasons for any exclusion. Patients who decline to participate or withdraw from the study will be given the opportunity to discuss/inform the research team of their reasoning behind their decision not to take part.

The patient's routine imaging on admission will be used, including any 'Major Trauma CT scan', and associated 'secondary survey' to identify the patient's injuries and calculate the Injury Severity Score (15 or less vs 16 or more) before randomisation. All major trauma patients in England are automatically considered for entry onto the national Trauma Audit and Research Network database, which requires the calculation of the Injury Severity Score. Therefore, all centres are familiar with the use of this major trauma scoring system.

Eligibility

Patients will be eligible for WHIST if:

They are aged 16 years or older

Present to hospital within 72 hours of injury

They have a major trauma injury and/or TARN eligible injury as defined by eligibility for the UK Trauma Audit Research Network (TARN) database

They have a lower limb fracture requiring a surgical incision.

Some patients have major trauma affecting just one limb, for example heel, pilon and tibial plateau fractures. Since the wounds associated with these injuries are always at risk, we will include these injuries even if the patient is subsequently not included in TARN.

Patients will be excluded from participation in WHIST if:

They have an open fracture of the lower limb which cannot be closed primarily.

There is evidence that the patient would be unable to adhere to trial procedures or complete questionnaires. It is expected that for a small proportion of patients, for example those with head injury, this exclusion criterion will only be determined after randomisation. These patients will then be excluded from the study.

Patients who sustain injuries to areas of the body other than the lower limbs, which may affect the primary outcome measure, will have their other injuries documented but will still be included in the analysis. For patients with more than one lower limb injury, only the most severe wound will be included as the 'WHIST' wound in the trial. It will be up to the surgeon's discretion to decide which injury is the most severe.

Consent to participating

Many patients with major trauma will be operated on immediately or on the next available trauma operating list. Some patients may be unconscious, all will be distracted by their injury and its subsequent treatment and all will have had large doses of opiates for pain relief, potentially affecting their ability to process study-related information. Similarly, patients' next of kin, carers and friends are often anxious at this time and may have difficulty in considering the large amounts of information that they are given about the injury and plan for treatment. In this emergency situation, the focus is on obtaining consent for surgery (where possible) and informing the patient and any next of kin about immediate clinical care. The consent procedure for this trial will reflect that of the surgery, with the attending clinician assessing capacity before taking consent for the surgical

procedure and this capacity assessment then being used to decide on the proper approach to consenting to the WHIST study. An appropriate method, in line with the mental capacity act and as approved by the National Research Ethics Service, will then be used to gain either prospective or retrospective consent from the patient or appropriate consultee, by an appropriately delegated member of the research team.

Randomisation

The treating surgeon will confirm participant eligibility at the end of the operative procedure but before the wound dressing is applied. Randomisation will be on a 1:1 basis, using a validated computer randomisation program managed centrally by the Oxford Clinical Trials Research Unit (OCTRU). A minimisation algorithm, will be used to ensure balanced allocation of patients across the two treatment groups, stratified by trial centre, open or closed fracture at presentation and Injury Severity Score (ISS) ≤15 vs ISS ≥16. The first 30 participants will be randomised using simple randomisation to seed the minimisation algorithm (generated by the trial statistician), and the minimisation algorithm will have probabilistic element of 0.8 introduced to ensure unpredictability of the treatment assignment. After the randomisation is received electronically by the surgical team, the allocated treatment can be administered immediately.

Post randomisation withdrawals/exclusions

Participants will be excluded in the post-randomisation phase if it is later established that they are unable to adhere to trial procedures or complete questionnaires.

Participants may decline to continue to take part in the trial at any time without prejudice. A decision to decline consent or withdraw will not affect the standard of care the patient receives.

Blinding

As the wound dressings and topical devices are clearly visible, the treating surgeon and trial participants cannot be blinded to treatment allocation. However, the treating surgeons will not be involved in study follow-up assessments or data collection for the trial. Data from Clinical Reporting forms will be entered onto a central database administered by a data clerk independent of the clinical team in the trial central office. Wound photographs taken at outpatient clinic at approximately 30 days post-surgery will be reviewed independently by two experienced assessors blinded to the treatment allocation.

Trial treatments

Patients with a fracture of the lower limb associated with major trauma usually have surgery on the next available trauma operating list. Some patients may be transferred to a Major Trauma Centre for definitive care – within the first 48 hours of injury – but will still have their initial surgery as soon as possible. All patients will receive general or regional anaesthesia. At the end of the initial operation, a dressing is applied to the surgical wound. WHIST will compare two types of wound dressing; standard dressing versus negative pressure wound therapy.

Standard dressing. The standard dressing for a surgical wound comprises a non-adhesive layer applied directly to the wound which is then covered by a sealed dressing or bandage. The standard dressing does not use 'negative pressure'. The exact details of the materials used will be left to the discretion of the treating surgeon as per their routine practice but the details of each dressing applied will be recorded.

Negative-pressure wound therapy. The NPWT dressing uses an 'open-cell', solid foam which is laid onto the wound as an intrinsic part of a sealed dressing. A sealed tube connects the dressing to a built in mini-pump which creates a partial vacuum over the wound.

The NPWT dressing will be applied to the wound at the end of the operation according to the treating surgeon's normal practice and the dressing manufacturer's instructions. The wound may be re-dressed again on the ward; any further wound dressing will be recorded and will follow the allocated treatment unless otherwise clinically indicated.

Post-operative Rehabilitation

Patients will usually be reviewed at 3 and 6 months, as per routine practice after this type of injury. Details about rehabilitation and additional follow-up appointments will be recorded but left entirely to the discretion of the treating clinicians, as the type of injury will vary between patients.

Adverse event management

Serious adverse events (SAE) will be entered onto the Serious Adverse Event reporting form and reported to the central study team. However, some adverse events are foreseeable as part of the proposed treatment, and will not be reported on an SAE reporting form, but recorded on a complications form. These events include: any complications of anaesthesia or surgery (wound infection, bleeding or damage to adjacent structures such as nerves, tendons and blood vessels, delayed unions/non-unions, delayed wound healing, further surgery to remove/replace metalwork and thromboembolic events). All participants experiencing SAEs will be followed-up as per protocol until the end of the trial.

End of trial

The end of the main phase of the trial will be defined as the collection of final six month outcome data from the last participant. Longer-term follow-up will be reported separately.

Analysis

Statistical analysis

Baseline characteristics and outcome measures will be reported overall and separately for the two treatment arms using standard statistical summaries (e.g. medians and ranges or means and variances, or proportions and percentages, dependent on the distribution of the outcomes) including graphical presentation where appropriate.

The primary analysis will investigate differences in the primary outcome measure, the proportion of patients with deep SSI, at 30 days post operation. Although 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 logistic (fixed-effects) regression approach to a mixed-effects logistic regression analysis. This model will be used to assess differences in the rate of deep SSI between the study intervention groups, with results presented as odds ratios with associated 95% confidence intervals. The mixed-effects model will include a random effect to account for any heterogeneity in response due to the recruitment centre and fixed effects to adjust for open versus closed fractures and the ISS, participant age and gender.

An identically structured and formulated mixed-effects linear or logistic regression model (as appropriate) will be used to assess the effects of the interventions on secondary outcomes DRI and EQ-5D-5L (at both 3 and 6 months, and for the long-term follow-up). Supplementary analyses for these outcomes will include using area under the curve summary statistics calculated from the mixed model parameter estimates to provide an overall estimate of recovery over time.[25] Other dichotomous outcome variables, such as complications related to the trial interventions will be analysed in the same manner as the primary outcome. 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.

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. Missing data will be minimised and the reasons for missing data will be ascertained and reported separately by treatment group. The

amount, nature and pattern of missing data will be carefully considered and missing data will be imputed, using multiple imputation if appropriate.

The primary population for analysis will be on an intention-to-treat (ITT) basis, i.e. analysed as they were randomised. In addition to the ITT analyses, sensitivity analyses including on the per-protocol population and to assess the missing data assumption if missing data imputation is used, will also be undertaken and reported in parallel to, but subsidiary to, the main analyses.

About 1-2% of patients are expected to die during follow-up, so this is unlikely to be a serious cause of bias. If appropriate, we will conduct a supplementary analysis taking account of the competing risk of death, using methods described by Varadhan et al.[26]

All reported 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).

A detailed statistical analysis plan (SAP) will be agreed with the Data Safety and Monitoring Committee (DSMC) at the commencement of or early in the study. This will be updated prior to the final data-lock following a blinded analysis of the data. Any subsequent changes to the analysis outlined in the SAP will be clearly stated and justified in the final report. Interim analyses of efficacy outcomes are not planned and will be performed only where requested by the independent DSMC.

Analyses will be undertaken using validated statistical software such as Stata (Stata Corp LP - http://www.stata.com) or the software package R (http://www.r-project.org/).

Economic evaluation

An economic evaluation will be integrated into the trial design. The economic evaluation will be conducted from the recommended NHS and personal social services (PSS) perspective [23]. Data will be collected on the health and social service resources used in the treatment of each trial participant during the period between randomisation and 6 months post-randomisation. Trial data collection forms will record the duration of each form of hospital care, surgical procedures, adjunctive interventions, medication profiles, tests and procedures. If required, information on additional staff and material inputs associated with clinical complications will be obtained directly from patient and clinical records. At 3 and 6 months post-randomisation, trial participants will be asked to complete postal questionnaires profiling hospital (inpatient and outpatient) and community health and social care resource use and, for the purposes of sensitivity analysis, out-of-pocket expenditures and costs associated with lost productivity. Current UK unit costs will be applied to each resource item to value total resource use in each arm of the trial. *Per diem* costs for hospital care, delineated by level or intensity of care, will be calculated by the health economics researcher using data from detailed questionnaires completed by the local finance departments, giving cost data and apportioning these to different

categories of patient using a 'top-down' methodology. The unit costs of clinical events that are unique to this trial will be derived from the hospital accounts of the trial participating centres, although primary research that uses established accounting methods may also be required. The unit costs of community health and social services will largely be derived from national sources, although some calculations from first principles using established accounting methods may also be required.[27] Responses to the EQ-5D-5L will be converted into multi-attribute utility scores using the algorithm currently under development to reflect societal preferences in England.[19 28 29] Crosswalking algorithms will be employed to generate supplementary utility values comparable with those derived from the EQ-5D-3L instrument.[18]

An incremental cost-effectiveness analysis, expressed in terms of incremental cost per quality-adjusted life year (QALY) gained, will be performed. Results will be presented using incremental cost-effectiveness ratios (ICERs) and cost-effectiveness acceptability curves (CEACs) generated via non-parametric bootstrapping. This accommodates sampling (or stochastic) uncertainty and varying levels of willingness to pay for an additional QALY. Issues with missing values, if they arise, will be accommodated using multiple imputation methods in line with the approach used in the clinical component of the trial.

Trial Oversight

The day-to-day management of the trial will be the responsibility of the Clinical Trial Manager, based at Nuffield Department of Orthopaedics, Rheumatology and Musculoskeletal Sciences and supported by the OCTRU staff. This will be overseen by the Trial Management Group, who will meet monthly to assess progress. It will also be the responsibility of the Clinical Trial Manager to undertake training of the research associates at each of the trial centres. The Trial Statistician and Health Economist will be closely involved in setting up data capture systems, design of databases and clinical reporting forms.

A Trial Steering Committee (TSC) and a Data & Safety Monitoring Committee (DSMC) will be set up. The study DSMC will adopt a DAMOCLES charter which defines its terms of reference and operation in relation to oversight of the trial. They will not be asked to review any formal interim comparative analyses of effectiveness. They will, however, see copies of data accrued to date, or summaries of that data by treatment group and they will assess the screening algorithm against the eligibility criteria. They will also consider emerging evidence from other related trials or research and review related SAEs that have been reported. They may advise the chair of the Trial Steering Committee at any time if, in their view, the trial should be stopped for ethical reasons, including concerns about participant safety. DSMC meetings will be held at least annually during the recruitment phase of the study.

Quality control

The study may be monitored, or audited in accordance with the current approved protocol, relevant regulations and standard operating procedures by the Host organization, Sponsor or appropriate Regulatory Authorities. A Monitoring Plan will be developed according to OCTRU standard operating procedures which involves a risk assessment. The monitoring activities are based on the outcome of the risk assessment and may involve central monitoring and site monitoring.

Ethics and Dissemination

National Research Ethic Committee approved this study on the 16th of February 2016 (16/WM/0006). The study monograph for the National Institute for Health Research Health Technology Assessment will be prepared by the trial management team within three months of completion of the trial. A manuscript for a high impact peer-reviewed journal will be prepared simultaneously, which will allow for the results to be disseminated across the orthopaedic and rehabilitation communities, the wider medical community, NICE and policy makers. Authorship will be determined in accordance with the ICMJE guidelines and other contributors will be acknowledged. The results of this trial will substantially inform clinical practice on the clinical and cost effectiveness of the treatment of this injury. The results of this project will be disseminated to patients via patient-specific newsletters and through local mechanisms at all participating centres and a lay summary of the results will be available on the study website.

Author contributions

MC/JB/JPM/JN wrote the background section and developed the research question. MC/JA/LS were responsible for the research methodology and management sections of the protocol. KV/SD wrote the sample size and statistical analysis sections of the protocol. JM wrote the health economic evaluation section of the protocol.

All authors reviewed and agreed the final manuscript.

Competing interest

MC is a member of the UK NIHR HTA General Board.

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SPIRIT 2013 Checklist: Recommended items to address in a clinical trial protocol and related documents*

Section/item	Item No	Description	Addressed on page number
Administrative information			
Title	1	Descriptive title identifying the study design, population, interventions, and, if applicable, trial acronym	_____1_____
Trial registration	2a	Trial identifier and registry name. If not yet registered, name of intended registry	_____2____
	2b	All items from the World Health Organization Trial Registration Data Set	_____n/a_____
Protocol version	3	Date and version identifier	_____n/a_____
Funding	4	Sources and types of financial, material, and other support	_____2+17_____
Roles and responsibilities	5a	Names, affiliations, and roles of protocol contributors	____1+17_____
	5b	Name and contact information for the trial sponsor	___n/a_____
	5c	Role of study sponsor and funders, if any, in study design; collection, management, analysis, and interpretation of data; writing of the report; and the decision to submit the report for publication, including whether they will have ultimate authority over any of these activities	_____17_____
	5d	Composition, roles, and responsibilities of the coordinating centre, steering committee, endpoint adjudication committee, data management team, and other individuals or groups overseeing the trial, if applicable (see Item 21a for data monitoring committee)	____n/a_____

Introduction

Background and rationale	6a	Description of research question and justification for undertaking the trial, including summary of relevant studies (published and unpublished) examining benefits and harms for each intervention	____4-5_____
	6b	Explanation for choice of comparators	____4-5_____
Objectives	7	Specific objectives or hypotheses	_____6_____
Trial design	8	Description of trial design including type of trial (eg, parallel group, crossover, factorial, single group), allocation ratio, and framework (eg, superiority, equivalence, noninferiority, exploratory)	____1_____

Methods: Participants, interventions, and outcomes

Study setting	9	Description of study settings (eg, community clinic, academic hospital) and list of countries where data will be collected. Reference to where list of study sites can be obtained	_____9_____
Eligibility criteria	10	Inclusion and exclusion criteria for participants. If applicable, eligibility criteria for study centres and individuals who will perform the interventions (eg, surgeons, psychotherapists)	_____9-10_____
Interventions	11a	Interventions for each group with sufficient detail to allow replication, including how and when they will be administered	_____11-12
	11b	Criteria for discontinuing or modifying allocated interventions for a given trial participant (eg, drug dose change in response to harms, participant request, or improving/worsening disease)	___n/a_____
	11c	Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence (eg, drug tablet return, laboratory tests)	_____
	11d	Relevant concomitant care and interventions that are permitted or prohibited during the trial	_____
Outcomes	12	Primary, secondary, and other outcomes, including the specific measurement variable (eg, systolic blood pressure), analysis metric (eg, change from baseline, final value, time to event), method of aggregation (eg, median, proportion), and time point for each outcome. Explanation of the clinical relevance of chosen efficacy and harm outcomes is strongly recommended	_____6-8_____

Participant timeline	13	Time schedule of enrolment, interventions (including any run-ins and washouts), assessments, and visits for participants. A schematic diagram is highly recommended (see Figure)	___8_____
Sample size	14	Estimated number of participants needed to achieve study objectives and how it was determined, including clinical and statistical assumptions supporting any sample size calculations	____9_____
Recruitment	15	Strategies for achieving adequate participant enrolment to reach target sample size	_____
Methods: Assignment of interventions (for controlled trials)			
Allocation:			
Sequence generation	16a	Method of generating the allocation sequence (eg, computer-generated random numbers), and list of any factors for stratification. To reduce predictability of a random sequence, details of any planned restriction (eg, blocking) should be provided in a separate document that is unavailable to those who enrol participants or assign interventions	____11_____
Allocation concealment mechanism	16b	Mechanism of implementing the allocation sequence (eg, central telephone; sequentially numbered, opaque, sealed envelopes), describing any steps to conceal the sequence until interventions are assigned	____11_____
Implementation	16c	Who will generate the allocation sequence, who will enrol participants, and who will assign participants to interventions	____11_____
Blinding (masking)	17a	Who will be blinded after assignment to interventions (eg, trial participants, care providers, outcome assessors, data analysts), and how	_____11____
	17b	If blinded, circumstances under which unblinding is permissible, and procedure for revealing a participant's allocated intervention during the trial	___n/a_____
Methods: Data collection, management, and analysis			
Data collection methods	18a	Plans for assessment and collection of outcome, baseline, and other trial data, including any related processes to promote data quality (eg, duplicate measurements, training of assessors) and a description of study instruments (eg, questionnaires, laboratory tests) along with their reliability and validity, if known. Reference to where data collection forms can be found, if not in the protocol	_____6-8_____

	18b	Plans to promote participant retention and complete follow-up, including list of any outcome data to be collected for participants who discontinue or deviate from intervention protocols	____n/a_____
Data management	19	Plans for data entry, coding, security, and storage, including any related processes to promote data quality (eg, double data entry; range checks for data values). Reference to where details of data management procedures can be found, if not in the protocol	_____
Statistical methods	20a	Statistical methods for analysing primary and secondary outcomes. Reference to where other details of the statistical analysis plan can be found, if not in the protocol	___13-15_____
	20b	Methods for any additional analyses (eg, subgroup and adjusted analyses)	___13-15_____
	20c	Definition of analysis population relating to protocol non-adherence (eg, as randomised analysis), and any statistical methods to handle missing data (eg, multiple imputation)	____13-15_____
Methods: Monitoring			
Data monitoring	21a	Composition of data monitoring committee (DMC); summary of its role and reporting structure; statement of whether it is independent from the sponsor and competing interests; and reference to where further details about its charter can be found, if not in the protocol. Alternatively, an explanation of why a DMC is not needed	_____15_____
	21b	Description of any interim analyses and stopping guidelines, including who will have access to these interim results and make the final decision to terminate the trial	___n/a_____
Harms	22	Plans for collecting, assessing, reporting, and managing solicited and spontaneously reported adverse events and other unintended effects of trial interventions or trial conduct	_____12_____
Auditing	23	Frequency and procedures for auditing trial conduct, if any, and whether the process will be independent from investigators and the sponsor	_____15_____
Ethics and dissemination			
Research ethics approval	24	Plans for seeking research ethics committee/institutional review board (REC/IRB) approval	__16_____

Protocol amendments	25	Plans for communicating important protocol modifications (eg, changes to eligibility criteria, outcomes, analyses) to relevant parties (eg, investigators, REC/IRBs, trial participants, trial registries, journals, regulators)	_____
Consent or assent	26a	Who will obtain informed consent or assent from potential trial participants or authorised surrogates, and how (see Item 32)	___10_____
	26b	Additional consent provisions for collection and use of participant data and biological specimens in ancillary studies, if applicable	___10_____
Confidentiality	27	How personal information about potential and enrolled participants will be collected, shared, and maintained in order to protect confidentiality before, during, and after the trial	_____
Declaration of interests	28	Financial and other competing interests for principal investigators for the overall trial and each study site	_____17_____
Access to data	29	Statement of who will have access to the final trial dataset, and disclosure of contractual agreements that limit such access for investigators	_____
Ancillary and post-trial care	30	Provisions, if any, for ancillary and post-trial care, and for compensation to those who suffer harm from trial participation	____n/a_____
Dissemination policy	31a	Plans for investigators and sponsor to communicate trial results to participants, healthcare professionals, the public, and other relevant groups (eg, via publication, reporting in results databases, or other data sharing arrangements), including any publication restrictions	___16_____
	31b	Authorship eligibility guidelines and any intended use of professional writers	___17_____
	31c	Plans, if any, for granting public access to the full protocol, participant-level dataset, and statistical code	_____
Appendices			
Informed consent materials	32	Model consent form and other related documentation given to participants and authorised surrogates	___n/a_____
Biological specimens	33	Plans for collection, laboratory evaluation, and storage of biological specimens for genetic or molecular analysis in the current trial and for future use in ancillary studies, if applicable	__n/a_____

*It is strongly recommended that this checklist be read in conjunction with the SPIRIT 2013 Explanation & Elaboration for important clarification on the items. Amendments to the protocol should be tracked and dated.

BMJ Open

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)

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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)

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Word count:

Abstract

Introduction

Patients with closed high-energy injuries associated with major trauma, have surprisingly high rates of surgical site infection in incisions created during fracture fixation. One factor which may reduce the risk of surgical site infection is the type of dressing applied over the closed surgical incision. In this multi-centre randomised clinical trial, negative-pressure wound therapy will be compared with standard dressings with outcomes of deep infection, quality of life, pain and disability.

Methods and analysis

Adult patients presenting to hospital within 72 hours of sustaining major trauma, requiring a surgical incision to treat a fractured lower limb are eligible for inclusion. Randomisation, stratified by trial centre, open/closed fracture at presentation, and Injury Severity Score ≤15 vs ISS ≥16 will be administered via a secure web-based service using minimisation. The random allocation will be to either standard wound management or negative pressure wound therapy.

Trial participants will usually have clinical follow-up at the local fracture clinic for a minimum of 6 months, as per standard NHS practice. Diagnosis of deep infection will be recorded at 30 days. Functional, pain and quality of life outcome data will be collected using the Disability Rating Index, Douleur Neuropathique Questionnaire and EQ-5D-5L questionnaires at 3 months and 6 months post-injury. Further data will be captured on resource use and any late post-operative complications.

Longer term outcomes will be assessed annually for five years and reported separately.

Ethics and Dissemination

National Research Ethic Committee approved this study on 16/02/2016 16/WM/0006

The NIHR Health Technology Assessment monograph and a manuscript to a peer-reviewed journal will be submitted upon completion of this trial. The results of this trial will inform clinical practice on the clinical and cost effectiveness of the treatment of this injury.

This study has been registered on the ISRCTN registry with reference number ISRCTN12702354

Abstract word count: 299

Strength and limitations of this study

- Broad eligibility criteria to ensure generalisability.
- Deep infection data will be supplemented with patient-reported outcomes.
- Assessment of outcomes at multiple time points will allow for information on recovery profile.
- In addition to a comparison of clinical outcomes, a full cost-effectiveness evaluation will be performed.
- It will not be possible to blind patients to their allocated treatment, as the type of wound dressing will be clearly visible.

Background

Major trauma is the leading cause of death in people aged under 45 years and a significant cause of short- and long-term morbidity. The National Audit Office (NAO) estimates that there are at least 20,000 cases of Major Trauma each year in England, resulting in 5,400 deaths and many survivors suffer permanent disabilities requiring long-term care. The NAO estimate that trauma costs the NHS between £0.3 and £0.4 billion a year for immediate treatment. This does not include the cost of subsequent hospital treatments, rehabilitation, home care support, or informal carers. The NAO estimate that the annual lost economic output from traumatic injury is between £3.3 billion and £3.7 billion.

Fractures of the limbs are extremely common injuries, with 85% of major trauma patients sustaining serious limb injuries. [1] In open fractures of the lower limb, where the broken bone is exposed to the environment by a breach in the skin, the risk of infection is particularly high.[1] However, even in closed high-energy injuries associated with major trauma, the rate of infection remains high. For example, tibial plateau fractures are associated with average infection rates of up to 27%,[2-6] while pilon fractures have an incidence of deep infections ranging from 5% to 40%[7-10]. If surgical site infection does occur, treatment frequently continues for years after the initial injury. This often involves prolonged courses of antibiotics, with attendant risk of antibiotic resistance in chronic wounds, and a huge health care cost associated with such injuries. A US study found that the average cost associated with infection was $163,000 if the limb could be salvaged and $500,000+ where amputation was necessary, and these only represent a fraction of the subsequent personal and societal costs[11].

Major trauma patients are at greater risk of infection due to several factors, including the presence of antibiotic resistant organisms in the ITU and high-dependency environment. Furthermore, the presence of a wound haematoma or postoperative wound leak oozing may predispose to infection in wounds created by surgical incisions. One of the factors which may reduce the risk of surgical site infection is the type of dressing applied over the closed incision at completion of the operative procedure. Dressings may reduce bacterial ingress into the wound. The published literature suggests that the type of dressing applied to the wound influences the healing process itself[12]. This trial concerns the type of dressing that is applied to the closed surgical incision at the end of the operation.

Traditionally, the surgical incision is covered with an adhesive dressing or gauze maintained in place with a bandage to protect the wound from contamination from the outside environment. These 'standard dressings' have been used throughout the NHS and in military practice for many years. Negative-pressure wound therapy (NPWT) or topical negative pressure is an alternative form of

dressing which may be applied to closed surgical incisions. In this treatment, an 'open-cell', solid foam overlies the incision and is covered with a semipermeable membrane which is only permeable to gas. A sealed tube is used to connect the foam to a pump, which creates a partial vacuum over the wound. This negative-pressure therapy provides a sealed environment, preventing bacterial ingress and removes blood and serous fluid exuding from the wound. The application of negative pressure to the foam leads to the application of positive pressure to the wound bed and has been shown to reduce the incidence of wound haematoma[13]. Recent laboratory studies suggest that NPWT shifts the cytokine profile to being less inflammatory, potentially promoting the production of pro-angiogenic growth factors and enzymes responsible for matrix remodelling, leading to improved wound healing.[12] However, NPWT for closed wounds is considerably more expensive than traditional wound dressings. There has been only one randomised trial comparing standard wound dressing with NPWT for patients with closed surgical wounds following major trauma to the lower limb.[13] This trial demonstrated a reduction in the rate of late/deep wound infection in the group of patients treated with NPWT (9%) versus the standard dressing group (15%). However, the reduction was of borderline statistical significance (p=0.049) and the study has been criticised in the subsequent Cochrane review for methodological flaws. [14]

The recent Cochrane review for surgical wounds concluded *that "it is still not clear whether NPWT promotes faster healing and reduces complications associated with clean surgery". "Given the cost and widespread use of NPWT, there is an urgent need for suitably powered, high-quality trials to evaluate the effects of the newer NPWT products that are designed for use on clean, closed surgical incisions. Such trials should focus initially on wounds that may be difficult to heal".* [14] The WHIST Trial aims to address this evidence gap.

Good Clinical Practice

The trial will be carried out in accordance with Medical Research council (MRC) Good Clinical Practice and applicable UK legislation using the following protocol.

CONSORT

The trial will be reported in line with the CONSORT statement using the non-pharmacological treatment interventions extension.

Trial design

Aim

The aim of this pragmatic randomised controlled trial is to compare negative-pressure wound therapy with standard wound dressings for the treatment of surgical incisions associated with major trauma to the lower limb on outcomes of deep infection, quality of life, pain and disability.

The primary objective for the RCT is:

To quantify and draw inferences on differences in the rate of 'deep surgical site infection (SSI)' of the lower limb in the 30 days after randomisation between treatment arms of standard wound dressing versus NPWT. Any wound infection that requires continuing medical intervention or has already led to amputation at the 30-day review will be considered a 'deep' infection.

The secondary objectives are:

i) To quantify and draw inferences on observed differences in the disability rating index (DRI) in the 6 months after the major trauma.

ii) To quantify and draw inferences on observed differences in general health-related quality of life in the 6 months after the major trauma.

iii) To quantify and draw inferences on the quality of wound healing, using a validated, patient-reported assessment of the scar. The patient-reported assessment will be supplemented with photographs taken at 6 weeks to objectively assess wound healing and apparent signs of infection.

iv) To determine the number and nature of complications in the first 6 months after the major trauma: including chronic pain, deep SSI at 90 days and further surgical interventions related to the injury.

v) To investigate the cost effectiveness, of negative pressure wound therapy versus standard dressing for wounds associated with major trauma to the lower limbs.

Outcome measures

The primary outcome measure for this study is **Deep Surgical Site Infection**; We will use the Centers for Disease Control and Prevention (CDC) definition of a "deep surgical site infection", that is a wound infection involving the tissues deep to the skin that occurs within 30 days of injury. [15]

The treating clinical team will make the diagnosis of 'infection', as per routine clinical practice. The treating clinicians will not be part of the research team. As the prompt diagnosis and treatment of

infection is fundamental to the patient's routine clinical care, the treating surgeon/clinician will always document such a change in management in the patient's medical record. The medical records will be reviewed by an independent research associate who will complete the Clinical Reporting Forms, which will include the specific criteria used by the CDC to define a "deep surgical site infection". Any infection that requires continuing medical intervention or has already led to amputation at or after the 30-day review will be considered a deep infection.

The secondary outcome measures in this trial are:

Disability Rating Index measured using a self-administered, 12-item Visual Analogue Scale questionnaire assessing the patients' own rating of their disability.[16] This measure was chosen as it addresses gross body movements rather than specific joints or body segments. Therefore, it will capture function and disability associated with different fractures and injuries of the lower limbs.

EuroQol EQ-5D-5L: 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. [17] An updated version of the EQ-5D with 5 response levels, the EQ-5D-5L, has recently been developed to enhance the responsiveness of the instrument to changes in patient health.[18] Responses to the health status classification system will be converted into multi-attribute utility (MAU) scores using tariffs currently under development for England.[19] These MAU scores will be combined with survival data to generate QALY profiles for the purposes of the economic evaluation. The EQ-5D has been validated to be completed by a patient's proxy in case of continued impaired capacity.

Wound Healing: A patient-reported scar assessment will be collected using the patient scale from the Patient and Observer Scar Assessment Scale[20] consisting of six questions regarding different aspects of the scar, as well as an overall assessment of the scar. This will be used to provide a subjective patient-assessment of wound healing. An objective assessment of wound healing using a standardised photograph of the wound from the 30-day review will be evaluated by two independent experienced assessors who are blind to the treatment allocation. Patients will also be asked to self-report any treatment for infection will be cross-referenced with the participant's medical record. This will allow us to report deep infection at later time-points, for example at 90 days.

Complications: Chronic pain: The proportion of patients reporting chronic pain post-injury with neuropathic characteristics will be measured using the Douleur Neuropathique Questionnaire

(DN4[21]). Chronic pain after surgery and trauma is common and disabling but no previous studies have assessed the prevalence of persistent painful neuropathic characteristics after lower limb fracture. The interview versions of the DN4 is a short validated neuropathic pain screening tool comprising seven questions. This screening tool is recommended for use by the International Association for the Study of Pain (IASP [22]). Scores of 3 or greater are likely to be indicative of neuropathic pain. Patients will also be asked to self-report (or a consultee on their behalf, in case of continued impaired capacity) at each of the follow-up points on wound healing complications, any treatment for infection and any medical/surgical intervention related to infection associated with their surgical wound. Any self-report of treatment for infection will be cross-referenced with the participant's medical record. This will allow us to report deep infection at later time-points, for example at 90 days. All other post-operative complications and surgical interventions related to the index wound will be recorded.

Resource use 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.[23] Where these are not available the unit cost will be estimated in consultation with the hospital finance department. 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 three and six months post major trauma. Patient self-reported (or consultee reported) information on service use has been shown to be accurate in terms of the intensity of use of different services.[24]

Data collection

Table 1 displays the time points when outcome measures are being collected.

TIME POINT	DATA COLLECTION
Baseline	DRI *and* EQ-5D *pre-injury and contemporary*,
30 days	Deep infection, complication records, scar assessment, operative record, photograph of limb wound
3 months	DRI, EQ-5D, DN4, scar assessment, record of complications/rehabilitation or other interventions and economics questionnaire
6 months	DRI, EQ-5D, DN4, scar assessment, record of complications/rehabilitation or other interventions and economics questionnaire
12 months	DRI, EQ-5D, DN4, record of complications/ further interventions
2,3,4,5 years	DRI, EQ-5D, DN4, record of complications/ further interventions

Table 1: outcome collection

For the purposes of long-term follow-up, patients will subsequently be contacted on an annual basis for 5 years to complete the EQ-5D-5L, DRI and DN4 questionnaires. Longer-term follow-up will be reported separately.

Sample size

There has only been one previous randomised trial to compare negative pressure wound therapy to standard dressings for surgical incisions associated with major trauma to the lower limb. This trial indicated that the rate of 'late' (deep) infection was 15% in the standard dressing group versus 9% in the NPWT group. [13]

In the absence of a 'Minimum Clinically Important Difference' for deep wound infection, we surveyed surgeons in the UK Orthopaedic Trauma Society who perform surgery for major trauma to the limbs (unpublished data 2015). The survey showed that those who responded to the survey considered that a 6% reduction in the rate of 'deep infection' would, universally, be sufficient to change clinical practice with regard to the choice of wound dressing.

Therefore, assuming a reduction in the proportion of patients having a deep infection from 15% to 9%, 615 patients would be required in each group to provide 90% power at the 5% level. Our previous experience in clinical trials of lower limb fracture surgery for major trauma indicates that up to 20% of primary outcome data may be lost during the follow-up period; due to death and loss to follow-up. Therefore, we aim to recruit **1540 patients** in total for this trial.

Methodology

Screening

Patients will be screened from the Emergency Department or Trauma Unit from participating trial centres. Throughout the study, screening logs will be kept at each site to determine the number of patients assessed for eligibility and any reasons for any exclusion. Patients who decline to participate or withdraw from the study will be given the opportunity to discuss/inform the research team of their reasoning behind their decision not to take part.

The patient's routine imaging on admission will be used, including any 'Major Trauma CT scan', and associated 'secondary survey' to identify the patient's injuries and calculate the Injury Severity Score (15 or less vs 16 or more) before randomisation. All major trauma patients in England are automatically considered for entry onto the national Trauma Audit and Research Network database, which requires the calculation of the Injury Severity Score. Therefore, all centres are familiar with the use of this major trauma scoring system.

Eligibility

Patients will be eligible for WHIST if:

They are aged 16 years or older

Present to hospital within 72 hours of injury

They have a major trauma injury and/or TARN eligible injury as defined by eligibility for the UK Trauma Audit Research Network (TARN) database

They have a lower limb fracture requiring a surgical incision.

Some patients have major trauma affecting just one limb, for example heel, pilon and tibial plateau fractures. Since the wounds associated with these injuries are always at risk, we will include these injuries even if the patient is subsequently not included in TARN.

Patients will be excluded from participation in WHIST if:

They have an open fracture of the lower limb which cannot be closed primarily.

There is evidence that the patient would be unable to adhere to trial procedures or complete questionnaires. It is expected that for a small proportion of patients, for example those with head injury, this exclusion criterion will only be determined after randomisation. These patients will then be excluded from the study.

Patients who sustain injuries to areas of the body other than the lower limbs, which may affect the primary outcome measure, will have their other injuries documented but will still be included in the analysis. For patients with more than one lower limb injury, only the most severe wound will be included as the 'WHIST' wound in the trial. It will be up to the surgeon's discretion to decide which injury is the most severe.

Consent to participating

Many patients with major trauma will be operated on immediately or on the next available trauma operating list. Some patients may be unconscious, all will be distracted by their injury and its subsequent treatment and all will have had large doses of opiates for pain relief, potentially affecting their ability to process study-related information. Similarly, patients' next of kin, carers and friends are often anxious at this time and may have difficulty in considering the large amounts of information that they are given about the injury and plan for treatment. In this emergency situation, the focus is on obtaining consent for surgery (where possible) and informing the patient and any next of kin about immediate clinical care. The consent procedure for this trial will reflect that of the surgery, with the attending clinician assessing capacity before taking consent for the surgical

procedure and this capacity assessment then being used to decide on the proper approach to consenting to the WHIST study. An appropriate method, in line with the mental capacity act and as approved by the National Research Ethics Service, will then be used to gain either prospective or retrospective consent from the patient or appropriate consultee, by an appropriately delegated member of the research team.

Randomisation

The treating surgeon will confirm participant eligibility at the end of the operative procedure but before the wound dressing is applied. Randomisation will be on a 1:1 basis, using a validated computer randomisation program managed centrally by the Oxford Clinical Trials Research Unit (OCTRU). A minimisation algorithm, will be used to ensure balanced allocation of patients across the two treatment groups, stratified by trial centre, open or closed fracture at presentation and Injury Severity Score (ISS) ≤15 vs ISS ≥16. The first 30 participants will be randomised using simple randomisation to seed the minimisation algorithm (generated by the trial statistician), and the minimisation algorithm will have probabilistic element of 0.8 introduced to ensure unpredictability of the treatment assignment. After the randomisation is received electronically by the surgical team, the allocated treatment can be administered immediately.

Post randomisation withdrawals/exclusions

Participants will be excluded in the post-randomisation phase if it is later established that they are unable to adhere to trial procedures or complete questionnaires.

Participants may decline to continue to take part in the trial at any time without prejudice. A decision to decline consent or withdraw will not affect the standard of care the patient receives.

Blinding

As the wound dressings and topical devices are clearly visible, the treating surgeon and trial participants cannot be blinded to treatment allocation. However, the treating surgeons will not be involved in study follow-up assessments or data collection for the trial. Data from Clinical Reporting forms will be entered onto a central database administered by a data clerk independent of the clinical team in the trial central office. Wound photographs taken at outpatient clinic at approximately 30 days post-surgery will be reviewed independently by two experienced assessors blinded to the treatment allocation.

Trial treatments

Patients with a fracture of the lower limb associated with major trauma usually have surgery on the next available trauma operating list. Some patients may be transferred to a Major Trauma Centre for definitive care – within the first 48 hours of injury – but will still have their initial surgery as soon as possible. All patients will receive general or regional anaesthesia. At the end of the initial operation, a dressing is applied to the surgical wound. WHIST will compare two types of wound dressing; standard dressing versus negative pressure wound therapy.

Standard dressing. The standard dressing for a surgical wound comprises a non-adhesive layer applied directly to the wound which is then covered by a sealed dressing or bandage. The standard dressing does not use 'negative pressure'. The exact details of the materials used will be left to the discretion of the treating surgeon as per their routine practice but the details of each dressing applied will be recorded.

Negative-pressure wound therapy. The NPWT dressing uses an 'open-cell', solid foam which is laid onto the wound as an intrinsic part of a sealed dressing. A sealed tube connects the dressing to a built in mini-pump which creates a partial vacuum over the wound.

The NPWT dressing will be applied to the wound at the end of the operation according to the treating surgeon's normal practice and the dressing manufacturer's instructions. The wound may be re-dressed again on the ward; any further wound dressing will be recorded and will follow the allocated treatment unless otherwise clinically indicated.

Post-operative Rehabilitation

Patients will usually be reviewed at 3 and 6 months, as per routine practice after this type of injury. Details about rehabilitation and additional follow-up appointments will be recorded but left entirely to the discretion of the treating clinicians, as the type of injury will vary between patients.

Adverse event management

Serious adverse events (SAE) will be entered onto the Serious Adverse Event reporting form and reported to the central study team. However, some adverse events are foreseeable as part of the proposed treatment, and will not be reported on an SAE reporting form, but recorded on a complications form. These events include: any complications of anaesthesia or surgery (wound infection, bleeding or damage to adjacent structures such as nerves, tendons and blood vessels, delayed unions/non-unions, delayed wound healing, further surgery to remove/replace metalwork and thromboembolic events). All participants experiencing SAEs will be followed-up as per protocol until the end of the trial.

End of trial

The end of the main phase of the trial will be defined as the collection of final six month outcome data from the last participant. Longer-term follow-up will be reported separately.

Analysis

Statistical analysis

Baseline characteristics and outcome measures will be reported overall and separately for the two treatment arms using standard statistical summaries (e.g. medians and ranges or means and variances, or proportions and percentages, dependent on the distribution of the outcomes) including graphical presentation where appropriate.

The primary analysis will investigate differences in the primary outcome measure, the proportion of patients with deep SSI, at 30 days post operation. Although 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 logistic (fixed-effects) regression approach to a mixed-effects logistic regression analysis. This model will be used to assess differences in the rate of deep SSI between the study intervention groups, with results presented as odds ratios with associated 95% confidence intervals. The mixed-effects model will include a random effect to account for any heterogeneity in response due to the recruitment centre and fixed effects to adjust for open versus closed fractures and the ISS, participant age and gender.

An identically structured and formulated mixed-effects linear or logistic regression model (as appropriate) will be used to assess the effects of the interventions on secondary outcomes DRI and EQ-5D-5L (at both 3 and 6 months, and for the long-term follow-up). Supplementary analyses for these outcomes will include using area under the curve summary statistics calculated from the mixed model parameter estimates to provide an overall estimate of recovery over time.[25] Other dichotomous outcome variables, such as complications related to the trial interventions will be analysed in the same manner as the primary outcome. 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.

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. Missing data will be minimised and the reasons for missing data will be ascertained and reported separately by treatment group. The

amount, nature and pattern of missing data will be carefully considered and missing data will be imputed, using multiple imputation if appropriate.

The primary population for analysis will be on an intention-to-treat (ITT) basis, i.e. analysed as they were randomised. In addition to the ITT analyses, sensitivity analyses including on the per-protocol population and to assess the missing data assumption if missing data imputation is used, will also be undertaken and reported in parallel to, but subsidiary to, the main analyses.

About 1-2% of patients are expected to die during follow-up, so this is unlikely to be a serious cause of bias. If appropriate, we will conduct a supplementary analysis taking account of the competing risk of death, using methods described by Varadhan et al.[26]

All reported 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).

A detailed statistical analysis plan (SAP) will be agreed with the Data Safety and Monitoring Committee (DSMC) at the commencement of or early in the study. This will be updated prior to the final data-lock following a blinded analysis of the data. Any subsequent changes to the analysis outlined in the SAP will be clearly stated and justified in the final report. Interim analyses of efficacy outcomes are not planned and will be performed only where requested by the independent DSMC.

Analyses will be undertaken using validated statistical software such as Stata (Stata Corp LP - http://www.stata.com) or the software package R (http://www.r-project.org/).

Economic evaluation

An economic evaluation will be integrated into the trial design. The economic evaluation will be conducted from the recommended NHS and personal social services (PSS) perspective [23]. Data will be collected on the health and social service resources used in the treatment of each trial participant during the period between randomisation and 6 months post-randomisation. Trial data collection forms will record the duration of each form of hospital care, surgical procedures, adjunctive interventions, medication profiles, tests and procedures. If required, information on additional staff and material inputs associated with clinical complications will be obtained directly from patient and clinical records. At 3 and 6 months post-randomisation, trial participants will be asked to complete postal questionnaires profiling hospital (inpatient and outpatient) and community health and social care resource use and, for the purposes of sensitivity analysis, out-of-pocket expenditures and costs associated with lost productivity. Current UK unit costs will be applied to each resource item to value total resource use in each arm of the trial. *Per diem* costs for hospital care, delineated by level or intensity of care, will be calculated by the health economics researcher using data from detailed questionnaires completed by the local finance departments, giving cost data and apportioning these to different

categories of patient using a 'top-down' methodology. The unit costs of clinical events that are unique to this trial will be derived from the hospital accounts of the trial participating centres, although primary research that uses established accounting methods may also be required. The unit costs of community health and social services will largely be derived from national sources, although some calculations from first principles using established accounting methods may also be required.[27] Responses to the EQ-5D-5L will be converted into multi-attribute utility scores using the algorithm currently under development to reflect societal preferences in England.[19 28 29] Crosswalking algorithms will be employed to generate supplementary utility values comparable with those derived from the EQ-5D-3L instrument.[18]

An incremental cost-effectiveness analysis, expressed in terms of incremental cost per quality-adjusted life year (QALY) gained, will be performed. Results will be presented using incremental cost-effectiveness ratios (ICERs) and cost-effectiveness acceptability curves (CEACs) generated via non-parametric bootstrapping. This accommodates sampling (or stochastic) uncertainty and varying levels of willingness to pay for an additional QALY. Issues with missing values, if they arise, will be accommodated using multiple imputation methods in line with the approach used in the clinical component of the trial.

Trial Oversight

The day-to-day management of the trial will be the responsibility of the Clinical Trial Manager, based at Nuffield Department of Orthopaedics, Rheumatology and Musculoskeletal Sciences and supported by the OCTRU staff. This will be overseen by the Trial Management Group, who will meet monthly to assess progress. It will also be the responsibility of the Clinical Trial Manager to undertake training of the research associates at each of the trial centres. The Trial Statistician and Health Economist will be closely involved in setting up data capture systems, design of databases and clinical reporting forms.

A Trial Steering Committee (TSC) and a Data & Safety Monitoring Committee (DSMC) will be set up. The study DSMC will adopt a DAMOCLES charter which defines its terms of reference and operation in relation to oversight of the trial. They will not be asked to review any formal interim comparative analyses of effectiveness. They will, however, see copies of data accrued to date, or summaries of that data by treatment group and they will assess the screening algorithm against the eligibility criteria. They will also consider emerging evidence from other related trials or research and review related SAEs that have been reported. They may advise the chair of the Trial Steering Committee at any time if, in their view, the trial should be stopped for ethical reasons, including concerns about participant safety. DSMC meetings will be held at least annually during the recruitment phase of the study.

Quality control

The study may be monitored, or audited in accordance with the current approved protocol, relevant regulations and standard operating procedures by the Host organization, Sponsor or appropriate Regulatory Authorities. A Monitoring Plan will be developed according to OCTRU standard operating procedures which involves a risk assessment. The monitoring activities are based on the outcome of the risk assessment and may involve central monitoring and site monitoring.

Ethics and Dissemination

National Research Ethic Committee approved this study on the 16th of February 2016 (16/WM/0006). The study monograph for the National Institute for Health Research Health Technology Assessment will be prepared by the trial management team within three months of completion of the trial. A manuscript for a high impact peer-reviewed journal will be prepared simultaneously, which will allow for the results to be disseminated across the orthopaedic and rehabilitation communities, the wider medical community, NICE and policy makers. Authorship will be determined in accordance with the ICMJE guidelines and other contributors will be acknowledged. The results of this trial will substantially inform clinical practice on the clinical and cost effectiveness of the treatment of this injury. The results of this project will be disseminated to patients via patient-specific newsletters and through local mechanisms at all participating centres and a lay summary of the results will be available on the study website.

Patient and Public Involvement

A series of formal qualitative interviews with patients and clinicians were performed in the development of this trial. The views of patients were used to inform and refine the trial interventions and processes. Two of the patients who contributed during the development work, have agreed to act as lay representatives on the Trial Management Team.

Towards the end of the trial, the lay representatives will lead the dissemination of the findings of this study through the wider audience. They will lead in the development of any material, including leaflets and website information used for this purpose.

Author contributions

MC/JB/JPM/JN wrote the background section and developed the research question. MC/JA/LS were responsible for the research methodology and management sections of the protocol. KV/SD wrote the sample size and statistical analysis sections of the protocol. JM wrote the health economic evaluation section of the protocol.

All authors reviewed and agreed the final manuscript.

Competing interest

MC is a member of the UK NIHR HTA General Board.

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SPIRIT 2013 Checklist: Recommended items to address in a clinical trial protocol and related documents*

Section/item	Item No	Description	Addressed on page number
Administrative information			
Title	1	Descriptive title identifying the study design, population, interventions, and, if applicable, trial acronym	_____1_____
Trial registration	2a	Trial identifier and registry name. If not yet registered, name of intended registry	_____2____
	2b	All items from the World Health Organization Trial Registration Data Set	_____n/a_____
Protocol version	3	Date and version identifier	_____n/a_____
Funding	4	Sources and types of financial, material, and other support	_____2+17_____
Roles and responsibilities	5a	Names, affiliations, and roles of protocol contributors	____1+17_____
	5b	Name and contact information for the trial sponsor	___n/a_____
	5c	Role of study sponsor and funders, if any, in study design; collection, management, analysis, and interpretation of data; writing of the report; and the decision to submit the report for publication, including whether they will have ultimate authority over any of these activities	_____17_____
	5d	Composition, roles, and responsibilities of the coordinating centre, steering committee, endpoint adjudication committee, data management team, and other individuals or groups overseeing the trial, if applicable (see Item 21a for data monitoring committee)	____n/a_____

Introduction

Background and rationale	6a	Description of research question and justification for undertaking the trial, including summary of relevant studies (published and unpublished) examining benefits and harms for each intervention	____4-5_____
	6b	Explanation for choice of comparators	____4-5_____
Objectives	7	Specific objectives or hypotheses	_____6_____
Trial design	8	Description of trial design including type of trial (eg, parallel group, crossover, factorial, single group), allocation ratio, and framework (eg, superiority, equivalence, noninferiority, exploratory)	____1_____

Methods: Participants, interventions, and outcomes

Study setting	9	Description of study settings (eg, community clinic, academic hospital) and list of countries where data will be collected. Reference to where list of study sites can be obtained	_____9_____
Eligibility criteria	10	Inclusion and exclusion criteria for participants. If applicable, eligibility criteria for study centres and individuals who will perform the interventions (eg, surgeons, psychotherapists)	_____9-10_____
Interventions	11a	Interventions for each group with sufficient detail to allow replication, including how and when they will be administered	_____11-12
	11b	Criteria for discontinuing or modifying allocated interventions for a given trial participant (eg, drug dose change in response to harms, participant request, or improving/worsening disease)	___n/a_____
	11c	Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence (eg, drug tablet return, laboratory tests)	_____
	11d	Relevant concomitant care and interventions that are permitted or prohibited during the trial	_____
Outcomes	12	Primary, secondary, and other outcomes, including the specific measurement variable (eg, systolic blood pressure), analysis metric (eg, change from baseline, final value, time to event), method of aggregation (eg, median, proportion), and time point for each outcome. Explanation of the clinical relevance of chosen efficacy and harm outcomes is strongly recommended	_____6-8_____

Participant timeline	13	Time schedule of enrolment, interventions (including any run-ins and washouts), assessments, and visits for participants. A schematic diagram is highly recommended (see Figure)	___8_____
Sample size	14	Estimated number of participants needed to achieve study objectives and how it was determined, including clinical and statistical assumptions supporting any sample size calculations	____9_____
Recruitment	15	Strategies for achieving adequate participant enrolment to reach target sample size	_____
Methods: Assignment of interventions (for controlled trials)			
Allocation:			
Sequence generation	16a	Method of generating the allocation sequence (eg, computer-generated random numbers), and list of any factors for stratification. To reduce predictability of a random sequence, details of any planned restriction (eg, blocking) should be provided in a separate document that is unavailable to those who enrol participants or assign interventions	____11_____
Allocation concealment mechanism	16b	Mechanism of implementing the allocation sequence (eg, central telephone; sequentially numbered, opaque, sealed envelopes), describing any steps to conceal the sequence until interventions are assigned	____11_____
Implementation	16c	Who will generate the allocation sequence, who will enrol participants, and who will assign participants to interventions	____11_____
Blinding (masking)	17a	Who will be blinded after assignment to interventions (eg, trial participants, care providers, outcome assessors, data analysts), and how	_____11____
	17b	If blinded, circumstances under which unblinding is permissible, and procedure for revealing a participant's allocated intervention during the trial	___n/a_____
Methods: Data collection, management, and analysis			
Data collection methods	18a	Plans for assessment and collection of outcome, baseline, and other trial data, including any related processes to promote data quality (eg, duplicate measurements, training of assessors) and a description of study instruments (eg, questionnaires, laboratory tests) along with their reliability and validity, if known. Reference to where data collection forms can be found, if not in the protocol	_____6-8_____

	18b	Plans to promote participant retention and complete follow-up, including list of any outcome data to be collected for participants who discontinue or deviate from intervention protocols	____n/a_____
Data management	19	Plans for data entry, coding, security, and storage, including any related processes to promote data quality (eg, double data entry; range checks for data values). Reference to where details of data management procedures can be found, if not in the protocol	_____
Statistical methods	20a	Statistical methods for analysing primary and secondary outcomes. Reference to where other details of the statistical analysis plan can be found, if not in the protocol	___13-15_____
	20b	Methods for any additional analyses (eg, subgroup and adjusted analyses)	___13-15_____
	20c	Definition of analysis population relating to protocol non-adherence (eg, as randomised analysis), and any statistical methods to handle missing data (eg, multiple imputation)	____13-15_____
Methods: Monitoring			
Data monitoring	21a	Composition of data monitoring committee (DMC); summary of its role and reporting structure; statement of whether it is independent from the sponsor and competing interests; and reference to where further details about its charter can be found, if not in the protocol. Alternatively, an explanation of why a DMC is not needed	_____15_____
	21b	Description of any interim analyses and stopping guidelines, including who will have access to these interim results and make the final decision to terminate the trial	___n/a_____
Harms	22	Plans for collecting, assessing, reporting, and managing solicited and spontaneously reported adverse events and other unintended effects of trial interventions or trial conduct	_____12_____
Auditing	23	Frequency and procedures for auditing trial conduct, if any, and whether the process will be independent from investigators and the sponsor	_____15_____
Ethics and dissemination			
Research ethics approval	24	Plans for seeking research ethics committee/institutional review board (REC/IRB) approval	__16_____

Protocol amendments	25	Plans for communicating important protocol modifications (eg, changes to eligibility criteria, outcomes, analyses) to relevant parties (eg, investigators, REC/IRBs, trial participants, trial registries, journals, regulators)	_____
Consent or assent	26a	Who will obtain informed consent or assent from potential trial participants or authorised surrogates, and how (see Item 32)	___10_____
	26b	Additional consent provisions for collection and use of participant data and biological specimens in ancillary studies, if applicable	___10_____
Confidentiality	27	How personal information about potential and enrolled participants will be collected, shared, and maintained in order to protect confidentiality before, during, and after the trial	_____
Declaration of interests	28	Financial and other competing interests for principal investigators for the overall trial and each study site	_____17_____
Access to data	29	Statement of who will have access to the final trial dataset, and disclosure of contractual agreements that limit such access for investigators	_____
Ancillary and post-trial care	30	Provisions, if any, for ancillary and post-trial care, and for compensation to those who suffer harm from trial participation	____n/a_____
Dissemination policy	31a	Plans for investigators and sponsor to communicate trial results to participants, healthcare professionals, the public, and other relevant groups (eg, via publication, reporting in results databases, or other data sharing arrangements), including any publication restrictions	___16_____
	31b	Authorship eligibility guidelines and any intended use of professional writers	___17_____
	31c	Plans, if any, for granting public access to the full protocol, participant-level dataset, and statistical code	_____
Appendices			
Informed consent materials	32	Model consent form and other related documentation given to participants and authorised surrogates	___n/a_____
Biological specimens	33	Plans for collection, laboratory evaluation, and storage of biological specimens for genetic or molecular analysis in the current trial and for future use in ancillary studies, if applicable	__n/a_____

*It is strongly recommended that this checklist be read in conjunction with the SPIRIT 2013 Explanation & Elaboration for important clarification on the items. Amendments to the protocol should be tracked and dated.