WHIST: Wound Healing In Surgery for Trauma

Statistical Analysis Plan: Short-term outcomes

Version 1.0 – 26Mar2018

Based on Protocol version 5.0 – 27Jun2017

Trial registration: ISRCTN 12702354

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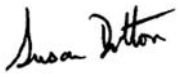
Senior Statistician	Susan Dutton	**OCTRU Lead Statistician**		26Mar2018
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CONTENTS

1. INTRODUCTION

This document details the proposed data presentation and analysis for the main paper(s) and final study reports from the ***NIHR funded randomised control trial of standard wound management versus negative pressure wound therapy in the treatment of adult patients having surgical incisions for major trauma to the lower limb (WHIST)***. The results reported in these papers should follow the strategy set out here. Subsequent analyses of a more exploratory nature will not be bound by this strategy, though they are expected to follow the broad principles laid down here. The principles are not intended to curtail exploratory analysis (for

example, to decide cut-points for categorisation of continuous variables), nor to prohibit accepted practices (for example, data transformation prior to analysis), but they are intended to establish the rules that will be followed, as closely as possible, when analysing and reporting the trial. This document follows the published guidelines regarding the content of statistical analysis plans for clinical trials [1].

The analysis strategy will be available on request when the principal papers are submitted for publication in a journal. Suggestions for subsequent analyses by journal editors or referees, will be considered carefully, and carried out as far as possible in line with the principles of this analysis strategy; if reported, the source of the suggestion will be acknowledged.

Any deviations from the statistical analysis plan will be described and justified in the final report of the trial. The analysis should be carried out by an identified, appropriately qualified and experienced statistician, who should ensure the integrity of the data during their processing. Examples of such procedures include quality control and evaluation procedures.

The analysis of this study will be conducted in two stages. The first stage concerns outcomes recorded up to 6 months post-randomisation, and includes the primary outcome. The second stage covers the long-term follow-up period, and concerns outcomes recorded annually from one to five years post-randomisation. This plan concerns the analysis of outcomes up to 6 months post-randomisation which will be the subject of the HTA monograph. A separate plan will be written detailing the analysis strategy for the outcomes from one to five years post-randomisation.

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1.2 Changes from previous version of SAP

A summary of key changes from earlier versions of SAP, with particular relevance to protocol changes that have an impact on the design, definition, sample size, data quality/collection and analysis of the outcomes will be provided. Include protocol version number and date.

Version number Issue date	Author of this issue	Protocol Version & Issue date	Significant changes from previous version together with reasons
V1.0_26Mar2018		Protocol_V5.0_27Jul2017	Not applicable as this is the 1st issue

2. BACKGROUND AND OBJECTIVES

2.1 Background and rationale

Major trauma is the leading cause of death in patients under 45 years and a significant cause of short- and long-term morbidity [2]. 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 of the survivors suffer permanent disabilities requiring long-term care.

Fractures of the limbs are extremely common in injuries in both the civilian and military populations, with 85% of major trauma patients sustaining serious limb injuries. In the context of major trauma, the wounds associated with surgery to fractured limbs are notoriously difficult to manage. Even in closed high-energy injuries associated with major trauma, the rate of infection in surgical incisions created during fracture fixation remains high; tibial plateau fractures are associate with average infection rates of up to 27% [3-7] while pilon fractures have an incidence of deep infection ranging from 5% to 40% [8-11]. If surgical site infection does occur, treatment frequently continues for years after the trauma with significant personal and societal costs [12].

One of the factors which may reduce the risk of surgical site infection in the surgical wounds of major trauma patients is the type of dressing applied over the closed incision at the completion of the operative procedure. 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. Negative-pressure wound therapy (NPWT) 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. A sealed tube is used to connect the foam to a pump which creates a partial vacuum over the wound.

There has only been one randomised trial comparing standard wound dressing with NPWT for patients with closed surgical wounds following major trauma to the limbs [13]. This trial demonstrated a reduction in the rate of late/deep wound infection in 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 since been criticised for numerous methodological flaws [14]. In addition, a recent Cochrane review concluded that further trials regarding the effects of NPWT are required [14]

2.2 Objectives

The aim of this pragmatic randomised controlled trial is to compare standard dressings with NPWT for the treatment of surgical incisions associated with major trauma to the lower limb. The primary and secondary objectives and endpoints for this study are described in Table 1.

Table 1: Primary and secondary objectives and endpoints

	Objectives	Endpoints
Primary	To quantify and draw inferences on differences in the rate of 'deep infection' of the lower limb in the 30 days after major trauma between standard dressing and NPWT	At 30 days post-injury: • Deep infection rate (as per CDC definition, see Section 2.7)
Secondary	(i) To quantify and draw inferences on observed differences in the DRI and general health-related quality of life in the 6 months after the major trauma.	At 3 and 6 months post-injury • DRI • EQ-5D-5L
	(ii) To quantify and draw inferences on the quality of wound healing, using a validated, patient-reported assessment of the scar.	At 30 days, 3 and 6 months post-injury: • Patient-reported assessment of scar
	(iii) To determine the number and nature of further surgical interventions related to the injury, in the first 6 months after major trauma.	At 3 and 6 months post-injury: • Record of complications
	(iv) To quantify and draw inferences on differences in the proportion of participants experiencing neuropathic pain in the 6 months after the major trauma.	At 3 and 6 months post-injury: • DN4 pain scale
	(v) To investigate, using appropriate statistical and economic analysis methods, the resource use, and thereby the cost effectiveness of NPWT versus standard dressing for wounds associated with major trauma to the lower limbs.	At 3 and 6 months post-injury: • EQ-5D-5L • Resource use questionnaire

3. STUDY METHODS

3.1 Trial Design/framework

The WHIST trial is a large-scale, multi-centre, parallel group, superiority randomised controlled trial designed to compare the rates of 'deep infection' in patients allocated to standard wound therapy versus patients allocated to NPWT. The trial is designed as a two-phase study; Phase 1 (Internal Pilot) will confirm the expected rate of recruitment and Phase 2 (Main Phase) will be the proposed randomised controlled trial in a minimum of 24 trauma centres across the UK. Patients recruited in the internal pilot will be included in the main trial. Eligible patients are those with a major trauma injury and/or a TARN eligible injury which can be closed primarily. The primary outcome is assessed at 30 days post-randomisation. Secondary outcomes will be assessed at baseline, 30 days, 3, and 6 months post-randomisation. In addition, some secondary outcomes will be collected on an annual basis for 5 years following injury; however, the planned analysis for these outcomes will be detailed in a separate document.

3.2 Randomisation and Blinding

The treating surgeon will confirm eligibility at the end of the operative procedure but before the wound dressing is applied. Eligible patients will be randomised via the OCTRU online randomisation system (RRAMP) on a 1:1 basis, using a validated computer randomisation program with a minimisation algorithm to ensure balanced allocation of patients across the two treatment groups, stratified by trial centre, open or closed fracture at presentation and ISS≤15 vs ISS ≥16. The first 30 participants will be randomised using simple

randomisation to seed the minimisation algorithm, which will have probabilistic element of 0.8 introduced to ensure unpredictability of the treatment assignment. All modern operating theatres include a computer with web-access, so a secure, 24-hour, web-based randomisation system will be used to generate the treatment allocation intra-operatively.

Full details of the randomisation are available in WHIST_RBP_v2.0_18May2017, stored in the confidential statistical section of the TMF.

As wound dressings are clearly visible, the patients cannot be blinded to their treatment. In addition, the treating surgeons will also not be blind to the treatment, but will take no part in post-operative research.

3.3 Sample Size

There has only been one previous randomised trial to compare NPWT to standard dressings for surgical incisions associated with major trauma to the lower limb [13]. This trial indicated that the rate of 'late' (deep) infection was reduced by 6%; from 15% in the standard treatment group to 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 a 6% reduction in the rate of 'deep infection' would, universally, be sufficient to change clinical practice with regard to the choice of 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 propose to recruit **1540 patients** in total for this trial.

A check of the sample size is detailed in a document stored in the confidential statistical section of the TMF, file name "WHIST_SampleSize_Verification_06Jun2016.rtf".

3.4 Statistical Interim Analysis, Data Review and Stopping guidelines

The Data and Safety Monitoring Committee (DSMC) is a group of independent experts external to the trial who will assess the progress, conduct, participant safety and, if required critical endpoints. The DSMC follows the charter as described in the document WHIST_DSMC_Charter_V1.0_06Jul2016 stored in the TMF. The DSMC will review accruing data, summaries of the data presented by treatment group and will assess the screening algorithm against eligibility criteria. They will also consider emerging evidence from other related trials or research and review related SAEs that have been reported. Full details of the interim analyses planned are available in the Interim Statistical Analysis Plan (ISAP), WHIST_ISAP_V1.2_16Feb2016 stored in the confidential statistical section of the TMF. Formal comparative interim analyses of the primary outcome is not planned during the trial. The DSMC may advise the chair of the TSC 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.

3.5 Timing of Final Analysis

The analysis of the outcomes up to 6 months after randomisation will be conducted once all randomised participants have reached this time point (short-term follow-up). This SAP concerns the methods which will be used to analyse these outcomes. The trial also includes long-term follow-up from one to five years post-randomisation and the analysis of this data will be reported separately. A separate analysis plan will be prepared detailing the methods which will be used to analyse these outcomes.

3.6 Blinded analysis

A blinded analysis of the data (not separated by treatment arm) will be undertaken prior to the final data lock to look into the distribution of variables, missing data distributions, and to finalise the per protocol population.

3.7 Statistical Analysis Outline

Standard statistical summaries (e.g. medians and ranges or means and variances, or proportions and percentages, dependent on the distribution of the outcomes) and graphical plots showing correlations will be presented for the primary outcome measure and all secondary outcome measures. Baseline data will be summarized to check comparability between treatment arms, and to highlight any characteristic differences (e.g. in age and gender mix) between those individuals in the study, those ineligible, and those eligible but withholding consent.

The main analysis will investigate differences in the primary outcome measure, the proportion of participants with deep infection, at 30 days post operation. Randomisation by minimisation procedure should ensure balance in the recruiting centre, participants presenting with open versus closed fractures and ISS in both treatment groups. 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 participants 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 deep infection rates 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, ISS level (≤15 vs ≥16), and participant gender as categorical factors and participant age as a continuous factor. An identically structured and formulated mixed-effects linear regression model will be used to assess the effects of the interventions on secondary outcomes DRI and EQ-5D (at both 3 and 6 months, and for the long-term follow-up) that, for the purposes of analysis, will be assumed to be approximately normally distributed. 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. Other dichotomous outcome variables, such as complications related to the trial interventions will be analysed in the same manner as the primary outcome, including the alternative definition of deep infection. 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. The main analyses will be conducted using specialist mixed-effects modelling functions available in validated statistical software such as Stata, Stata Corp LP (http://www.stata.com) or the software package R (http://www.r-project.org/). The primary focus will be the comparison of the two treatment groups of patients on an intention-to-treat (ITT) basis, and this will be reflected in the analysis, which will be reported together with appropriate diagnostic plots that check the underlying model assumptions. In addition to the ITT analyses, per-protocol (as treated) analyses will also be undertaken and reported in parallel to, but subsidiary to, the main analyses.

It seems likely that some data may not be available due to voluntary withdrawal of patients, lack of completion of individual data items or general loss to follow-up. Where possible the reasons for missing data will be ascertained and reported. Although missing data is not expected to be a problem for this study, the nature and pattern of the 'missingness' will be carefully considered — including in particular whether data can be treated as missing at random (MAR). If judged appropriate, missing data will be imputed, using multiple imputation. The resulting imputed datasets will be analysed and reported, together with appropriate sensitivity analyses. Any imputation methods used for scores and other derived variables will be carefully considered and justified. Reasons for ineligibility, non-compliance, withdrawal or other protocol violations will be stated if available and any patterns summarized. More formal analysis, for example using logistic regression

with 'protocol violation' as a response, may also be appropriate and aid interpretation. About 1-2% of patients are expected to die during follow-up, so this is unlikely to be a serious cause of bias. However, we will conduct a secondary analysis taking account of the competing risk of death, using methods described by Varadhan et al [15].

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 and Safety Monitoring Committee (DSMC) at the commencement of or early in the study. Any subsequent amendments to this initial 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 DSMC. Results from this trial will also be compared with results from other trials and reported in accordance with CONSORT guidelines

4. STATISTICAL PRINCIPLES

4.1 Statistical Significance and Multiple Testing

There is no multiple testing as only a single primary outcome is considered. Therefore, significance levels used will be 0.05 and 95% confidence intervals will be reported. All secondary analyses will be considered as supporting the primary analysis and will also be analysed using a significance level of 0.05 with 95% confidence intervals.

Interim analyses of primary and secondary outcomes will not be carried out unless requested by the DSMC. In this case p-values of 0.001 will be used for significance and 99% confidence intervals will be presented.

4.2 Definition of Analysis Populations

Populations for analysis are defined as follows:

Intent to treat (ITT): all participants randomised analysed in their randomised groups. Participants who: (i) prospectively declined consent but were subsequently randomised in error; (ii) retrospectively declined consent and requested that all their data was removed; or (iii) withdrew and requested that all their data was removed, will be excluded from this population.

Per protocol (PP): participants who received the intervention as intended will be analysed according to the treatment they actually received. Participants will be excluded from the per-protocol analysis if:

- They did not satisfy the eligibility criteria listed in Section 2.3 (e.g. wound could not be closed primarily)
- Insufficient data are available on the primary outcome

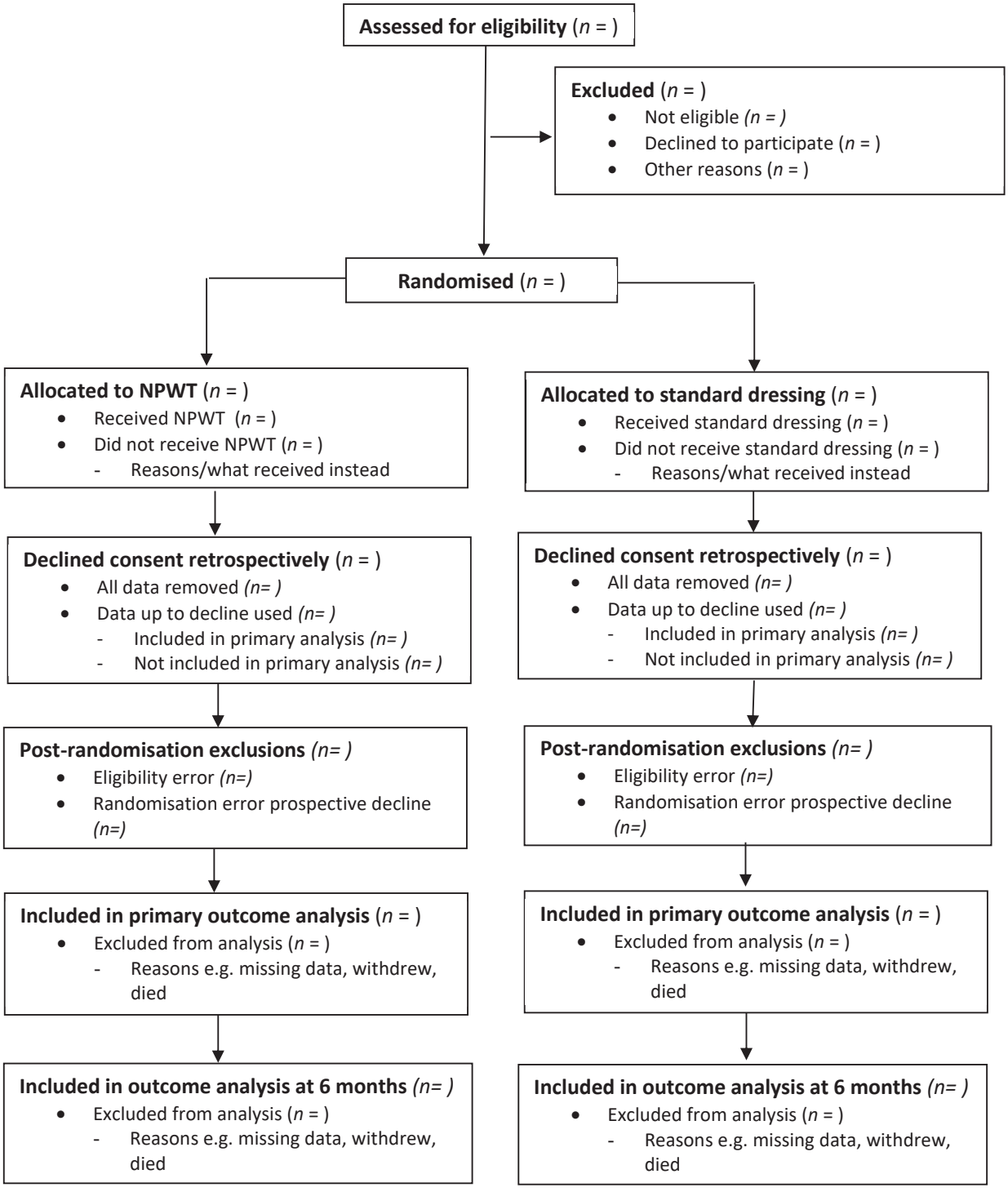
Exact exclusion criteria for the PP analysis will be chosen based on a blinded analysis of the data (not separated by treatment arm) prior to the final data lock.

5. TRIAL POPULATION AND DESCRIPTIVE ANALYSES

5.1 Representativeness of Study Sample and Patient Throughput

The flow chart shown in Figure 1 will be used to summarise the flow of participants through each stage of the trial, including the number of individuals screened, eligible, randomised to each arm, receiving allocated treatment, and included in the primary analysis as suggested in the CONSORT guidelines. Reasons for ineligibility, loss to follow-up and exclusion from the primary analysis will be summarised, as will the number of patients declining consent both prospectively and retrospectively.

Figure 1: CONSORT flow diagram for participants in trial up to 6 months follow-up



5.2 Withdrawal from treatment and/or follow-up

The numbers (and percentages) of losses to follow-up and withdrawals along with the reasons for these will be reported by intervention arm at each time point (see Table 2). To ensure that there are not differential losses between the two groups this will be tested using absolute risk differences (with 95% confidence intervals) and a chi-squared test. Any deaths (and their causes) will be reported separately.

Table 2: Details of loss to follow-up and withdrawals

Questionnaire	Standard dressing		NPWT	
	N	%	N	%
30 days post randomisation				
Completed	X	X	X	X
Loss to follow-up	X	X	X	X
Reason 1	X	X	X	X
Reason 2	X	X	X	X
…	X	X	X	X
Withdrawal	X	X	X	X
Reason 1	X	X	X	X
Reason 2	X	X	X	X
…	X	X	X	X
3 months post randomisation				
Completed	X	X	X	X
Loss to follow-up	X	X	X	X
Reason 1	X	X	X	X
…	X	X	X	X
Withdrawal	X	X	X	X
Reason 1	X	X	X	X
…	X	X	X	X
6 months post randomisation				
Completed	X	X	X	X
Loss to follow-up	X	X	X	X
Reason 1	X	X	X	X
…	X	X	X	X
Withdrawal	X	X	X	X
Reason 1	X	X	X	X
…	X	X	X	X

The patterns of availability of data for primary and key secondary outcomes from baseline to end of follow-up will be summarised for the two treatment groups (see Table 3). Where appropriate, differentiation will be made between partially completed and fully missing outcome data.

Table 3: Compliance with baseline and follow-up questionnaires by treatment arm and overall

Questionnaire	Standard dressing			NPWT		
	Expected (n)	Received (n)	Compliance (%)	Expected (n)	Received (n)	Compliance (%)
Baseline						
DRI	X	X	X	X	X	X
Short-term follow-up post-injury						
Deep infection (30 days)	X	X	X	X	X	X
DRI (3 months)	X	X	X	X	X	X
DRI (6 months)	X	X	X	X	X	X

5.3 Baseline Comparability of Randomised Groups

Baseline comparability of the randomised groups on both minimisation factors and important prognostic factors will be considered by comparing the numbers and percentages in each group for categorical factors and the mean and standard deviations (or medians and IQRs) for continuous factors.

For each of the minimisation factors, the number and percentage of patients from each category randomised to each treatment arm will be summarised as outlined in Table 4. The total number of patients in each category will also be recorded. This table will include details of all who are randomised including those who prospectively declined consent but were subsequently randomised in error and those who decline consent retrospectively and request for all of their data to be removed. These individuals will be excluded from all further analyses.

Table 4: Minimisation factors split by intervention arm at baseline

	NPWT		Standard dressing		Total
	n	%	n	%	n
Type of fracture					
Open	X	X	X	X	X
Closed	X	X	X	X	X
Injury Severity Score (ISS)					
≤15	X	X	X	X	X
16+	X	X	X	X	X
Trial Centre					
Coventry	X	X	X	X	X
Middlesbrough	X	X	X	X	X
Nottingham	X	X	X	X	X
Oxford	X	X	X	X	X
Bristol	X	X	X	X	X
…	X	X	X	X	X

The patients in the two treatment arms will be described both overall and separately in terms of descriptive characteristics at baseline (see Table 5) and operation details (see Table 6). Numbers (with percentages) for binary and categorical variables and means (and standard deviations), or medians (with lower and upper quartiles) for continuous variables will be presented; there will be no tests of statistical significance nor confidence intervals for differences between randomised groups on any baseline variable. Those who are randomised in error or who decline consent retrospectively and request for all of their data to be removed will be excluded from this table.

Table 5: Descriptive characteristics at baseline. Values are n (%) for categorical variables and mean (SD) for continuous variables.

	NPWT	Standard dressing	Total
Sex			
Male	X (X)	X (X)	X (X)
Female	X (X)	X (X)	X (X)
Age	X (X)	X (X)	X (X)
BMI	X (X)	X (X)	X (X)
Marital status			
Single	X (X)	X (X)	X (X)
Separated	X (X)	X (X)	X (X)
Married/civil partner	X (X)	X (X)	X (X)
Living with a partner	X (X)	X (X)	X (X)
Divorced	X (X)	X (X)	X (X)
Widowed	X (X)	X (X)	X (X)

Ethnicity			
White	X (X)	X (X)	X (X)
Black Caribbean	X (X)	X (X)	X (X)
Black African	X (X)	X (X)	X (X)
Black Other	X (X)	X (X)	X (X)
Indian	X (X)	X (X)	X (X)
Pakistani	X (X)	X (X)	X (X)
Bangladeshi	X (X)	X (X)	X (X)
Chinese	X (X)	X (X)	X (X)
Other	X (X)	X (X)	X (X)
Training post school			
None	X (X)	X (X)	X (X)
Formal work qualifications	X (X)	X (X)	X (X)
College/University non-degree	X (X)	X (X)	X (X)
Degree from college/university	X (X)	X (X)	X (X)
Employment status			
Full-time employed	X (X)	X (X)	X (X)
Part-time employed	X (X)	X (X)	X (X)
Self-employed	X (X)	X (X)	X (X)
Retired/looking after home/inactive	X (X)	X (X)	X (X)
Unpaid work	X (X)	X (X)	X (X)
Unemployed	X (X)	X (X)	X (X)
Full-time student	X (X)	X (X)	X (X)
Mechanism of injury			
Low energy fall	X (X)	X (X)	X (X)
High energy fall	X (X)	X (X)	X (X)
Road traffic accident	X (X)	X (X)	X (X)
Crush injury	X (X)	X (X)	X (X)
Contact sports injury	X (X)	X (X)	X (X)
Other	X (X)	X (X)	X (X)
Any other injuries			
Yes	X (X)	X (X)	X (X)
No	X (X)	X (X)	X (X)
Diagnosed with diabetes			
Yes	X (X)	X (X)	X (X)
No	X (X)	X (X)	X (X)
Regular smoker			
Yes	X (X)	X (X)	X (X)
No	X (X)	X (X)	X (X)
Alcohol consumption per week			
0-7 units	X (X)	X (X)	X (X)
8-14 units	X (X)	X (X)	X (X)
15-21 units	X (X)	X (X)	X (X)
More than 21 units	X (X)	X (X)	X (X)
Regular analgesia before injury			
Yes	X (X)	X (X)	X (X)
No	X (X)	X (X)	X (X)
Other medication before injury			
Yes	X (X)	X (X)	X (X)
No	X (X)	X (X)	X (X)
Pre-injury DRI	X (X)	X (X)	X (X)
Pre-injury EQ-5D (utility)	X (X)	X (X)	X (X)
Pre-injury EQ-5D (VAS)	X (X)	X (X)	X (X)
Day 1 EQ-5D (utility)	X (X)	X (X)	X (X)
Day 1 EQ-5D (VAS)	X (X)	X (X)	X (X)

Table 6: Operative procedure details at baseline. Values are n (%) for categorical variables and mean (SD) for continuous variables.

	NPWT	Standard dressing	Total
Lead surgeon grade			
Consultant	X (X)	X (X)	X (X)
Associate specialist	X (X)	X (X)	X (X)
Specialist Trainee	X (X)	X (X)	X (X)
Other	X (X)	X (X)	X (X)
Wound limb			
Right	X (X)	X (X)	X (X)
Left	X (X)	X (X)	X (X)
Wound location			
Hip	X (X)	X (X)	X (X)
Femur	X (X)	X (X)	X (X)
Patella	X (X)	X (X)	X (X)
Tibia	X (X)	X (X)	X (X)
Foot	X (X)	X (X)	X (X)
How fixed?			
Nail	X (X)	X (X)	X (X)
Plate and screws	X (X)	X (X)	X (X)
Wires/tension band wires	X (X)	X (X)	X (X)
External fixator – half pin	X (X)	X (X)	X (X)
External fixator – fine pin	X (X)	X (X)	X (X)
Other	X (X)	X (X)	X (X)
How closed?			
Interrupted sutures	X (X)	X (X)	X (X)
Skin clips	X (X)	X (X)	X (X)
Subcuticular suture	X (X)	X (X)	X (X)
Any skin closure used	X (X)	X (X)	X (X)
Steristrips	X (X)	X (X)	X (X)
Glue	X (X)	X (X)	X (X)
Other	X (X)	X (X)	X (X)
Any intra-operative complications?			
Yes	X (X)	X (X)	X (X)
No	X (X)	X (X)	X (X)
If yes what?			
Nerve injury	X (X)	X (X)	X (X)
Vascular injury	X (X)	X (X)	X (X)
Tendon injury	X (X)	X (X)	X (X)
Extension of fracture	X (X)	X (X)	X (X)
Other	X (X)	X (X)	X (X)
Any other surgery?			
Yes	X (X)	X (X)	X (X)
No	X (X)	X (X)	X (X)
If yes what?			
Head	X (X)	X (X)	X (X)
Chest	X (X)	X (X)	X (X)
Abdomen	X (X)	X (X)	X (X)
Pelvis	X (X)	X (X)	X (X)
Spine	X (X)	X (X)	X (X)
Upper limbs	X (X)	X (X)	X (X)
Ipsilateral limb	X (X)	X (X)	X (X)
Contralateral limb	X (X)	X (X)	X (X)
Prophylactic antibiotics?			

Yes	X (X)	X (X)	X (X)
No	X (X)	X (X)	X (X)
Number of surgeons present	X (X)	X (X)	X (X)
Duration of Operation	X (X)	X (X)	X (X)

5.4 Unblinding

This is not a blinded trial and as such it is not possible for unblinding to occur. Wound photographs taken at the 30 day visit will be reviewed by two assessors who are blind to the treatment allocation. These assessors will be independent of the trial and will not have interaction with the participants.

5.5 Description of Compliance with Intervention

The randomised intervention in this trial is the dressing (standard or NPWT) applied to the closed fracture wound at the end of surgery. As such, the intervention occurs at a single time point and compliance is therefore defined as the proportion of patients in each arm receiving the treatment to which they were randomised. The number (and percentage) of patients receiving the assigned dressing and receiving another dressing or no dressing in each arm will be summarised, as well as the reasons for not receiving the randomised treatment. Details of what treatment was received instead will also be recorded. These will be summarised as outlined in Table 7.

Table 7: Details of compliance with intervention

	Standard dressing		NPWT	
	N	%	N	%
Received allocated dressing	X	X	X	X
Received other dressing or no dressing	X	X	X	X
Reason 1	X	X	X	X
Reason 2	X	X	X	X
…	X	X	X	X

5.6 Reliability

To ensure consistency, validation checks of the data will be conducted. This will include checking for duplicate records, checking the range of variable values and validating potential outliers by comparing with CRFs and referring back to sites if necessary. Calculations and processes performed by a computer program, including the construction of derived data such as the primary outcome, will be checked by hand calculations. This check will be conducted for 20 participants randomly sampled from the dataset. These checks will also confirm whether the data has been imported into the statistical software correctly and will check any merging of different datasets. Clarification will be sought from the trial office in the case of discrepancies.

For each variable, missing value codes will be checked for consistency and the proportion of missing values per variable will be presented. Patterns of missing data will be explored. Where missing data imputation is used, imputed values will also be verified using the validation techniques described above. Sensitivity analyses will be conducted to explore the missing data assumptions used.

6. ANALYSIS

6.1 Outcome Definitions

The **primary outcome measure** for this study is '*deep infection*'; the Centre for Disease Control and Prevention (CDC) definition of a "deep surgical site infection", that is a wound infection involving tissues deep to the skin that occurs within 30 days of injury [16], will be used. The treating clinical team will make the diagnosis of 'deep infection', as per routine clinical practice. In addition, an Independent Outcome Classification Group will

review the data collected in the Case Report Forms (CRFs,) which will include the specific criteria used by the CDC to define a "deep surgical site infection" to confirm/refute the 'deep infection' diagnosis. Several diagnostic markers of 'deep infection' (Purulent drainage, positive deep wound culture, spontaneous dehiscence (opening up) of the wound) will be used.

A binary variable indicating whether a participant has experienced 'deep infection' by the 30 day assessment will be created by reference to responses to Section 2 of the CRF at 30 days. An individual is classed as having 'deep infection' as per the CDC diagnosis if they belong in one or more of the following categories:

1. Fluid is leaking from the wound (Question 1e) AND the fluid is pus
2. At least one criterion from each of the following lists is satisfied:
    a. Either the wound is gaping open (dehisced) (Question 1f) OR Surgeon has deliberately opened wound (Question 2)
    b. Either the area around the wound is painful or tender (Question 1c) OR any fever of 38°C since surgery (Question 1d)
3. Any sign of abscess or infection on direct examination or imaging (e.g. ultrasound) (Question 1g)

Since the trial started, the CDC definition of a deep surgical site infection has been widened to include wound infections occurring up to 90 days after injury, all other indications remaining the same [17]. This alternative definition of the primary outcome will be included as a supplementary analysis to ensure the study can be utilised in future systematic reviews and meta-analyses.

The **secondary outcome measures** in this trial are:

Disability rating index (DRI) – a self-administered, 12-item Visual Analogue Scale questionnaire assessing the patients' own rating of their disability [18]. For each item, patients score their ability to carry out the activity from 0 (without difficulty) to 100 (not at all). Total DRI scores are calculated as an average across all 12 items with higher scores indicating greater disability. An example of this questionnaire is included in Appendix 2 (see Figure 2)

EuroQol EQ-5D-5L – a validated measure of health-related quality of life consisting of a five dimension health status classification system with 5 response levels and a separate visual analogue scale [19, 20]. Responses to the health status classification system will be converted into multi-attribute utility (MAU) scores using tariffs currently under development for England [21]. The scale is such that 1 is equivalent to perfect health, 0 is equivalent to death, and negative scores are possible. 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. The VAS ranges from 0 (worst health) to 100 (best health). An example of this questionnaire is included in Appendix 2 (see Figures 3 and 4).

Patient-reported scar assessment **–** the patient scale from the Patient and Observer Scar Assessment Scale [22] consists of six questions regarding different aspects of the scar as well as an overall assessment of the scar. Each item is scored out of 10. The first six questions are summed to give an overall score out of 60. This will be used to provide a subjective patient-assessment of wound healing. An example of this questionnaire is included in Appendix 2 (see Figure 6).

Douleur Neuropathique Questionnaire (DN4) – a short validated neuropathic pain screening tool comprising seven questions [23]. This screening tool is recommended for use by the International Association for the Study of Pain (IASP [24]). Each question is a yes/no question and total scores are the number of questions which were answered yes. Scores of 3 or greater are likely to be indicative of neuropathic pain. An example of this questionnaire is included in Appendix 2 (see Figure 5).

Complications – all complications and surgical interventions related to the index wound will be recorded. This will take place as part of routine follow-up and via SAE forms. Standardised photographs of the wound at 30 days will also be used. The photographs will be reviewed by two independent experienced assessors who are blind to the treatment allocation. The assessors will classify each wound as 'healed' or 'not healed' and if not

healed as 'infected' or 'uninfected' and the agreement between these statistics will be calculated using Cohen's Kappa.

Complications will be grouped into three categories for analysis: (i) local complications related to the injury or operation – this will include an independent assessment of wound healing at 30 days using photographs, signs of superficial infection up to 6 months and other local complications; (ii) systemic complications related to the injury or operation – this will include other related SAEs; and (iii) unrelated SAEs.

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 [25]. 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 3 and 6 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 different services [26].

6.2 Analysis Methods

Primary outcome

The numbers and percentages of 'deep infections' occurring up to 30 days post-randomisation in the two study intervention groups, NPWT and standard dressing, will be calculated and reported (see Table 8). The rates of deep infection in the two study groups will be compared using a mixed effects logistic regression model. The model will include a random effect to account for any heterogeneity in the response due to recruitment centre, and fixed effects to adjust for open versus closed fractures, ISS level (≤15 vs ≥16), participant age and participant gender. The results will be reported as odds ratios (ORs) with associated 95% confidence intervals and p-values for comparison between the two treatment groups (see Table 8). The unadjusted OR and associated 95% confidence interval will also be reported. This analysis will be conducted for the ITT population (see Section 4.2) using the available case dataset (see Section 6.3). Sensitivity analyses will be conducted to explore different analysis populations and missing data approaches (see Section 6.4).

This analysis will be repeated using the alternative definition of 'deep infection' (up to 90 days after injury), these results will also be reported as outlined in Table 8.

Table 8: Analysis of primary outcome

	NPWT		Standard dressing		OR (95% CI)		p-value
	n	%	n	%	Raw	Adjusted	
Deep infection up to 30 days							
ITT (available case)	X	X	X	X	X (X,X)	X (X,X)	X
ITT (imputed)	X	X	X	X	X (X,X)	X (X,X)	X
PP (available case)	X	X	X	X	X (X,X)	X (X,X)	X
Deep infection up to 90 days							
ITT (available case)	X	X	X	X	X (X,X)	X (X,X)	X

Secondary outcomes

The continuous secondary outcomes (DRI, EQ-5D-5L, and patient-reported scar assessment) will each be assessed to establish approximate normality and the mean and SD for each intervention arm will be reported (see Table 9). Assuming approximate normality is established, multi-level mixed-effects linear regression models, using repeated measures (level 1) nested within participants (level 2), will be used. The model will include a random effect to account for any heterogeneity in response due to recruitment centre (level 3). The model will also include fixed effects to adjust for open versus closed fractures, ISS level (≤15 vs ≥16), participant age, participant gender, and, where appropriate, pre-injury values (DRI and EQ-5D-5L). Trends over

time will be examined, and, if appropriate, interactions between treatment and time will be included in the model. The adjusted difference between the treatment arms at each time point will be reported (see Table 9). This analysis will be conducted for the ITT population (see Section 4.2) using the available case dataset (see Section 6.3).

If, for any of these variables, approximate normality is not appropriate, the first approach will be to consider a transformation of the data or the use of a different metric such as change from baseline to attain normality. If normality cannot be achieved by transformation, the data will be analysed using a non-parametric equivalent with no adjustment and medians and interquartile ranges will be reported for each treatment arm.

Table 9: Analysis of continuous secondary outcomes at 3 and 6 months (ITT population, available case dataset)

		NPWT		Standard dressing		Adjusted difference	p-value
		Mean (SD)	n	Mean (SD)	n	(95% CI)	
DRI	**3 months**	X (X)	X	X (X)	X	X (X,X)	X
	6 months	X (X)	X	X (X)	X	X (X,X)	X
EQ-5D utility	**3 months**	X (X)	X	X (X)	X	X (X,X)	X
	6 months	X (X)	X	X (X)	X	X (X,X)	X
EQ-5D VAS	**3 months**	X (X)	X	X (X)	X	X (X,X)	X
	6 months	X (X)	X	X (X)	X	X (X,X)	X
Patient-reported scar assessment	**30 days**	X (X)	X	X (X)	X	X (X,X)	X
	3 months	X (X)	X	X (X)	X	X (X,X)	X
	6 months	X (X)	X	X (X)	X	X (X,X)	X

In addition, supplementary analyses of the DRI and EQ-5D utility variables will be conducted using area under the curve (AUC) summary statistics [27]. Parameter estimates from the mixed effects models described above will be used to calculate the AUC from baseline to 6 months for each intervention arm. This will provide an overall estimate of recovery over time in each group which will be presented with the associated 95% CI (see Table 10). The difference between the two groups will be calculated and compared using a t-test (Table 10).

Table 10: AUC analysis of DRI and EQ-5D utility

	NPWT	Standard dressing	Difference (95% CI)	p-value
	AUC (95% CI)	AUC (95% CI)		
DRI	X (X,X)	X (X,X)	X (X,X)	X
EQ-5D utility	X (X,X)	X (X,X)	X (X,X)	X

The DN4 will be analysed using similar methods to those outlined for the primary outcome. The number and proportion of individuals deemed to have neuropathic pain (DN4 ≥ 3) will be reported for each treatment arm (see Table 11). A multilevel, mixed effects logistic regression model with repeated measures (level 1) nested within participants (level 2) will be used. The model will be adjusted for recruitment centre as a random effect (level 3), and fixed effects will be included to adjust for open versus closed fractures, ISS level (≤15 vs ≥16), participant age and participant gender. Trends over time will be examined, and, if appropriate, interactions between treatment and time will be included. Results will be presented as ORs with associated 95% CIs (see Table 11). The unadjusted OR and associated 95% CI will also be calculated and reported. This analysis will be conducted for the ITT population (see Section 4.2) using the available case dataset (see Section 6.3).

Table 11: Analysis of DN4 at 3 and 6 months post-injury (ITT population, available case dataset)

		NPWT		Standard dressing		OR (95% CI)		p-value
		n	%	n	%	Raw	Adjusted	
DN4	**3 months**	X	X	X	X	X (X,X)	X (X,X)	X
	6 months	X	X	X	X	X (X,X)	X (X,X)	X

Complications will also be analysed using similar methods to the primary outcome. The number and percentage of people experiencing each complication in each treatment arm will be reported. If there are sufficient numbers of events, a mixed-effects logistic regression model will be used to compare the rates of complications between intervention arms. This model will include a random effect for recruitment centre and fixed effects for open versus closed fractures, ISS level (≤15 vs ≥16), participant age, and participant gender. Otherwise unadjusted ORs will be calculated using a chi-squared test. These results will be reported as outlined in Tables 12-16. This analysis will be conducted for the ITT population (see Section 4.2) using the available case dataset (see Section 6.3).

Temporal patterns of 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.

(i) Local complications related to injury or operation

Table 12: Wound healing assessment at 30 days using independently assessed photographs

	NPWT		Standard dressing		OR (95% CI)		p-value
	n	%	n	%	Raw	Adjusted	
Wound healed	X	X	X	X	X (X, X)	X (X,X)	X
Wound infected	X	X	X	X	X (X, X)	X (X,X)	X

Table 13: Signs of infection up to 3 months post-randomisation

	NPWT		Standard dressing		OR (95% CI)		p-value
	n	%	n	%	Raw	Adjusted	
Red and inflamed	X	X	X	X	X (X, X)	X (X, X)	X
Swollen	X	X	X	X	X (X, X)	X (X, X)	X
Painful/tender	X	X	X	X	X (X, X)	X (X, X)	X
Fluid leaking	X	X	X	X	X (X, X)	X (X, X)	X
Fluid (pus) cloudy	X	X	X	X	X (X, X)	X (X, X)	X
Gaping open	X	X	X	X	X (X, X)	X (X, X)	X
Fever > 38	X	X	X	X	X (X, X)	X (X, X)	X
Culture swab taken	X	X	X	X	X (X, X)	X (X, X)	X
Antibiotics for wound infection	X	X	X	X	X (X, X)	X (X, X)	X

Table 14: Other local complications up to 6 months post-randomisation

	NPWT		Standard dressing		OR (95% CI)		p-value
	n	%	n	%	Raw	Adjusted	
Further surgery	X	X	X	X	X (X, X)	X (X,X)	X
DVT	X	X	X	X	X (X, X)	X (X,X)	X
Other	X	X	X	X	X (X, X)	X (X, X)	X

(ii) Systemic complications related to the injury or operation

Table 15: Comparing related SAEs across treatment arms up to 6 months post-randomisation

	NPWT		Standard dressing		OR (95% CI)		p-value
	n	%	n	%	Raw	Adjusted	
Surgical	X	X	X	X	X (X, X)	X (X,X)	X
Medical	X	X	X	X	X (X, X)	X (X,X)	X
Trauma	X	X	X	X	X (X, X)	X (X, X)	X
Psychiatric	X	X	X	X	X (X, X)	X (X, X)	X
Anaesthetic	X	X	X	X	X (X, X)	X (X, X)	X

Total	X	X	X	X	X (X, X)	X (X, X)	X

(iii) Unrelated SAEs

Table 16: Comparing unrelated SAEs across treatment arms up to 6 months post-randomisation

	NPWT		Standard dressing		OR (95% CI)		p-value
	n	%	n	%	Raw	Adjusted	
Surgical	X	X	X	X	X (X, X)	X (X,X)	X
Medical	X	X	X	X	X (X, X)	X (X,X)	X
Trauma	X	X	X	X	X (X, X)	X (X, X)	X
Psychiatric	X	X	X	X	X (X, X)	X (X, X)	X
Anaesthetic	X	X	X	X	X (X, X)	X (X, X)	X
Total	X	X	X	X	X (X, X)	X (X, X)	X

6.3 Missing Data

The number and percentage of individuals in the missing category will be presented for each study arm, as well as reasons for missing-ness if known. The pattern of missing-ness will also be explored and the suitability of the missing at random (MAR) assumption considered.

Two analysis datasets will be considered:

Available case dataset: All observed data

Imputed dataset: Missing data imputed will be imputed as follows:

- Using a best case worst case analysis for binary outcomes. This will consider the situation where all patients in the NPWT group are assumed to have a positive outcome and all those in the Standard dressing group are assumed to have a negative outcome and vice versa.
- Using multiple imputation (MI) under the missing at random (MAR) assumption for continuous outcomes. The imputation model will be sufficiently general to include baseline variables thought to be important predictors.

The main analyses of the outcomes as described above will be conducted using the ITT population (see Section 4.2) and the available case dataset.

6.4 Sensitivity Analysis

Primary outcome

The analysis of the rates of 'deep infection' up to 30 days as outlined in Section 6.2 will be repeated for different analysis populations and under different missing data assumptions:

1. The ITT population using an imputed dataset. Data will be imputed using a best case worst case analysis.
2. The PP population using the available case dataset.

These results will be reported as demonstrated in Table 8.

If any of these sensitivity analyses demonstrate substantially different results to the primary analysis, the sensitivity analyses will be repeated for the rates of deep infection up to 90 days.

In addition, sensitivity analysis taking account of the competing risk of death, using methods described by Varadhan et al [15] will be conducted if a sufficient number of deaths have occurred prior to 30 days.

Secondary outcomes

The analysis of the DRI using multilevel mixed-effects linear regression models outlined in Section 6.2 will be repeated using the imputed dataset as defined in Section 6.3. Data will be imputed using MI under the MAR assumption.

6.5 Pre-specified Subgroup Analysis

If a significant treatment effect of NPWT is identified in the primary analysis, an exploratory subgroup analysis will be conducted to investigate whether this effect is moderated by the underlying risk level of the wound. This will be done by repeating the primary analysis and including wound location (above or below the knee) as a covariate. Wound location will be used a proxy for wound risk level due to differences in soft-tissue bone cover.

6.6 Supplementary/ Additional Analyses and Outcomes

No further analyses are planned.

6.7 Health Economics and Cost Effectiveness (where applicable)

The statistician is not undertaking this analysis. A separate health economics analysis plan (HEAP) will be written by the trial health economist and all cost effectiveness analysis will be undertaken following that plan by the health economist.

6.8 Meta-analyses (if applicable)

There is no planned meta-analysis in this study.

7. VALIDATION OF THE PRIMARY ANALYSIS

To validate the primary outcome and key secondary outcomes a statistician not involved in the trial will independently repeat the analyses detailed in this SAP, by using different statistical software (if possible). The results will be compared and any discrepancies will be reported in the Statistical report (See OCTRU SOP STATS-005 Statistical Report).

8. SPECIFICATION OF STATISTICAL PACKAGES

All analysis will be carried out using appropriate validated statistical software such as STATA, SAS, SPLUS or R. The relevant package and version number will be recorded in the Statistical report.

9. REFERENCES

The TMF can be found at: Z:\KC_WHIST\WHIST eTMF V3.0
The Statistical TMF can be found at: N:\OCTRU CONFIDENTIAL\STATS\OCTRU Trials - Funded\WHIST
The current data management plan is in the Stats TMF: \Data Management\WHIST-DataManagementPlan_V2.0_07Nov2017

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APPENDIX 1: GLOSSARY OF ABBREVIATIONS

BNF	British National Formulary
CI	Confidence Interval
CRF	Clinical Reporting Form
DN4	Doleur Neuropathic Questionnaire
DRI	Disability Rating Index
DSMC	Data and Safety Monitoring Committee
EQ-5D-5L	EurQol (5 levels)
HTA	Health Technology Assessment
ISS	Injury Severity Score
ITT	Intention to treat
MAR	Missing At Random
MAU	Multi-Attribute Utility
MI	Multiple imputation
NPWT	Negative Pressure Wound Therapy
PP	Per Protocol
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SD	Standard Deviation
TARN	Trauma Audit Research Network
TSC	Trial Steering Committee

APPENDIX 2: QUESTIONNAIRES

The questionnaires which were used to measure some of the secondary outcomes (DRI, EQ-5D-5L, DN4 and patient-reported scar assessment) are provided here. Coding regimes are also indicated.

Disability rating index (DRI)

Section 1 — Disability Rating Index *(to be completed by the patient only)*

What is the date you are completing this form: D D M O N Y Y Y Y

When you are asked to mark a point on the line you should mark it in the following way. For example if your answer to the question is with some difficulty you should mark on the line in the following way.

Example — How do you manage walking? — Without difficulty — Not at all

How do you manage the following activities?
After each question, please mark ONE POINT on the line

PLEASE ANSWER ALL QUESTIONS

Without difficulty — Not at all

With some difficulty - With difficulty - With great difficulty

Office use:

- Dressing (without help)
- Out-door walks
- Climbing stairs
- Sitting longer time
- Standing bent over a sink
- Carrying a bag
- Making a bed
- Running
- Light work
- Heavy work
- Lifting heavy objects
- Participating in exercise/sports

Figure 2: The Disability Rating Index questionnaire

EQ-5D-5L

Figure 1: EQ-5D-5L (UK English sample version)

Under each heading, please tick the **ONE** box that best describes your health **TODAY**

MOBILITY

I have no problems in walking about ❑
I have slight problems in walking about ❑
I have moderate problems in walking about ❑
I have severe problems in walking about ❑
I am unable to walk about ❑

SELF-CARE

I have no problems washing or dressing myself ❑
I have slight problems washing or dressing myself ❑
I have moderate problems washing or dressing myself ❑
I have severe problems washing or dressing myself ❑
I am unable to wash or dress myself ❑

USUAL ACTIVITIES *(e.g. work, study, housework, family or leisure activities)*

I have no problems doing my usual activities ❑
I have slight problems doing my usual activities ❑
I have moderate problems doing my usual activities ❑
I have severe problems doing my usual activities ❑
I am unable to do my usual activities ❑

PAIN / DISCOMFORT

I have no pain or discomfort ❑
I have slight pain or discomfort ❑
I have moderate pain or discomfort ❑
I have severe pain or discomfort ❑
I have extreme pain or discomfort ❑

ANXIETY / DEPRESSION

I am not anxious or depressed ❑
I am slightly anxious or depressed ❑
I am moderately anxious or depressed ❑
I am severely anxious or depressed ❑
I am extremely anxious or depressed ❑

Page | 7

Figure 3: EQ-5D-5L utility

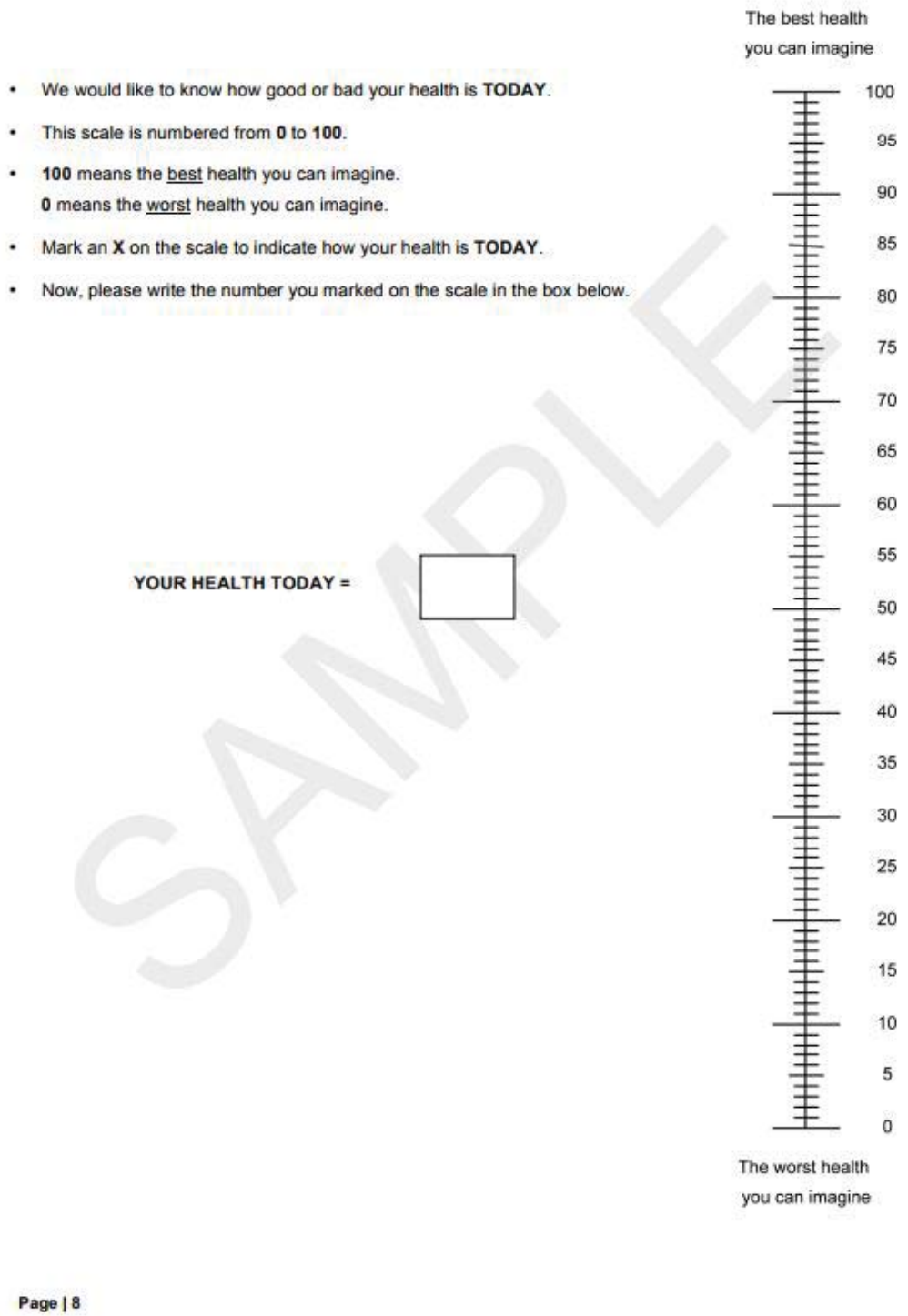

Figure 4: EQ-5D-5L VAS

Doleur Neuropathique 4 (DN4)

DN4

Questionnaire DN4 – Interview

Please complete this questionnaire by ticking one answer for each item in the 2 questions below:

Question 1: Does the pain have one or more of the following characteristics?

	YES	NO
1 - Burning	❒	❒
2 - Painful cold	❒	❒
3 - Electric Shocks	❒	❒

Question 2: Is the pain associated with one or more of the following symptoms in the same area?

	YES	NO
4 - Tingling	❒	❒
5 - Pins and Needles	❒	❒
6 - Numbness	❒	❒
7 - Itching	❒	❒

Patient Score: /7

Figure 5: The Doleur Neuropathique 4 questionnaire

Patient-reported scar assessment

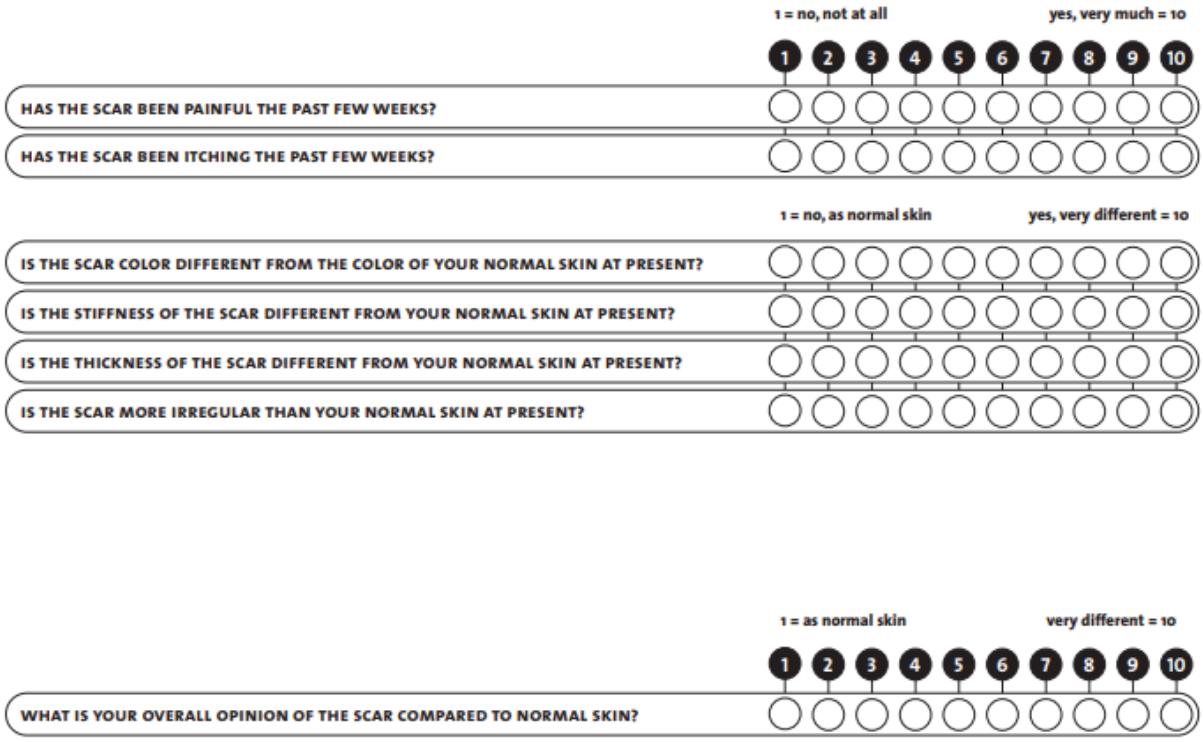

Figure 6: The patient-reported scar assessment questionnaire.