SWHSI-2

A pragmatic, multicentre, randomised controlled trial to assess the clinical effectiveness of negative pressure wound therapy versus usual care for surgical wounds healing by secondary intention

STATISTICAL ANALYSIS PLAN

V1.0

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1. Document scope and relevant SOPs and guidance documents

This statistical analysis plan (SAP) deals only with the statistical analysis of clinical effectiveness; the cost-effectiveness analysis will be detailed in a separate plan. This SAP was written prior to the completion of recruitment and was prepared according to York Trials Unit (YTU) standard operating procedures and guidance documents.

2. Definition of terms/acronyms

A definition of any terms or acronyms used in the SAP is provided below.

AE	Adverse Event
CACE	Complier Average Causal Effect
CDC	Centres for Disease Control and Prevention
CONSORT	Consolidated Standards Of Reporting Trials
CRF	Case Report Form
DMEC	Data Monitoring and Ethics Committee
NPWT	Negative Pressure Wound Therapy
RCT	Randomised Controlled Trial
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SSI	Surgical Site Infection
SWHSI	Surgical Wound Healing by Secondary Intention
TMG	Trial Management Group
TSC	Trial Steering Committee
WHQ	Wound Healing Questionnaire
YTU	York Trials Unit

3. Design

SWHSI-2 is a pragmatic, multicentre, cross-surgical speciality, two-arm, parallel group, randomised controlled, superiority trial. Eligible patients with a surgical wound that is left to heal by secondary intention (a SWHSI) will be enrolled into the trial. Negative pressure wound therapy (NPWT, a type of wound dressing) is often used in the management of SWHSI. Participants will be randomised to one of two arms for treatment of their SWHSI: NPWT or usual care. Usual care may include use of other health technologies and dressing types but should not include NPWT. For participants with more than one SWHSI, the largest will be identified (the reference wound) and used for assessment of outcomes.

The study includes an internal pilot phase to assess recruitment assumptions and optimise trial processes.

Recruitment commenced on 14th May 2019 and the first participant was randomised on 15th May 2019. The study initially had a 24-month recruitment period, including an internal pilot followed by the main recruitment period. However, due to the COVID-19 global pandemic, and in agreement with the Sponsor and funder, recruitment at sites was paused for approximately four months on

23rd March 2020. Recruitment recommenced on 28th July 2020 and is currently on-going (planned end 31st December 2022).

The trial also includes two embedded studies within a trial (SWATs) to assess the effectiveness of strategies to improve recruitment (infographic plus participant information sheet (PIS) vs PIS only) and retention (thank you card sent between follow-up time points vs no card). These were funded by the MRC PROMETHEUS Programme (MR/R013748/1). Analysis of these SWATs are detailed in appendices to this SAP.

Full details of the background and design of the trial are presented in the published protocol (Chetter et al. 2021).

4. Trial Objectives

4.1 Primary objective

The aim of the trial is to assess the clinical and cost-effectiveness of Negative Pressure Wound Therapy (NPWT) when compared to usual care (no NPWT) in treating surgical wounds healing by secondary intention. We will undertake a parallel group randomised controlled trial (RCT) to test the hypothesis that NPWT is superior to usual care (no NPWT) in treating SWHSI based on time to healing in days from randomisation.

4.2 Secondary objectives

1. To include a six-month internal pilot phase to obtain robust estimates of recruitment rates and confirm trial feasibility.
2. To evaluate the effectiveness of NPWT for the treatment of SWHSI in terms of the secondary outcomes of key clinical events (hospital admission or discharge, treatment status, reoperation, amputation, antibiotic use and death), wound infection and wound pain.
3. To conduct a detailed economic evaluation to compare the cost-effectiveness of NPWT to usual care (no NPWT) to determine the most efficient provision for future care and resources (this analysis will be detailed in a separate Health Economic Analysis Plan and not discussed further here).

5. Follow-up

Participants will receive weekly clinical follow-ups for the purposes of the study and will be asked to complete participant self-reported questionnaires at three, six and 12 months post randomisation (Table 1).

Table 1: Schedule of Assessments

TIMEPOINT	**Pre-randomisation/ baseline**	**Randomisation**	**Weekly Telephone Contact to point of healing**	**Postal Questionnaire 3-month post-randomisation**	**Postal Questionnaire 6-month post-randomisation**	**Postal Questionnaire 12-month post-randomisation**	**Post Healing Assessment visits (x3)**
ENROLMENT							
Eligibility screen	X						
Informed consent	X						
Baseline questionnaire	X						
Allocation		X					
ASSESSMENTS							
Wound Healing			X				X
Wound Photographs	X						X
Dressing Changes			X				
Clinical Events			X				
Adverse Events			X				
Bluebelle WHQ	X			X	X	X	X
CDC Assessment							X
EQ-5D-5L	X			X	X	X	
Pain (VAS)	X			X	X	X	
Resource Use	X			X	X	X	

5.1 Weekly Telephone Follow Up

Randomised participants will be contacted weekly via telephone, on a pre-agreed day and time, to assess:

- Wound healing (defined using the commonly used and clinically certified criteria 'complete epithelial cover in the absence of a scab (eschar)'). Participants will be asked if a healthcare professional has indicated that their reference wound has healed. If the participant believes the wound is healed, but this has not been confirmed by a healthcare professional, the research nurse will seek confirmation/further information from the clinical team.
- Clinical events (inpatient admission and discharge, wound infection and return to theatre for further treatment)
- Treatment status (dressing type used, number of changes, where dressing care is provided)
- Adverse events

Information collected will be recorded in a case report form (CRF). These assessments are mostly conducted by a research nurse from the site but can be completed by members of the research team at YTU (from April 2020 to ease the burden on sites caused by COVID-19). The name of the person completing the assessment is recorded on the CRF.

5.2 Post Healing Follow Up

When the participant reports that their clinician or nurse has indicated that their wound is healed, clinical assessments will be completed with the participant on three consecutive weeks. The first healing visit will be completed, ideally within 48 hours of confirmation of healing, by the research nurse to the participant at home, or in a clinical care setting if preferred. A standardised photograph will be taken at the initial healing visit for blinded outcome verification. Subsequent healing visits (weeks two and three) may then be completed by telephone, if preferred, to confirm continued wound healing.

Where healing is still confirmed after the three visits, participants will cease weekly assessments, and the photo taken at the initial healing visit will be subsequently assessed by the blinded outcome assessors for healing verification. However, where the wound reopens or healing becomes in doubt during this time, the participant will return to weekly assessments until healing is once again confirmed. Participants remain in follow-up for participant questionnaires at three, six and 12 months regardless of their healed status unless they specifically request to be withdrawn from follow-up.

Where the first healing visit cannot be completed face to face, for example due to participants having moved locality during the study or due to local or national COVID-19 restrictions, a video consultation will take place with a screen shot being taken of the wound. Where video consultation is not possible, telephone consultation will take place and participants will be asked to take and return a photograph of the wound themselves. Study specific instructions will be provided to the participant, and they will be encouraged to ask a friend or relative to assist with this should the wound location mean it is difficult for them to take a photograph independently. If a photograph cannot be obtained, the reason for this will be recorded.

Where a member of YTU has conducted the weekly assessments for a participant, as opposed to a research nurse, then YTU will continue to conduct the post-healing assessments. These will be conducted remotely via telephone.

The Wound Healing Questionnaire (WHQ) will be completed, and a Centres for Disease Control and Prevention (CDC) assessment performed by the research nurse face to face at the initial assessment visit following wound healing. The CDC assessment will ask how many wound infections the participant has had during the trial, the start date of each infection, and which clinical features were present for each infection. However, where the initial healing visit is conducted remotely by YTU staff, a CDC assessment of the wound is not possible.

5.3 Participant Questionnaires

Participants will also be followed up by postal questionnaire, sent by YTU, at three, six and 12 months post randomisation to assess:

- Surgical site infection (Bluebelle WHQ (Bluebelle Study Group, 2019))
- Pain (using a Visual Analogue Scale)
- EQ-5D-5L
- Resource use

Where no response is provided to a questionnaire, a reminder letter will be sent to the participant after two weeks to encourage completion and return of the questionnaire; that has been shown to increase the likelihood of response. Where no further response is obtained, the participant will be contacted by telephone (up to three attempts) to collect questionnaire data.

Use of incentives have been found to be effective in facilitating the return of postal questionnaires. We will therefore include a monetary incentive of £5 with both the six and 12-month questionnaires. Participants will be pre-notified of this unconditional token in the letter that accompanies their initial questionnaire (at three months).

Postal follow-up was not possible for a time during the COVID-19 pandemic (from 1st April 2020) and so follow-up was conducted remotely (over the telephone) by members of the YTU research team. At least three telephone contact attempts were made to collect data. Postal follow-up recommenced in August 2020; however, telephone follow-up remains in use for participants who fail to respond to postal questionnaires.

5.4 12-Month Resource Use Questionnaire

A study investigator (site principal Investigator or a delegated member of staff) will complete a CRF for each participant to collect medication and health service use data (hospital admissions, outpatient appointments, A&E visits, use of hospital transport) over their 12-month trial follow-up. In addition, for participants who withdraw from weekly clinical assessment during the study but continue to consent to their medical records being accessed, this form will collect healing data.

6. Outcomes

6.1 Primary outcome

The primary outcome is time to healing in days from randomisation. The date of healing will be taken as the date healing of the reference SWHSI is confirmed by a healthcare professional. This will be elicited by the research nurse and recorded on the Weekly Assessment CRF. Where a date cannot be elicited, the date of the Weekly Assessment will be taken as the date of healing.

In addition, there may be participants who withdraw from weekly clinical assessments before healing (but who still consent for their medical records to be accessed) for whom healing (with a healing date) is reported on their 12-Month Resource Use CRF.

6.2 Secondary outcomes

Secondary outcomes are:

- *Healing as verified by blinded outcome assessment* will be a secondary outcome. Blinded outcome verification is crucial for studies with subjective outcomes such as healing and infection. The photograph taken at the initial healing visit will be used by clinically experienced, independent, blinded assessors to confirm reference wound healing, and details of these assessments will be recorded on the Blinded Outcome Assessment CRF.

  Each photograph will be assessed by three reviewers, who will report whether they think the wound is healed (yes, no, unsure). Where there is consensus among the three, this decision will be reported as the final outcome. However, where there is discordance, the three reviewers will be asked to reassess the photo. If there is consensus after this second review then this decision will be recorded as the final outcome. Where there is still discordance, then the majority view will be taken. It is possible that even after second review the outcome will be 'unsure'; we will attempt to ascertain the reason why the 'unsure' option was used.

  Assessors will be asked whether they think they know what treatment the participant received based on the photograph, and if yes, to indicate what treatment they believe the participant received.

- *Clinical events* including antibiotic treatment, hospital admission or discharge, treatment status (including reasons for dressing or treatment failure or change), re-operation (including skin grafting and closure surgery*), wound infection, amputation and death.

**The decision for closure surgery will be made blinded to treatment allocation as far as possible. Where this is not possible, details on whether the clinician was aware of the treatment allocation and reasons for unblinding will be recorded where given.*

- *Wound infection*: Assessed using the Bluebelle Wound Healing Questionnaire (WHQ). The questionnaire includes items to assess signs, symptoms and wound care interventions indicative of surgical site infection (SSI) and can be completed by patient self-report or by

healthcare professionals. The WHQ will be completed by the participants at baseline, three, six and 12-months and also at the initial healing visit. The original 18-item WHQ (developed and validated for patients with closed surgical wounds) was modified for this trial for relevance to patients with open wounds by removing three items relating to spontaneous or deliberate wound dehiscence and use of dressings since these would not be relevant in this population. Modifications also included the recall period for participants to consider when completing the questionnaire to reflect the time period since the participant had first had their open wound (for the baseline and initial post-wound healing assessments), or since the last WHQ questionnaire was completed (for the three, six and 12-month assessments) rather than the time since hospital discharge used in the original version of the WHQ. The modified WHQ used in this study consists of: nine items scored 0=”Not at all”, 1=”A little”, 2=”Quite a bit”, and 3=”A lot”; and six items scored 1=”Yes” and 0=”No”. A WHQ total score can be obtained by adding the item scores together, providing a possible range of scores between 0 and 33. A lower score represents a better wound healing outcome.

There are currently no specifications on how to deal with missing item data when calculating a WHQ total score. So far, analyses (e.g. Bluebelle study) have only included participants with 'valid' total scores - i.e. where all items were completed - primarily because there has been very little item-level missing data. However, in this study, we will explore approaches to deal with missing item-level data (see Section 10.9).

The WHQ has been validated for primary closed wounds in a cohort of 800 patients receiving abdominal surgery. Inclusion of a modified version of the WHQ in this study will provide valuable validation data for its use in patients with SWHSI. A reference surgical site infection (SSI) assessment using the CDC classification for SSI will be collected as part of the WHQ validation. This will be performed for each participant by the research nurse face to face (after the participant has completed the WHQ) at the initial assessment visit following wound healing (not possible during remote consultations).

- *Pain*: A visual analogue scale will be used to assess wound pain (with anchors 0 ‘no pain’ and 10 ‘worst imaginable pain’). The visual analogue scale will be completed by the participants at baseline, three, six and 12 months.

- *Quality of Life:* The EQ-5D-5L generic instrument will be used to collect information on quality of life, consistent with NICE recommendations. The EQ-5D-5L measures health related quality of life in terms of five dimensions: mobility, ability to undertake usual activities, pain and discomfort, anxiety and depression. The EQ-5D-5L will be completed by the participants at baseline, three, six and 12 months. Analysis of this outcome forms part of the health economic evaluation and so is not detailed in this SAP.

- *Resource use:* Wound related NHS consultations, support (e.g. occupational therapy) and out of pocket costs will be collected using a patient reported questionnaire at baseline, three, six and 12 months. Details of wound dressing changes (frequency and type) will be collected at weekly follow up and details of medications prescribed and secondary care visits will be

collected retrospectively at 12 months using the 12 Month Resource Use CRF. Analysis of this outcome forms part of the health economic evaluation and so is not detailed in this SAP.

6.3 Other collected variables

Baseline data

The following data will be collected at baseline via the Baseline Investigator CRF: patient demographics (date of birth, gender, ethnicity), body mass index, comorbidities, smoking status, alcohol intake, concomitant medications, surgical procedure details (e.g. type, date, urgency, contamination level), details about the SWHSI (number, previous history, clinical features, size, current treatment), and a wound photograph.

The primary location of the wound is recorded on the screening form.

Wound size (area) and location are used as stratification factors in the randomisation (see Section 9), and therefore will be included as covariates in the primary, and other, analysis (see Section 11). Wound area is dichotomised as $<28cm^2$ or $\geq 28cm^2$ for the purposes of randomisation; however, in order not to lose information, this variable will be included in its continuous form as a covariate. Wound location is categorised as: foot, leg, abdomen or other, for the randomisation and the variable in this form will be used as a covariate for the analysis. We collect more granular detail on the location, e.g. head, neck, arm, etc, but this will be too many categories for use in the analysis.

Treatment received

Any and all treatment received by the participant for their SWHSI will be recorded in the Treatment Delivery CRF and the Weekly Assessments, including details of usual care, NPWT, and other/concurrent treatments.

For participants allocated to receive NPWT, this should ideally be started within 48 hours of randomisation. Time elapsed between date of randomisation and start of NPWT will be calculated. Where this is over 48 hours, the reason for treatment delay is obtained:

- NPWT machine unavailable
- NPWT pump on order
- Trained staff member unavailable
- Patient unwilling to wait for treatment prior to discharge
- Patient moving to different care provider
- Other

Other NPWT details recorded are: type of machine, amount and type of pressure applied, type of NPWT dressing, whether a liner was used with the dressing, and if so whether it was silver impregnated. Any changes to any of these elements of NPWT treatment made throughout follow-up are recorded.

The type of usual care treatment and any other treatment received, and any changes made to this throughout follow-up, are recorded.

Reasons for change from or to allocated treatment will be reported as:

- Wound improving

- Wound healed
- Wound bed prepared
- Wound too dry
- Deterioration of wound
- Failure to maintain seal
- Treatment caused pain
- No change to wound
- Other

Participants will be classed as crossing-over between treatments if:

- They are allocated to usual care but receive NPWT for their SWHSI at any point during follow-up; or
- They are allocated to receive NPWT but do not receive this at any point during follow-up.

Adverse events

Adverse event (AE) data will be collected and should be entered onto the AE reporting form and reported to YTU within five days of discovery or notification of the event. Serious Adverse Events (SAE) should be entered onto the SAE reporting form and reported to YTU within 24 hours of discovery or notification of the event. Once received, causality and expectedness of SAEs will be confirmed the Chief Investigator or another clinical member of the trial management group if the Chief Investigator is unavailable. Definitions of AEs and SAEs can be found in the trial protocol.

AEs that might be expected with these wounds include minor wound infection, cellulitis, maceration and retention of product in the wound. For the purposes of the SWHSI-2 trial, hospitalisation for the treatment of major wound infection, osteomyelitis, wound bleeding, fistulation, for removal of embedded wound filler and for limb amputation, will not be considered a SAE but will be reported using the AE form.

7. Sample Size

A conservative estimate of a 25% decrease in median time to healing, assuming a median time to healing of 86 days in the usual care group, between the two treatment groups will be sought. This equates to a 21-day reduction in time to healing to 65 days in the NPWT group.

To detect a 25% reduction in median time to healing (from 86 days with usual care to 65 days with NPWT), with 90% power, and allowing for 20% attrition (Chetter, 2019; Armstrong, 2005; Blume, 2008), 696 participants are required to be recruited and randomised (348 NPWT; 348 usual care).

The 25% reduction in time to healing used here, has been selected on the following basis:

- Cost-effectiveness: Models generated using observation data obtained in our previous cohort study suggest a 57.4% difference in time to healing would be required to demonstrate cost-effectiveness of NPWT (Saramago, 2020). This should however be interpreted with caution given this is derived from observational data.

- Current literature: The average median time to healing in the control group of previous observational and RCT studies is 86 days, with an average decrease in time to healing of 25% (Armstrong, 2005; Monsen, 2014; Biter, 2014; Danne, 2017).
- Significance to patients: Patients are frequently disappointed by the slow healing process of a SWHSI and complete wound healing is therefore a major focus for patients (McCaughan, 2018). Patient representatives have confirmed that the proposed reduction in time of 21 days with NPWT is likely to be significant for patients.

The proposed attrition rate used here, is derived from rates observed in previous studies: RP-PG-0609-10171 cohort study (n=66/393, 16.8%); Armstrong et al (n=38/162, 23%); and Blume et al (n=103/341, 30%).

Sample size calculations were conducted in STATA v.15.

8. Randomisation, allocation concealment and blinding

Once informed consent has been obtained, baseline data will be collected. Where patients are screened pre-operatively, consent will be obtained pre-operatively and randomisation completed either in theatre or post operatively.

A delegated member of the research team will then contact YTU by telephone, or via the internet, to access a secure randomisation service. The randomisation service will record information and check eligibility to avoid inappropriate entry of patients into the trial.

Participants will be randomised 1:1 (NPWT: usual care), using block randomisation, with variable block sizes, stratified by wound location (foot (i.e. hind, mid or fore foot areas) and ankle), leg (i.e. upper leg, lower leg and knee), abdomen, other), wound area (<28cm^2, ≥28cm^2), and study site. The allocation schedule was generated by trial statistician, Caroline Fairhurst, using the *ralloc* command in Stata v15.

Neither patients nor health care practitioners will be blinded to treatment allocation as the treatments cannot be adequately concealed. The primary outcome will however be verified by independent, blinded observers using standardised photographs.

9. Analysis of internal pilot trial/phase

The first six months of recruitment will constitute an internal pilot phase and will be evaluated on the following predefined criteria to ascertain our ability to recruit and randomise:

1. To set up at least 10 sites
2. To randomise 100 patients (on average, one to two patients per site per month)
3. 80% of patients to receive intervention within 48 hours of randomisation
4. Feasibility of follow up (>80% response rate to three-month questionnaire)

Recruitment assumptions and intervention rate will be assessed initially at three months, and again at six months. Feasibility of follow up and preparing of study sites to open for recruitment will be completed at six months to allow sufficient data to be collected.

Assumptions will be assessed against pre-defined ‘traffic light’ stop go criteria:

- Green: Recruitment and intervention rate > 80%; Nonresponse to three month questionnaire ≤15%
- Amber: Recruitment and intervention rate 60 - 80%; Nonresponse to three month questionnaire 15-20%
- Red: Recruitment and intervention rate <60%; Nonresponse to three month questionnaire >20%

Findings from internal plot phase

Data, correct as of 03/01/2020, were used to evaluate the progression criteria. Analyses were descriptive only, with no formal hypothesis testing:

- 12 sites were open to recruitment. This exceeded the target for site set up (10 sites) and therefore put the trial in the 'green' range (>80%) for this criterion.
- 63 participants had been randomised. While this was put the trial in the 'amber' (60-80%) range for this criterion, the observed average recruitment rate per site per month was 1.07, which was on target.
- 27 participants had been randomly allocated to the NPWT group, of which 26 (96.3%) received NPWT within 48 hours of randomisation. This put the trial in the 'green' (>80%) range for this criterion.
- 29 participants had reached the three-month time point, of which 13 (44.8%) had completed the 3-month CRF which put the trial in the 'red' range for this criterion (>20% non-response); however, only 21 participants would have received and been expected* to have responded by 03/01/2020, giving a response rate of 61.9%.

*A CRF would not be expected to have been returned if a participant has died within the three month period or if the participant had only been sent their postal questionnaire in the past 4 weeks (to allow time for completion).

The funder was satisfied that the trial was viable and agreed continuation to the main trial phase.

10. Final analysis

10.1 Analysis software

All analyses will be conducted in STATA v17 (StataCorp, 4905 Lakeway Drive, College Station, Texas 77845 USA), or later (to be confirmed in final report).

10.2 Analysis principles and populations

Analyses will follow the principles of intention-to-treat with participant's outcomes analysed according to their original, randomised group, where data are available, irrespective of deviations based on non-compliance. During recruitment, there were a few instances of participants being randomised more than once in error, mainly because the research nurse was not sure the first randomisation had been successful. In such instances, the first allocation was used and the other

allocations were withdrawn. These will technically count as randomisations but the duplicates will be excluded from all summaries and analyses thereafter.

Statistical tests will be two-sided at the 5% significance level and parameter estimates will be presented with 95% confidence intervals (CIs) and p-values as appropriate.

10.3 Screening, eligibility, recruitment and follow-up data

The trial will be reported according to the CONSORT (Consolidated Standards of Reporting Trials Statement) guidelines for a parallel group RCT. The flow of participants through each stage of the trial, including reasons for non-eligibility/non-participation where available, will be presented in a CONSORT diagram.

The number of sites recruited and patient recruitment by site will be summarised. The average recruitment rate per month, and per site per month, will be presented. Recruitment graphs presenting the overall recruitment by month, and the actual vs target recruitment will be produced.

For each time point (three, six and 12 months), the number (%) of participant questionnaires sent and returned/completed with mean days to return/completion (min, max) will be presented by trial arm and overall. The number of questionnaires completed via post or over the telephone will be reported.

The number of weekly assessment visits completed per participant will be summarised as will the frequency of these visits.

The type and timing of withdrawals will be presented overall and by randomised group, with reasons where available.

10.4 Baseline data

Baseline data will be summarised descriptively by trial arm and overall, both as randomised and for those who complete at least one post-randomisation clinical assessment (Dumville, 2006), using descriptive statistics for continuous variables (n, mean, standard deviation, median, minimum and maximum) and count and percentage for categorical variables. Variables used as stratification factors, wound area and location, will be presented both in the way they are categorised for the randomisation (i.e. location: foot, leg, abdomen, other; wound area: $<28cm^2$, $\geq 28cm^2$) and in their more granular forms (i.e. location as head, neck, arm, etc; wound area as continuous variable). No formal statistical comparison of baseline data will be made between the groups.

10.5 Primary analysis

All outcomes will be summarised descriptively by randomised group, including the level of missing data.

Healing rates (recorded as healed or not within 12-month follow-up) will be presented overall and by trial arm. Time to healing will be right-censored at the last point at which the wound is known to still be unhealed i.e. earliest of 12 months post-randomisation, loss-to-follow-up, full withdrawal, death or amputation of the SWHSI. Kaplan-Meier survival curves will be produced for the two groups and the median time to healing with a 95% CI will be presented. If the estimated survivor

function is greater than 0.5 throughout the study then it will not be possible to estimate the median survival time and other percentile survival values (e.g. 25%) will be presented. A proportional hazards Cox regression model will be used to compare the healing times between the two groups, adjusting for wound size at baseline (in its continuous form), duration of wound in days (time between wound start date and randomisation), and wound location (foot, leg, abdomen, other) as fixed effects, and site as a shared frailty effect. The proportional hazards assumption will be assessed by considering plots of the Schoenfeld residuals and the Therneau and Grambsch test. If the assumption is violated for any particular covariate (except treatment group) this variable will be removed in a sensitivity analysis. A hazard ratio (HR) for the treatment effect will be presented with a 95% CI and p-value. HRs for the covariates will also be presented.

Analysis of the primary outcome will be checked by a second statistician before release of results, and recorded in the YTU *F16: Primary Analysis Sign Off* Form.

10.6 Sensitivity analyses

Treatment received – compliance and cross-over

Treatment received for the SWHSI will be summarised by trial arm to assess for compliance with allocated treatment and instances of cross-over. The number and percentage of participants receiving NPWT within 48 hours of randomisation, and at any point throughout follow-up, will be reported, along with reasons for delayed/non application of NPWT. Length of application of NPWT, type of machine used, amount and type of pressure applied and type of NPWT dressing used will be summarised. Details of usual care dressings applied will also be summarised, as will any other treatment received for the SWHSI.

Where there are changes to the treatment received throughout the follow-up, these will be reported with reasons for change.

To assess the impact of compliance on the primary outcome we will consider a Complier Average Causal Effect (CACE) analysis that will produce an unbiased estimate of the treatment effect in the presence of non-compliance (defined as participants in the NPWT group who do not receive NPWT). Participants in the standard care group who receive NPWT will be considered as a cross-over.

In addition, we will investigate the effectiveness of NPWT treatment alone, in the absence of switching, using a method called the iterative parameter estimation algorithm (Branson and Whitehead, 2002; Morden, 2011), which is an extension of the rank preserving structural failure time models developed by Robins and Tsiatis (Robins and Tsiatis, 1991; White, 2002; White, 1999).

Stratification errors

There have been at least two instances where participants have been randomised using the incorrect strata for their wound size, e.g. their wound size is less than 28cm^2 but they were randomised in the strata for ≥28cm^2. This will have negligible impact on the randomisation and does not impact the primary analysis since we are including wound size in its continuous form rather than dichotomised. However, if we find that any wound locations have been incorrectly specified (e.g. randomised as if on the foot, when actually it is on the leg) then we shall conduct the primary analysis using the classification used for randomisation, but repeat the analysis as a sensitivity where the classification is corrected (taken from screening CRF).

Death and amputation as competing events

The primary analysis will be repeated treating death and amputation (which removes the reference SWHSI) as a competing risk, rather than censoring at these events. This will be conducted using the *stcrreg* command in Stata which implements competing risks regression based on Fine and Gray's proportional subhazards model.

Baseline imbalances

During recruitment, a chance imbalance in the proportion of participants who are current smokers and in alcohol consumption was noted in baseline data between the randomised groups (based on visual observation rather than formal comparison testing). Should this imbalance still be seen at the end of recruitment, the DMEC recommended that a sensitivity analysis be considered for the primary outcome, in which the primary analysis is repeated additionally adjusting for current tobacco smoking status and consumption of alcohol. It will be made clear in the publication of results that this analysis was planned based on sight of accumulating baseline data.

10.7 Subgroup analyses

A subgroup analysis shall consider previous history of SWHSI. The primary analysis model will be repeated but additionally including a covariate for previous history of SWHSI (dichotomous, Yes/No) and an interaction between this factor and treatment allocation.

10.8 Analysis of secondary outcomes

Blinded outcome assessment of healing

There may be a small number of instances where healing is considered following the post-healing visits, and so weekly assessments cease, but the final decision based on blinded outcome assessment is one of not healed or unsure (or where there is no photo available). Details of the blinded outcome assessment will be summarised including whether or not the independent assessors thought they could tell which treatment the participant had received and if so whether they were correct in this. Level of agreement between the independent assessors will be reported. For any instances where a blinded outcome assessment was completed and the assessor judged that the wound had not healed or that they were unsure, reasons for this assessment will be summarised.

The primary analysis will be repeated considering as healed only wounds that are verified as 'healed' by blinded outcome assessment. Other wounds treated as healed in the primary analysis will be censored at the healing date in this analysis.

Wound healing questionnaire at three, six and 12 months

The WHQ total scores at three, six and 12 months will be analysed using a covariance pattern mixed model incorporating all time points. Time, trial arm, time-by-arm interaction, baseline WHQ score, wound size at baseline, duration of wound in days, and wound location will be specified as fixed

effects. Participant and site will be random effects to model the correlation of the repeated measures across time by participant, and the clustering of participants within site. The different covariance structures for repeated measurements that are available as part of the analysis software will be applied to the model. The most appropriate pattern will be used for the final model based on diagnostics including Akaike's information criterion (smaller values are preferred). Estimates of the adjusted mean difference between trial arms in WHQ total scores will be extracted for all time points and overall with 95% CIs and p-values. Model coefficients for the covariates with 95% CIs will additionally be presented to aid understanding of the fitted model. Participants will only be included in the model if they have full data for the baseline covariates and a valid WHQ total score for at least one post-randomisation time point. Depending on the degree of item-level of missing data, models will be compared for WHQ total scores with and without imputed data (see Section 10.9). Model assumptions will be checked as follows: the normality of the standardised residuals will be checked using a QQ plot, and homoscedasticity will be assessed by means of a scatter plot of the standardised residuals against fitted values. If the model assumptions are in doubt, transformations of the outcome data will be considered in sensitivity analyses. A log transformation will be tried in the first instance, and then others as suggested by the Stata ladder command as appropriate.

Wound pain at three, six and 12 months

Pain scores at three, six and 12 months will be analysed in the same way as described for the WHQ, except baseline WHQ score will be swapped for baseline pain score as a covariate.

Wound healing questionnaire at initial healing visit

WHQ score will also be recorded at the initial healing visit. For those participants for whom healing is subsequently verified by blinded outcome assessment we shall compare this WHQ score (scored with and without imputing missing item-level data, see Section 10.9) between the NPWT and usual care groups using a linear mixed effects regression model adjusting for baseline WHQ score, wound size at baseline, duration of wound in days, and wound location as fixed effects, and site as a random effect. The WHQ score at healing will also be used to validate the WHQ for patients with SWHSI – see Section 10.9.

Key clinical events

The number and percentage of key clinical events will be reported by trial arm:

- hospital admission
- reoperation
- amputation
- wound infection
- antibiotic use
- death

Where there are at least five events in each arm, these outcomes will be compared between the groups using a mixed effect logistic regression model adjusting for wound size at baseline, duration of wound in days, and wound location as fixed effects, and site as a random effect.

Infection – CDC

Details of wound infections as collected via the CDC assessment will be summarised by trial arm and overall. This will include the total number of recorded infections, the average number experienced per participant, the time to first infection, and clinical features present.

Amputation

Over the course of their follow-up, participants may undergo an amputation that removes the reference SWHSI. In the primary analysis, the healing will be censored at the date of amputation. If the amputation site is closed, then weekly assessments for the participants will cease. However, if the amputation site is left open to heal by secondary intention, then weekly follow-ups will continue with reference to the new SWHSI until the point of healing or end of follow-up. Details about this extended follow-up with relation to the new SWHSI (following amputation) will be summarised.

10.9 Validation of the modified WHQ for use with patients with SWHSI

WHQ scores at healing will be summarised, along with extent of item-level and total-score missingness. Missing data will be explored to examine whether there are patterns, for example, in the particular items that have been missed. Demographic and clinical characteristics for patients with missing data will be examined. Reasons for non-completion of items, and any other difficulty with completing the WHQ, are being recorded and will be reported. These data will be used as a measure of acceptability and feasibility for using the WHQ in patients with SWHSI. Data will be used, for example, to establish whether there are items that may be difficult for this patient group to answer.

Previous studies to date have concentrated on scoring the WHQ only for participants who have provided a valid response to each item, where a response would be expected. In this study, we will score the WHQ in this way, but will also explore methods for dealing with missing item-level data. The suggested approach would be to impute the mean score of the other available responses: i) for the nine symptom items that are scored 0 to 3, when there are up to four items missing; and ii) for the six yes/no items, when there are up to two items missing.

The following analyses will then be conducted using the two scores and the findings compared:

Internal consistency (the degree of the interrelatedness amongst the items) of the modified WHQ at the post-healing visit will be assessed using Cronbach's alpha; a value greater than 0.7 is considered good internal consistency.

Criterion validity (the degree to which the scores are an adequate reflection of a 'gold standard') of the modified version of the WHQ will be assessed by comparing WHQ scores with the SSI reference standard (CDC diagnosis). A contingency table (cross-tabulation) of participants' WHQ total score and the CDC diagnosis (a generated binary variable indicating 'no wound infection' or 'at least one wound infection experienced') will be examined for participants with complete CDC and WHQ data at the healing assessment timepoint. Data will be used to examine how well the WHQ score discriminates between participants who had or had not experienced a wound infection during the trial. Sensitivity (the probability of correctly classifying a participant as having had an SSI) and specificity (the probability of correctly classifying a participant as not having had an SSI) values for a series of incremental WHQ score cut-off thresholds (dichotomised variables created by a cut-off

score of, for example, less than or equal to seven) will be calculated and plotted on a receiver operating characteristic (ROC) curve. An area under the ROC (AUROC) curve approaching 1.0 is considered to indicate good discrimination with high sensitivity and specificity, whereas a value of 0.5 is interpreted as not being able to discriminate at all. A potential optimal WHQ score cut-off threshold, that is, the threshold where the least number of misclassifications of SSI occur, will be considered.

Changes in total WHQ score at three, six and 12 months will be examined for participants with complete data at these timepoints. It is expected that WHQ scores will improve (i.e. be lower) as the wound heals.

10.10 Adverse events

Serious and non-serious adverse events (and follow-up of these) will be summarised by trial arm and overall, including details of the event, action taken, time to onset, length of event, outcome, relationship to study treatment, and expectedness.

10.11 Planned formal interim analyses

There are no planned formal interim analyses of clinical outcomes. Analysis of feasibility outcomes were analysed following an internal pilot trial (see Section 9).

11. SAP amendment log

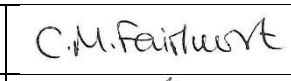
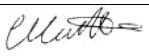
Please note all changes that are made to the Statistical Analysis Plan following initial sign-off in the box below. Include details of the changes made, any notes/justification for these changes, the new version number if applicable, who the changes were made by, and the date.

Amendment/addition to SAP and reason for change	New version number, name and date
SAP completed and signed-off	*V1.0, A.N.Other, xx/xx/xxxx*
Adjusted primary analysis by factor X - Recent evidence from literature that X associated with treatment response (ref)	*V1.1, A.N.Other, xx/xx/xxxx*

12. Signatures of approval

Sign-off of the final approved version of the Statistical Analysis Plan by the Chief Investigator, trial statisticians and trial manager are detailed here.

Name	Trial Role	Signature	Date
Kalpita Baird	Statistician	Kalpita Baird	14/12/2022

Caroline Fairhurst	Senior Statistician		14/12/2022
Catherine Hewitt	Deputy Director, YTU		14.12.22
Catherine Arundel	Trial Manager		14.12.22
Ian Chetter	Chief Investigator		20.12.2022

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14. Appendices

SWATs

Infographic SWAT for recruitment

To supplement recruitment, a SWAT testing an infographic to aid recruitment is nested within the SWHSI-2 trial. This SWAT will evaluate the effects of presentation of the study design to participants on recruitment rate. Participants will be cluster randomised (at the site level) to receive an infographic (visual document explaining the study) plus the standard PIS or just the PIS.

Minimisation will be utilised to allocate sites based on the following factors: (i) whether the site is recruiting cross specialty or in a single specialty and (ii) expected number of eligible participants as reported on the site feasibility assessment cut at the median (≤7/>7).

The primary outcome of the recruitment infographic SWAT will be the recruitment rate, i.e. the proportion of participants in each group who are randomised into the host trial. Secondary outcomes will be the proportion of patients in each group who are screened but do not go on to be randomised, and the cost-effectiveness of the intervention.

Thank you card SWAT for retention

Participants will be individually randomised 1:1 to either receive a thank you card at months four and nine following recruitment or to receive no thank you card at these time points using block randomisation stratified by host trial treatment arm, using randomly varying block sizes.

For the retention thank you card SWAT, the primary outcome will be questionnaire response rate, i.e. the proportion of participants who return their completed questionnaires at month six and 12 follow-up in each group. Secondary outcomes will be whether a reminder notice is required, completeness of response and cost of the intervention per participant retained.

Analyses

For both SWATs, logistic regression will be used to assess the difference in binary outcomes, e.g. recruitment and retention rates. Factors used in the minimisation will be included as fixed effects in the analysis models for in the recruitment SWAT, with main trial allocation being adjusted for in the retention SWAT. For all analyses, site will be included as a random effect. The difference in costs per recruited and retained participants will be calculated, including direct and indirect costs where applicable.

Results and dissemination

The recruitment SWAT will be analysed following the completion of recruitment, with the aim to submit the results for publication before the end of follow-up for the main trial. The retention SWAT will be analysed at the same time as the main trial analysis. Results will be summarised in the funders' report and also written up for publication in a peer-reviewed journal article.