A pragmatic, multicentre, randomised controlled trial to assess the clinical and cost effectiveness of negative pressure wound therapy versus usual care for surgical wounds healing by secondary intention (SWHSI-2)

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Note: All site Principal Investigators and delegated staff must sign their relevant Training Log and be clearly identified on the site Delegation of Authority and Signature log before commencing work on the SWHSI-2 trial.

Amendment History

Amendment No.	Protocol Version No.	Date issued	Author(s) of changes	Details of Changes made
Pre Approval	1.1	21.03.19	Catherine Arundel	- Change to Inclusion criteria relating to participant age. Reduced from 18 years to 16 years at request of the approving Research Ethics Committee
	1.2		Catherine Arundel	- Clarification on derivation of sample size - Clarification to exclusion criteria - Addition of details of engagement with sites - Addition of wound photograph at Baseline - Removal of CDC assessment at 3 months, in selected sites

Contents

1. Abbreviations

AE	Adverse Event
CACE	Complier Average Causal Effect
CI	Chief Investigator
CONSORT	Consolidated Standards of Reporting Trials
CRF	Case Report Form
DMC	Data Monitoring Committee
EQ-5D-5L	EuroQol 5 dimension 5 level questionnaire
GCP	Good Clinical Practice
GP	General Practitioner
HTA	Health Technology Assessment Programme
ISF	Investigator Site File
KCI	Kinetic Concepts
LPLV	Last Patient Last Visit
MRC	Medical Research Council
MUST	Malnutrition Universal Screening Tool
NHS	National Health Service
NICE	National Institute for Health and Care Excellence
NIHR	National Institute for Health Research
NPWT	Negative Pressure Wound Therapy
PAG	Patient Advisory Group
PI	Principal Investigator
PPI	Patient and Public Involvement
PIS	Patient Information Sheet
RCT	Randomised Controlled Trial
REC	Research Ethics Committee
SAE	Serious Adverse Event

SSI	Surgical Site Infection
SWHSI	Surgical Wounds Healing by Secondary Intention
TMF	Trial Master File
TMG	Trial Management Group
TSC	Trial Steering Committee
WHQ	Wound Healing Questionnaire
YTU	York Trials Unit

2. Background and Rationale

2.1 Background

More than 10 million surgical operations are performed in the NHS every year (1). Wounds are usually closed by apposing the wound edges - “healing by primary intention”. When closure is not possible, or when primarily closed wounds break down (dehisce), they are usually left open to heal from the bottom up, through formation of granulation tissue - “healing by secondary intention”.

Surgical wounds healing by secondary intention (SWHSI) are a common, complex problem. A recent survey estimated the UK prevalence of SWHSI to be 4.1 per 10,000 population, and identified colorectal, plastics and vascular as the surgical specialities most commonly associated with SWHSI (2).

Treatment of these wounds presents a significant financial burden to the NHS, with costs of SWHSI estimated to be £1,060 per patient, before inclusion of treatment costs. The healing pathway of SWHSI patients is often prolonged and complex with a variety of treatment options, ranging from basic, relatively inexpensive wound dressings (around £441 per month) to complex, expensive treatments such as Negative Pressure Wound Therapy (NPWT, around £1,323 per month (3)).

These wounds pose a unique management challenge; they can remain open for many months, may require a multitude of treatments, are highly susceptible to infection, and may require prolonged hospitalisation and/or further operations (4). The healing pathway of patients with an open wound is therefore often prolonged and complex, which has a substantial impact on patient quality of life (5, 6). In a recent cohort study (400 SWHSI patients), the median time to healing was 86 days (95% CI 75 to 130) and in specific wound sites (e.g. foot/leg) the duration was almost double that of wounds elsewhere on the body (7). Infection (32.1%), hospital re-admission (24.7%) and further surgical procedures (16.8%) were all common (7).

SWHSI patients often require frequent dressing changes, and the use of complex expensive treatments like NPWT has increased; from 6% to 29% of SWHSI in a one-year period (8).
NPWT was developed in the 1990s as a treatment for full thickness wounds. The device applies a controlled negative pressure (vacuum) to a wound via a specialist dressing, removing wound fluid into a canister (9). KCI, the manufacturer who pioneered the use of NPWT in their V.A.C® device, claim that the mechanical forces generated by the negative pressure create a wound environment that is conducive to healing by removing infective materials and exudate, reducing oedema and promoting perfusion and granulation (http://www.kci1.com/KCI1/sciencebehindwoundtherapy). NPWT is not anticipated to be used to the point of healing, rather its use is promoted as part of the treatment pathway to reduce the time taken for healing to be achieved.

2.2 Rationale and Justification

Ongoing and previous research has investigated the use of NPWT, in complex chronic and closed wounds, primarily for prevention of surgical site infections (10-15). Despite the increasing number of trials assessing NPWT, there has been limited research evaluating NPWT as a treatment for SWHSI. Recent systematic reviews have identified only three randomised controlled trials (RCTs) assessing NPWT as a

treatment for SWHSI; however, all were small, and with caution advised with regards the interpretation of findings (9, 18).

Two small RCTs comparing NPWT with standard care for SWHSI (combined total n = 69), were identified in a recent Cochrane systematic review (9). The data were poorly analysed and reported, and thus presented uncertain evidence for the effectiveness of NPWT compared with standard care in terms of time to healing. Other data (e.g. adverse events) were also limited (9). One of the two included trials compared NPWT with an alginate dressing in participants with a groin SWHSI following arterial surgery (16). Median time to healing was shorter in the NPWT group (n=10, 57 days, range 25 to 115) than in the alginate dressing group (n=10, 104 days, range 57 to 175). Analysis of time to event data was, however, not undertaken appropriately so was not considered robust. The second trial compared NPWT with silicone dressing in participants who had undergone pilonidal sinus excision (17). Median time to healing was shorter in the NPWT group (n=24, 84 days, range 34 to 349) than in the dressing group (n=25, 93 days range 43 to 264). The review authors urge caution in interpretation of these findings, given it was unclear how the analysis was undertaken. The review concluded that there was no rigorous RCT evidence for the clinical effectiveness of NPWT in the treatment of SWHSI and that potential benefits and harms remain uncertain.

A second Cochrane review of NPWT for treating diabetic foot wounds identified a further RCT of NPWT versus dressings in participants who had a SWHSI following diabetic foot amputation (18). Median time to healing was significantly shorter in the NPWT group (n=43, 56 days, range 26 to 92) than in the dressing group (n=33, 77 days, range 40 to 112) (19). Caution in interpretation was again recommended given this RCT included patients with adequate foot perfusion (therefore not necessarily representative of patients with diabetic foot wounds), was commercially funded, and was deemed to be at risk of performance bias (18).

A further study taking place in Germany (20) to assess the effectiveness of NPWT for abdominal SWHSI has been identified however results are not yet publically available.

Given this evidence, NPWT as a treatment for SWHSI has been introduced into clinical practice without high quality evidence supporting its clinical or cost effectiveness. Given the increasing use of this device in routine care, a full and sufficiently powered randomised controlled trial is essential to evaluate the effectiveness of this treatment for SWHSI. The SWHSI-2 trial has therefore been designed as a pragmatic, multi-centre randomised controlled trial to evaluate the clinical and cost effectiveness of NPWT vs usual care for the treatment of SWHSI.

3. Aims and Objectives

3.1 Aim

To assess the clinical and cost-effectiveness of Negative Pressure Wound Therapy (NPWT) as compared to usual care (no NPWT) in treating surgical wounds healing by secondary intention (SWHSI).

3.2 Objectives

i. To include a six-month internal pilot phase to obtain robust estimates of recruitment rates and confirm trial feasibility.

ii. To undertake a parallel group randomised controlled trial 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.

iii. 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.

4. Trial Design

4.1 Design

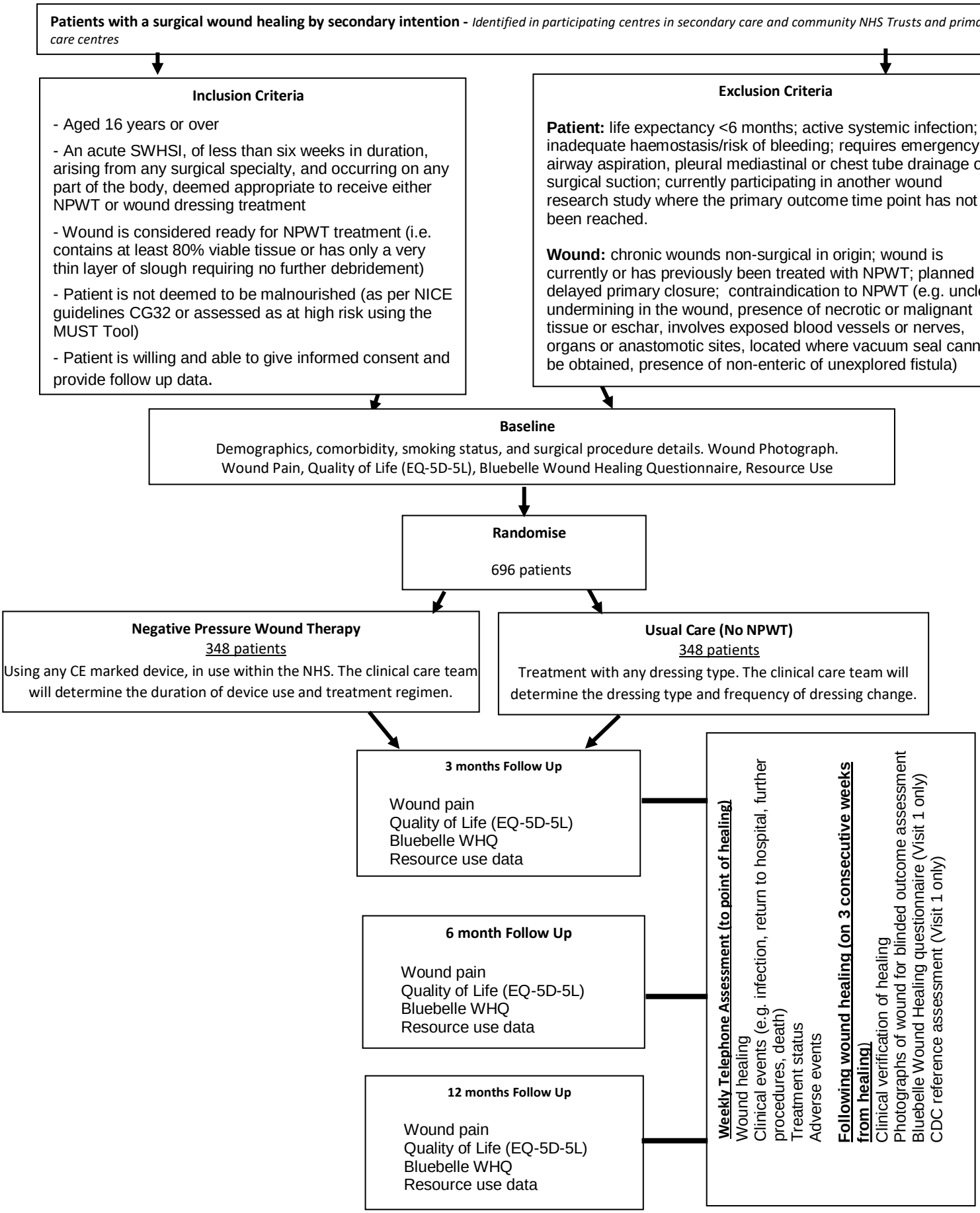
SWHSI-2 is a pragmatic, multi-centre, cross surgical specialty, two-arm, parallel group, pragmatic, randomised controlled, superiority trial. The study includes an internal pilot phase to assess recruitment assumptions and optimise trial processes.

The study has a 24-month recruitment period, including an internal pilot followed by the main recruitment period. Following randomisation, participants will receive weekly clinical telephone follow up and outcome assessments will be conducted at 3, 6, and 12 months post randomisation. A flow diagram demonstrating the patient pathway through the study is provided in Figure 1.

Neither patients nor health care practitioners will be blinded to treatment allocation as the treatments cannot be adequately concealed. The primary outcome (time to healing – defined using the commonly used and clinically certified criteria '*complete epithelial cover in the absence of a scab (eschar)*') will however be verified by independent, blinded observers using standardised photographs.

The trial will be pragmatic: the inclusion criteria will be relevant to a broad range of patients and wounds; NPWT device, wound dressing and co-intervention choices (including but not limited to dressings and wound packing, antimicrobial gels and emollients, and debridement) will be left to the discretion of the clinical care team; and all types of SWHSI will be eligible for inclusion, provided that the patient is otherwise appropriate.

Figure 1 – Study Flow Diagram



4.2 Setting

The study will enlist 20 sites (NHS hospitals, community NHS Trusts and primary care centres) to recruit one to two patients per site per month, over the two-year recruitment period. This rate is based on experience within our recent, feasibility RCT (RP-PG-0609-10171) (21).

We will incentivise participating sites by offering collaborative authorship, for named co-investigators, where recruitment, on average, exceeds one patient per month at that site (22).

We will work closely with participating sites from the outset to engage relevant surgical specialties to promote the study and encourage recruitment activity.

4.3 Outcomes

4.3.1 Primary Outcome

The primary outcome is time to healing in days from randomisation (defined using the commonly used and clinically certified criteria '*complete epithelial cover in the absence of a scab (eschar)*').

Confirmation of wound healing by a health care professional will initially be participant-reported through weekly telephone contact with the research nurse. Participants will be asked to report if their clinician or nurse has indicated that their wound is healed. In the event the participant reports their wound to be healed, but this has not been confirmed by a healthcare professional, the research nurse will contact the clinical care team to obtain this confirmation. Once wound healing has been confirmed by a healthcare professional and treatment has ceased, participants will undergo clinical assessments on three subsequent consecutive weeks during which standardised photographs will be taken of the wound for blinded outcome verification.

Blinded outcome verification is crucial for studies with subjective outcomes such as healing and infection (23). Therefore, time to healing within the SWHSI-2 trial will be verified using photographs by clinically experienced, independent, blinded observers in order to prevent reporting bias. A robust photography protocol, and associated training, will be established to ensure standardisation of imaging throughout the trial.

4.3.2 Secondary Outcome

- 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*), amputation and death.

  * The decision for closure surgery will be made blinded to treatment allocation as far as possible.

- Wound infection: Assessed using the Bluebelle Wound Healing Questionnaire (WHQ) (24).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 tool may be used to assess wounds in hospital or after the patient has been discharged. The WHQ will be completed by the participant themselves at baseline, 3, 6 and 12 month follow up assessments, and will also be completed by the patient at the initial healing visit.

The WHQ has been validated for primary closed wounds in a cohort of 800 patients receiving abdominal surgery (25). Inclusion of the WHQ in this study will provide valuable validation data for its use in patients with SWHSI. A reference SSI assessment (using the Centres for Disease Control and Prevention (CDC) classification for SSI) will be collected as part of the WHQ validation. The research nurse will complete the reference assessment after the participant has completed the WHQ at the initial assessment visit following wound healing.

- Pain: A visual analogue scale will be used to assess wound pain (with anchors 0 ‘no pain’ and 10 ‘worst imaginable pain’).

- Quality of Life: Information on quality of life will be collected at baseline and 3, 6 and 12 months, post randomisation using EQ-5D-5L (26) generic instrument 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.

- Resource use: Wound-related NHS consultations, support (e.g. occupational therapy, in home adaptions) and out of pocket costs will be collected using a patient reported questionnaire at baseline, 3, 6 and 12 months. Details of wound dressing changes (frequency and type) will be collected at weekly follow up.

In addition, epidemiological data including patient demographics (including date of birth, gender, ethnicity), comorbidities, smoking status, surgical procedure details (e.g. urgency, contamination level (27), type), and a wound photograph will be collected at baseline.

5.0 Study Population

We will include all adult patients with a SWHSI who fulfil all of the Inclusion Criteria detailed, and none of the Exclusion Criteria below.

5.1 Inclusion Criteria

1) Aged 16 years or over.

2) Has an acute SWHSI *(i.e. a wound left open as planned following surgery or a wound initially closed using sutures, clips, or other closure methods and dehisced along the whole or part of its length, and of less than 6 weeks in duration)*, arising from any surgical specialty and occurring on any part of the body, deemed appropriate to receive either NPWT or wound dressing treatment.

3) Has a SWHSI that is considered ready for NPWT treatment (i.e. contains at least 80% viable tissue or has only a very thin layer of slough requiring no further debridement).

4) Patient is not deemed to be malnourished, as per NICE guidelines CG 32 (28) (BMI <18.5 kg/m^2 ; unplanned* weight loss >10% in the last 3-6 months; BMI <20kg/m^2 and unplanned* weight loss >5% in the last 3-6 months) or assessed as at high risk of malnutrition using the Malnutrition Universal Screening Tool (MUST) (29).
**Patients with weight loss arising either from underlying comorbidity (e.g. ulcerative colitis) or from the reasons for surgery being completed (e.g. bowel cancer) may be included at the clinician's discretion.*

5) Willing and able to give informed consent and provide follow-up data.

5.2 Exclusion Criteria

1) Life expectancy of less than 6-months e.g. undergoing end stage palliative care.

2) Active systemic infection (including osteomyelitis) at baseline as defined by clinical and/or laboratory assessment. *Note: Patients who have an active infection, but are improving following 1 week's duration of antibiotics may be included at the clinician's discretion.*

3) Inadequate haemostasis or patients who are at risk of bleeding.

4) Chronic wounds non-surgical in origin (e.g. pressure ulcers or foot ulcers*).
*Note diabetic foot ulcers which have been incised and drained, or debrided as an inpatient in theatre may be included given this constitutes a surgical wound

5) Current wound has previously been, or is currently being, treated with NPWT.

6) Planned delayed primary closure of the wound.

7) Contraindication to NPWT including:
   a. Presence of unclear undermining in the wound cavity (i.e. the deepest point of the wound cannot be measured)
   b. Presence of necrotic tissue, malignant tissue or eschar

c. Wounds involving exposed blood vessels and/or organs, anastomotic sites and/or nerves (including the “open abdomen” where the abdominal fascia is open)
d. Wounds situated where, in the opinion of the treating clinician, a vacuum seal cannot be obtained.
e. Presence of a non-enteric or unexplored fistula
f. People requiring emergency airway aspiration, pleural mediastinal or chest tube drainage or surgical suction.

8) Currently participating in another wound research study, where the primary outcome time point has not yet been reached.

6.0 Trial Processes

6.1 Participant Identification and Randomisation

Screening to identify eligible patients for the trial will initially occur in the surgical departments of participating NHS hospitals. Patients may also be recruited from community NHS trusts or primary care settings.

Patients with a potential planned SWHSI (pre-operatively) or a SWHSI occurring at any point following surgery will be screened for potential eligibility by their clinical care team or GP. The research team will work closely with the treating clinicians at each participating site to optimise the local screening and recruitment processes.

Potential participants will be approached with further details of the trial, including an information sheet. This may be completed in person by the surgeon, regular nurse or research nurse during a ward round, routine care or home visit.

It will be clearly stated that the participant is free to withdraw from the study at any time for any reason without prejudice to future care, and with no obligation to give the reason for withdrawal. Should new information arise during the study which may affect a participant's willingness to take part, this will be reviewed for addition to the patient information sheet and a revised consent form will be completed as necessary.

The participant will be allowed as much time as they wish to consider the information, and given the opportunity to question the Principal Investigator, the research team, their GP or other independent parties to decide whether they will participate in the study.

Potential participants will then be shown the consent form and will be given the opportunity to ask questions about the study.

Informed consent will be obtained by a suitably qualified and experienced local research nurse or clinician who has been authorised to do so by the Chief or Principal Investigator, as detailed on the study Delegation of Authority and Signature Log for the study site. The participant must personally sign and date the latest approved version of the informed consent form before any study specific, baseline procedures are performed.

The original signed form will be retained at the study site within the Investigator Site File (ISF); while copies will be given to the participant, retained in the participant's medical notes, and provided to the study coordinating centre.

Once informed consent has been obtained, baseline data will be collected. This includes:

- Surgical Site Infection (Bluebelle Wound Health Questionnaire (WHQ))
- EQ-5D-5L
- Pain (using a Visual Analogue Scale)
- Epidemiological data (e.g. demographics, comorbidities, smoking status, surgical procedure details)
- Wound location and area
- Photograph of the patients wound.

A delegated member of the research team, will then contact York Trials Unit (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. Independent random allocation 1:1 (NPWT:Usual Care), 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 centre will then be completed. Variable block sizes within strata will be used. Treatment will be allocated on an individual named patient basis and the patient started on treatment as soon as possible after randomisation.

Where patients are screened pre-operatively, consent will be obtained pre-operatively and randomisation completed either in theatre or post operatively. Baseline data will be collected post operatively.

6.2 Participant 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 3, 6, and 12 months post randomisation. Details of assessments are summarised below and in the study procedure summary in Figure 2.

Figure 2 – Study Procedure Summary

	Enrolment	Allocation					
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 Visual analogue scale	X			X	X	X	
Resource use	X			X	X	X	

6.2.1 Weekly Telephone Follow Up

Randomised participants will be contacted weekly by 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)*')
- Clinical events
- Treatment Status
- Adverse events.

Information collected will be recorded in a case report form (CRF). Where a participant cannot be contacted, further contact attempts will be made on the following two consecutive days.

6.2.2 Post Healing Face to Face Follow Up

When the participant reports that their clinician or nurse has indicated that their wound is healed, the research nurse will visit the participant, within 48 hours of the report of healing being made, to confirm that the wound has healed. In the event the participant reports their wound to be healed, but this has not been confirmed by a healthcare professional, the research nurse will contact the clinical care team to obtain this confirmation prior to visiting the participant. Clinical assessments will then be completed with the participant on three consecutive weeks (commencing with the initial healing visit), by the research nurse to the participant at home, or in a clinical care setting if preferred, and photographs taken for blinded outcome verification.

The WHQ will be completed and a CDC assessment will also be performed by the research nurse face to face (after the participant has completed the WHQ) at the initial assessment visit following wound healing.

6.2.3 Postal Questionnaire

Participants will also be followed up by postal questionnaire, sent by York Trials Unit, at 3, 6 and 12 months post randomisation to collect:

- EQ-5D-5L (26)
- Pain (using a Visual Analogue Scale)
- Surgical site infection (Bluebelle WHQ (24))
- Resource use.

Participants will be provided with a freepost envelope to facilitate return of the completed questionnaire to York Trials Unit for processing.

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; this has been shown to increase the likelihood of response (30).

Use of incentives have been found to be effective in facilitating the return of postal questionnaires (30). We will therefore include a monetary incentive of £5 with both the 6 month and 12 month questionnaires. Participants will be pre-notified of this unconditional token in the letter that accompanies their initial questionnaire (at 3 months).

6.3 Participant Withdrawal

Each participant has the right to withdraw from the study at any time without prejudice. In addition, the investigator may advise that a participant be discontinued from the study at any time if the investigator considers it necessary for any reason, however the decision on full withdrawal will remain with the participant at all times.
The reason for withdrawal will be recorded in a CRF. If the participant is withdrawn due to an adverse event, the investigator will complete follow-up visits or telephone calls until the adverse event has resolved or stabilised.

Participants who request to fully withdraw during a study assessment will be asked if they are willing to complete the questionnaires prior to withdrawal. Where a participant fully withdraws outside of a scheduled study visit, completion of further follow up questionnaires will not be requested.

If the participant withdraws consent, they will be asked to confirm the elements they wish to withdraw from i.e. all data collection, postal data collection or telephone data collection. Where a participant requests withdrawal from all or telephone data collection, the participant will be asked if the research team can try to obtain outcome data through contact with healthcare professionals. Where full withdrawal is requested, patients will be asked if they are happy for their personal details to continue to be stored; and if they are happy for anonymised data collected until the time of withdrawal to be kept for study analysis purposes.

Where participants lose capacity to consent during their time in the study, they will be withdrawn from further follow up however data collected until this point will be retained for use. No further data would be collected or any other research procedures conducted in relation to the participant.

6.4 Source Data

Source documents are original documents, data, and records from which participants' CRF data are obtained. These include, but are not limited to, hospital records (from which medical history and previous and concurrent medication may be summarised into the CRF), clinical and office charts, diaries, correspondence, completed scales and quality of life questionnaires.

CRF entries will be considered source data if the CRF is the site of the original recording (e.g., there is no other written or electronic record of data). In this study the CRF will be used as the source document as outlined in the Source Data Verification form.

All documents will be stored safely in confidential conditions. Any paper forms containing participant identifiable information (e.g. patient details form and consent form) will be held in a location separate to the questionnaire data. Identifiable information will be stored securely in a locked filing cabinet, in an office only accessible via registered swipe card access held by the York Trials Unit research team (As per YTU Standard Operating Procedure YT03).

Personal data held electronically, will be stored on the study specific participant management system which will record identifiable information and participant activity to enable study coordination. This will be accessible via individual password. Permissions for access of this information will also be detailed within the study delegation log. The server on which the management system will be housed is secure and is subject to rigorous testing and continued backup.

Photographs collected to record participant wound healing at the three post wound healing assessment visits will be anonymised prior to electronic transfer by sites to the University of York, where they will be stored in an encrypted and password protected drive. All data will be stored in accordance with data protection principles.

On all study-specific documents, other than the signed consent, the participant will be referred to by the study participant number/code, not by name.

7.0 Study Treatments

7.1 Intervention: Negative Pressure Wound Therapy

Negative Pressure Wound Therapy (NPWT) consists of a computer-controlled vacuum pump into which disposable components fit. A disposable, plastic canister slots into the pump to collect wound exudate. The canister is attached to pressure resistant tubing that connects to the wound dressing creating an airtight seal, and is removed and replaced either when it becomes full, or at least once a week.

The wound is filled with a suitable dressing, for example: black, polyurethane foam dressings with reticulated (open) pores to help evenly distribute negative pressure across the wound bed; white, polyvinyl alcohol foam with high tensile strength, pre-moistened with sterile water; and antimicrobial gauze (impregnated with Polyhexamethylene biguanide). The choice of dressing can depend on factors such as the size, shape and location of the wound, the quantity and viscosity of the exudate, availability, patient and professional preferences and experience. To ensure the pragmatic nature of the trial, dressing selection will be left to the discretion of the clinical care team.

Negative pressure or suction is achieved in the wound cavity by using either a drain (flat or channel) or a port connected to the tubing. The wound is sealed with a transparent adhesive polyurethane film. Occasionally a liner is placed in the wound bed prior to the application of foam or gauze to protect vulnerable structures such as blood vessels or organs and prevent dressing adherence.

The device is generally used as part of the SWHSI treatment pathway rather than to the point of healing and is administered by both nurses and clinicians.

The use of any CE marked NPWT device, providing pressure of 60-150mmHg, in use within the NHS will be permitted in this trial, given that the principles of any device are similar and there is no evidence to suggest clinical or cost effectiveness differences between devices. The device will be used in accordance with manufacturer guidance, and the clinical care team, in conjunction with local treatment guidelines, will determine the duration of device use, and whether this includes continuous or intermittent pressure cycles. Treatment regimen and details will be recorded during weekly telephone follow up.

7.2 Control: Usual Care (no NPWT)

Usual care will be that used locally, without NPWT. This is most likely to be other sorts of wound dressings.

Given that there is no evidence to suggest any one dressing is more clinically and cost effective than another (31), use of any dressing type will be permitted. The clinical care team will determine the dressing type (primary and secondary) and frequency of dressing change and details will be recorded will be recorded during weekly telephone follow up.

8.0 Adverse Event Management

8.1 Adverse Events (AE)

For the purposes of the SWHSI-2 trial, adverse events (AE) are defined as any untoward medical occurrence (i.e. any unfavourable and unintended sign, symptom or disease), experienced by a clinical trial participant and which is temporally associated with study treatment (interventions or control) and is related to the wound or to the study intervention or control treatments.

Adverse events, which might be expected with these wounds include minor wound infection, cellulitis, oedema, maceration and retention of product in the wound e.g. wound filler embedding in granulated tissue.

8.2 Serious Adverse Events (SAE)

To ensure no confusion or misunderstanding of the difference between the terms "serious" and "severe", which are not synonymous, the following note of clarification is provided:

The term "severe" is often used to describe the intensity (severity) of a specific event (as in mild, moderate, or severe myocardial infarction); the event itself, however, may be of relatively minor medical significance (such as severe headache). This is not the same as "serious," which is based on patient/event outcome or action criteria usually associated with events that pose a threat to a participant's life or functioning. Seriousness (not severity) serves as a guide for defining reporting obligations.

Serious adverse events are defined as any untoward medical occurrence that:

1) Results in death

2) Is life threatening

NOTE: The term "life-threatening" in the definition of "serious" refers to an event in which the participant was at risk of death at the time of the event; it does not refer to an event that hypothetically might have caused death if it were more severe.

3) Requires hospitalisation or prolongation of existing inpatients' hospitalisation

4) Results in persistent or significant disability or incapacity

5) Is a congenital anomaly or birth defect

6) Any other important medical condition that, although not included in the above, may require medical or surgical intervention to prevent one of the outcomes listed.

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 SWHSI-2 Adverse Event Form.

8.3 Reporting Procedures for Adverse and Serious Adverse Events

Adverse events (AE) should be entered onto the Adverse Event reporting form and reported to York Trials Unit within 5 days of discovery or notification of the event.

Serious adverse events (SAE) should be entered onto the Serious Adverse Event reporting form and reported to York Trials Unit within 24 hours of discovery or notification of the event. Once received, causality and expectedness of serious adverse events will be confirmed by the Chief Investigator or another clinical member of the Trial Management Group (if the CI is unavailable).

SAEs that are deemed to be unexpected and related to the trial will be notified to the Research Ethics Committee (REC) and Sponsor within 15 days. All such events will be reported to the Trial Steering Committee and Data Monitoring Committee at their next meetings.

All events will be followed up until the event resolves or a decision is made for no further follow up. Participants experiencing SAEs which are deemed to be related to the trial treatments (intervention or control) and which remain ongoing at the time of participant trial exit will be followed up for one further month beyond trial exit.

Where repeated adverse events (serious or non-serious) of a similar type are observed, these will be discussed with the Data Monitoring Committee (DMC) and will be onward reported to the REC and Sponsor should concerns be raised in relation to the type of event and/or frequency observed.

9. Statistical and Health Economics Considerations

9.1 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, 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 observational 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 (3). 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% (16, 17, 19, 32).

- 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 (6). 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%) (7); Armstrong et al (n=38/162, 23%) (19); Blume et al (n=103/341, 30%) (33).

Recruiting 696 patients, and assuming an attrition rate of 20%, we would also have over 80% power to detect an absolute difference of 10% in the percentage of participants experiencing wound healing if the healing rate in the control group was between 20% and 80%.

9.2 Internal Pilot 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 3-month questionnaire)

Reasons for treatment discontinuation will also be monitored.

Recruitment assumptions and intervention rate will be assessed initially at 3 months, and again at 6 months. Feasibility of follow up and preparing of study sites to open for recruitment will be completed at 6 months to allow sufficient data to be collected.
Assumptions will be assessed against pre-defined 'traffic light' stop go criteria:
Green – Recruitment rate and intervention rate >80%; Non response to month 3 questionnaire ≤15%
Amber – Recruitment and intervention rate 60-80%; Non response to month 3 questionnaire 15 – 20%
Red – Recruitment and intervention rate <60%; Non response to month 3 questionnaire > 20%.

9.3 Statistical Analysis

Full details for the analysis will be provided in a statistical analysis plan, which will be prepared by the trial statistician and reviewed by the Trial Management Group, and Trial Steering and Data Monitoring Committees prior to the completion of data collection. Analyses are described in brief here.

This trial will be reported according to the CONSORT guidelines for clinical trials (34). A CONSORT diagram will be produced to show the flow of participants through the trial, providing reasons for non-participation and withdrawal where available (34).

Analysis will be undertaken using Stata version 15 or later (College Station, TX: StataCorp LLC).

Baseline data will be summarised by randomised group, as randomised and as included in the primary analysis (35), using descriptive statistics for continuous variables (n, mean, standard deviation, median, minimum, and maximum) and count and percentage for categorical variables. No formal statistical comparison of baseline data will be made between the groups.

All outcomes will be summarised descriptively by randomised group. Outcome analyses will be conducted following the principles of intention-to-treat with participant's outcomes analysed according to their original, randomised group irrespective of deviations based on non-compliance.

Significance tests will be two-sided at the 5% significance level. Parameter estimates will be presented with associated 95% confidence intervals (CI) and p-values as appropriate. For all outcomes, the level of missing data and the missing data mechanism will be assessed, and if required appropriate imputation techniques will be considered.

Our primary outcome is time to healing of the reference wound derived as the difference in days between randomisation and the first date of complete healing. Healing rates will be presented overall and by trial arm. Kaplan–Meier survival curves will be produced for the two groups and the median time to healing with a 95% CI 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, duration of wound in days (time between wound start date and randomisation), and wound location as fixed effects, and centre as a shared frailty effect. To assess the impact of compliance on the primary outcome we will consider a Complier Average Causal Effect (CACE) analysis which 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.

Secondary outcomes, including adverse events, will be analysed where appropriate using regression techniques appropriate for the type of data.

9.4 Health Economic Analysis

The economic analysis will aim to evaluate the lifetime cost-effectiveness of NPWT, compared to all relevant comparators, in the treatment of SWHSI. The perspective of the cost-effectiveness analysis will be of the UK NHS and the Personal Social Services. The primary economic outcome will be the incremental cost-effectiveness ratio for NPWT vs alternatives, expressed as cost per Quality Adjusted Life Years (QALYs) gained.

To best assist decision-making, we aim to build a *de-novo* decision analytic model to establish which of the relevant treatment(s) are most cost-effective, with current information. Evidence taken from the SWHSI-2 RCT will be key to inform parameters of the economic model. The wider existing evidence base, identified through literature reviews, will also be used. As the decision analytic model will require accommodating multiple different and relevant information sources, when required and suitable, evidence synthesis techniques will be used to pool data to best inform specific decision model input parameters.

Regression approaches will be used to derive costs and health benefits (health utility measured using EQ-5D-5L), allowing for correlation between these as well as adjusting for key covariates. Alternative scenarios regarding the extrapolation of the primary outcome over the lifetime of the model, and the evidence informing it, will be explored. Uncertainty in the evidence base used to populate the decision analytic model will be characterised using appropriate distributions and any uncertainty in the adoption decision will be demonstrated using probabilistic sensitivity analysis. The value of further data collection will be established using value of information analysis.

10.0 Ethical Arrangements

10.1 Ethical Approval

The SWHSI-2 trial will be conducted in accordance with the Clinical Trials Regulations (2004/1031) and will be subject to approval from the Research Ethics Committee and the Health Research Authority prior to study activity commencing. The study will be conducted in accordance with the Research Governance Framework and Medical Research Council (MRC) Good Clinical Practice (GCP) Guidance (36, 37).

Before being enrolled in the SWHSI-2 trial, participants must consent to participate after the nature, scope, and possible consequences of participating in the clinical study have been explained in a form understandable to them. The Investigator will not undertake any measures specifically required only for the clinical study until valid consent has been obtained.

A Patient Information Sheet (PIS) that includes information about the study and a consent form will be given to the participant. These documents will contain all the elements required by the ICH E6 Guideline for GCP and any additional elements required by local regulations. The PIS will give a balanced account of the possible benefits and known risks of the interventions. It will state explicitly that quality of care will not be compromised if the participant decides to a) not enter the trial or b) withdraw their consent. We will make it clear that there is no obligation to participate.
Patients will be given the opportunity to ask questions and the nature and objectives of the study will be explained. At the time of consent, written informed consent must be confirmed by the personally dated signature of the participant and the person conducting the informed consent discussions.

The original signed consent form will be retained in the study files. Other copies of the consent form are required:

- One copy of the informed consent form will be sent securely to YTU (by secure fax or encrypted email) and filed in the Trial Master File.
- One copy of the informed consent form will be kept in the patient's clinical notes where applicable. If a patient does not have clinical notes at the trial site, the informed consent document will be filed in a separate folder.
- One copy will be given to the patient.

Consent is an ongoing process and will be reassessed at each study visit.

10.2 Risks and Benefits

Side effects for NPWT or wound dressings are uncommon, and both treatments are routinely used in the NHS for patients with SWHSI. Risks to participants because of any of the treatments are not increased through trial participation.

There are however some associated risks with NPWT. This treatment uses a portable machine which may present a trip hazard for patients and their families. The nature of NPWT also means that dressing or foam used for this treatment may

adhere to the wound surface, particularly as granulated tissue forms. Where patients are recruited with an abdominal wound, there is also a potential risk of fistulation. Patients will be advised of these risks in the information sheet.

10.3 Informing Participants of Potential Risks and Benefits

Informed consent will be obtained by the trained local research nurse or clinician using a detailed patient information sheet developed with the help of service users, which will explain the risks and benefits clearly. In the unlikely event that new information arises during the trial that may affect participants' willingness to take part, this will be reviewed by the Trial Steering Committee for addition to the patient information sheet. A revised consent form will also be completed if necessary.

10.4 End of Trial

The end of the SWHSI-2 trial will be the Last Patient Last Visit (LPLV), defined as:

- Completion of 12 month follow up assessment in the study
- Withdrawal from follow up due to any reason

10.5 Retention of Trial Documentation

In line with the principles of Good Clinical Practice/UK Clinical Trials Regulations, essential Trial documentation will be kept with the Trial Master File and Investigator Site Files. This documentation will be retained for a minimum of 5 years after the conclusion of the trial to comply with standards of Good Clinical Practice, and Sponsor requirements.

Case Report Forms will be used to record all the information required from the protocol and will be stored for a minimum of 5 years after the conclusion of the trial as paper records (stored in a secure storage facility either on or off-site) and a minimum of 5 years in electronic format (on a password protected server) in accordance with guidelines on Good Research Practice (37).

10.6 Compliance with Medicines Devices Directive

The techniques under investigation are in routine use within the NHS and are internationally accepted surgical procedures using CE-marked implants and medical devices. We do not therefore require prior authorisation by the UK Competent Authority, the MHRA, under the Medical Devices Regulations (2002).

11. Trial Finance and Insurance

11.1 Trial Funding

The SWHSI-2 trial is funded by the NIHR Health Technology Assessment (HTA) Programme (HTA Reference: 17/42/94).

The Schedule of Events and Statement of Activity approved by the Health Regulatory Authority details all related costings for the SWHSI-2 trial.

All interventions are standard treatment options currently available in the NHS. We anticipate therefore that there will be no excess treatment costs for these interventions.

11.2 Trial Insurance

The Clinical Negligence Scheme for Trusts is able to provide insurance to cover for liabilities and prospective liabilities arising from negligent harm. Clinical negligence indemnification will rest with the participating NHS Trust or Trusts under standard NHS arrangements.

12. Project Management

12.1 Trial Sponsor

The trial will be sponsored by Hull University Teaching Hospitals NHS Trust.

12.2 Trial Management

York Trials Unit (YTU) at the University of York will manage the study. YTU will also provide quality assurance for trial processes through centralised monitoring of key trial procedures (e.g. consent and eligibility) and documentation completion, in addition to routine checks with sites with regards documentation held in Investigator Site Files.

Each site will have a site Principal Investigator (PI) who will be responsible locally for the study. All trial staff will be trained in the trial procedures by YTU during site set up, thereby meeting the Sponsors (and NIHR) standards. Where required by the NHS Trust site, trial staff will have current GCP certification.

To ensure continued engagement with, and to provide support to, participating research sites, bi-monthly meetings will be convened and all active research sites invited to participate. Meetings will include sharing best practice in relation to recruitment and retention, problem solving, and sharing any key information relating to the trial or to emerging evidence in relation to open surgical wounds or associated treatments.
A Twitter account (@SWHSI2_Trial) will also be used to provide updates on progress to study sites, and to engage the wider research community with the trial.

The Trial manager, on behalf of the Chief Investigator, will submit and, where necessary, obtain approval from all relevant parties for all substantial amendments to the original approved documents.
Regular progress reports will be submitted as required to the Funding Body.

12.3 Trial Management Group

A Trial Management Group (TMG) will monitor the day-to-day management of the trial including the detailed design, set up, initiation and supervision of the study. This will comprise the Chief Investigator (CI), all co-applicants, trial team at YTU, trial statistician, and trial health economist. A representative of the Sponsor will also be invited to attend. The group will meet bi-monthly (as a minimum) from the start of the study to the end of the pilot phase and quarterly thereafter to manage the detailed design, set up, initiation and supervision of the study.

12.4 Trial Steering and Data Monitoring Committees

Independent oversight of the study will be conducted by the Trial Steering Committee (TSC), who will monitor the progress of the trial and provide independent advice. The TSC will comprise of independent clinicians and health service researchers with appropriate expertise and an independent patient representative. The TSC meetings will also be attended by the trial statistician and the study Sponsor will be invited to attend.

The study will be regularly reviewed by the Data Monitoring Committee (DMC), comprising of independent clinicians and health service researchers with appropriate expertise. The DMC will monitor the data arising from the study and recommend whether there are any ethical or safety reasons why the trial should not continue.
Both the TSC and DMC will meet at regular intervals to provide project oversight to the trial.

12.5 Patient and Public Involvement (PPI)

Patients and the public have been involved in the development of this study in a number of ways:

- Our Patient Advisory Group (PAG), established for nearly a decade, has contributed to the development of this study through involvement in an earlier NIHR Programme Grant for Applied Research (PGfAR (RP-PG-0609-1017)) which has been used to develop this application.

- Patients have also identified the importance of this research question; qualitative semi-structured interviews with SWHSI patients identified wound healing as the most important outcome measure (6).

- An experienced patient representative has been actively involved in the development of this study, providing input on proposed follow-up methods and outcomes, feedback on application drafts and in writing the plain English summary.

Patient and public involvement (PPI) will continue to be integral throughout the conduct and dissemination of the trial.

We will engage with our Patient Advisory Group (PAG) on a bi-annual basis and will ask them to contribute thoughts on the design, delivery, management and interpretation of this trial. The group will have the opportunity to: review all patient related documentation, specifically to explain the risks and benefits of this research clearly; to review case report forms to ensure all aspects of care important to patients are captured; to review procedures including the consent process; and to make ongoing recommendations as necessary to help improve recruitment and retention.

Independent patient representatives will also participate in the Trial Management Group and Trial Steering and Data Monitoring Committees contributing to trial design, conduct and dissemination. Financial support for PPI attendance at meetings will be provided through reimbursement of time and travel at rates recommended by INVOLVE (38).

At the end of the trial, the management team will develop a patient friendly version of the results summary, based on trial findings. We will ask service users (as represented by the PAG) to review and revise this so that it is appropriate for a lay audience.

The PAG will assist in developing content for updating the entry on Wikipedia and will help to write the Map of Medicine entry on SWHSI management. In this way, service users will actively participate in dissemination of the conclusions of this research in a manner that is easily accessible by other patients. Representatives from the PAG may also assist with presenting the findings of this research at the Wounds Research Network or Tissue Viability Service meetings, or at local patient focused groups.

We do not anticipate any formal training requirements for our PPI representatives, however they will be directed to, and will have access to, further information regarding involvement in research from INVOLVE (39).

13. Dissemination and projected outputs

Results from this study will be written up and submitted to peer-reviewed journals, irrespective of the magnitude or direction of effect. A publications policy will be generated in advance to detail authorship, acknowledgements and review processes for any publications arising from the SWHSI-2 trial.

The executive summary and copy of the trial report will be sent to the National Institute for Health and Care Excellence (NICE) and other relevant bodies, including Clinical Commissioning Groups, so that study findings can be translated into clinical practice nationally. We will also work with the relevant National Clinical Director in the Department of Health to help ensure the findings of the trial are considered when implementing policy and will work with the Speciality Advisory Committees (SAC) to incorporate the findings into the training curriculum for clinicians who will undertake treatment of SWHSI.

A summary of the study report will be produced and made available to participants, members of our patient advisory group and relevant patient-focused websites. Patient information will also be generated for “Shared Decision Making”, the entry on Wikipedia and the Map of Medicine entry. Service users involved in the SWHSI-2 patient advisory group will be asked to actively participate in dissemination of the conclusions of this study to ensure these are easily accessible to patients.

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