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Treating open surgical

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(called exudate) which is difﬁcult to manage. Treatment options include wound dressings and the use of negative pressure wound

therapy (NPWT), which is becoming a common treatment for a variety of wound types. NPWT involves the application of a wound

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wounds healing by secondary intention.

**Surgical wounds healing by secondary intention: characterising and quantifying the problem, identifying effective treatments, and assessing the feasibility of conducting a randomised controlled trial of negative pressure wound therapy versus usual care**

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**Conflicts of Interest**

Dr Claxton reports personal fees from F. Hoffmann-La Roche Ltd, personal fees from Heron (PAREXEL), outside the submitted work.

Professor Torgerson reports grants from NIHR, outside the submitted work, and is director is a CTU funded by NIHR.

Professor Welton reports grants from NIHR, during the conduct of the study; and she is PI for a research grant jointly funded by the MRC and Pfizer.

All other authors have no conflicts of interest to declare.

**Key words**

Surgical wounds, Secondary intention, Healing, Treatments, Negative Pressure Wound Therapy

# Abstract

**Background:** Most surgical incisions heal by primary intention (i.e. wound edges are apposed with sutures, clips or glue); however some heal by secondary intention (i.e. the wound is left open and heals by formation of granulation tissue). There is, however, a lack of evidence regarding the epidemiology, management, and impact on patients’ quality of life of these surgical wounds healing by secondary intention (SWHSI), resulting in uncertainty regarding effective treatments and difficulty in planning care and research.

**Objectives:**  To derive a better understanding of the nature, extent, costs, impact and outcomes of SWHSI, effective treatments and the value and nature of further research.

**Design:** Cross-sectional survey; inception cohort; cost-effectiveness and value of implementation analyses; qualitative interviews; and a pilot, feasibility randomised controlled trial (RCT).

**Setting:** Acute and community care settings in Leeds and Hull, Yorkshire, UK.

**Participants:** Adults with (or for qualitative interviews, patients or practitioners with previous experience of) a SWHSI. Inclusion criteria varied between the individual Workstreams.

**Interventions:** The pilot, feasibility RCT compared negative pressure wound therapy (NPWT) – a device applying a controlled vacuum to a wound via a dressing - with Usual Care (no NPWT).

**Results:** Survey data estimated that treated SWHSI have a point prevalence of 4.1 per 10,000 population (95% CI: 3.5 to 4.7). SWHSI most frequently occurred following colorectal surgery (n=80, 42.8% - Cross-sectional survey, n=136, 39.7% - Inception cohort), and were often planned before surgery (n=89, 47.6% - Survey, n=236, 60.1% - Cohort). Wound care was frequently delivered in community settings (n=109, 58.3%) and most patients (n=184, 98.4%) received active wound treatment.

Cohort data identified hydrofibre dressings (n=259, 65.9%) as the most common treatment, although 29.3% (n=115) participants used NPWT at some time during the study. SWHSI healing occurred in 81.4% (n=320) of participants at a median of 86 days (95% CI: 75 to 103). Baseline wound area (p=<0.01), surgical wound contamination (determined during surgery) (p=0.04) and wound infection at any time (p=<0.01) (i.e. at baseline or post-operatively) were found to be predictors of prolonged healing.

Econometric models, using observational, cohort study data, identified that with little uncertainty, that NPWT treatment is more costly and less effective than standard dressing treatment for the healing of open surgical wounds: Model A (ordinary least squares with imputation): Effectiveness: 73 days longer than those who did not receive NPWT (95% Credible Interval (CrI): 33.8 to 112.8); Cost Effectiveness (Associated incremental quality adjusted life years): -0.012 (SE 0.005) (Observables); -0.008 (SE 0.011) (Unobservables) , Model B (Two Stage Model – Logistic and linear regression): Effectiveness: 46 days longer the those who did not receive NPWT (95% CrI: 19.6 to 72.5); Cost Effectiveness (Associated incremental quality adjusted life years): -0.007 (Observables) and -0.027 (Unobservables) (SE 0.017).

Patient interviews (n=20) identified initial reactions to SWHSI of shock and disbelief. Impaired quality of life characterised the long healing process, with particular impact on daily living for patients with families or in paid employment. Patients were willing to try any treatment promising wound healing. Health professionals (n=12) had variable knowledge of SWHSI treatments, and frequently favoured NPWT despite the lack of robust evidence,

The pilot, feasibility RCT screened 248 patients for eligibility and subsequently recruited and randomised 40 participants to receive NPWT or Usual Care (no NPWT). Data indicated that it was feasible to complete a full RCT to provide definitive evidence for the effectiveness of NPWT as a treatment for SWHSI. Key elements and recommendations for a larger RCT were identified.

**Limitations:** This research programme was conducted in a single geographical area (Yorkshire and the Humber, UK) and local guidelines and practices may have affected treatment availability and so may not represent UK wide treatment choices. A wide range of wound types were included, however, some wound types may be underrepresented meaning this research may not represent the overall SWHSI population.

The lack of RCT data on the relative effects of NPWT in SWHSI resulted in much of the economic modelling being based on observational data. Observational data, even with adjustment, does not negate the potential for unresolved confounding to affect the results. This may reduce confidence in the conclusions drawn and may lead to calls for definitive evidence from an RCT.

**Conclusions:** This research has provided new information regarding the nature, extent, costs, impacts and outcomes of SWHSI, treatment effectiveness and the value and nature of future research; addressing previous uncertainties regarding the problem of SWHSI. Aspects of our research indicate that NPWT is more costly and less effective than standard dressing for the healing of open surgical wounds. However, because this conclusion is based solely on observational data it may be affected by unresolved confounding. Should a future RCT be considered necessary, its design should reflect careful consideration of the findings of this programme of research.

**Trial registration:** Pilot, feasibility RCT registration: ISRCTN12761776.

**Funding:** This project was funded by the NIHR Programme Grants for Applied Research (RP-PG-0609-10171).

**Word Count: 748**

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# Abbreviations

|  |  |  |  |
| --- | --- | --- | --- |
| **BNF** | British National Formulary | **OR** | Odds Ratio |
| **BPI** | Brief Pain Inventory | **QALY** | Quality Adjusted Life Year |
| **CI** | Confidence Interval | **SAE** | Serious Adverse Event |
| **CrI** | Credible Interval | **SD** | Standard Deviation |
| **EQ-5D-3L** | EuroQol Five Dimensions 3 Levels | **SE** | Standard Error |
| **GP** | General Practitioner | **SF-12** | Short Form 12 |
| **HRQoL** | Health Related Quality of Life | **SUSAR** | Suspected Unexpected Serious Adverse Reaction |
| **ISRCTN** | International Standard Randomised Controlled Trials Number | **SWHSI** | Surgical Wound Healing by Secondary Intention |
| **IV** | Instrumental Variable | **VAS** | Visual Analogue Scale |
| **NHS** | National Health Service |  |  |
| **NICE** | National Institute for Health and Care Excellence |  |  |
| **NIHR** | National Institute for Health Research |  |  |
| **NPWT** | Negative Pressure Wound Therapy |  |  |
| **NSAE** | Non Serious Adverse Event |  |  |
| **OLS** | Ordinary Least Squares |  |  |

# Scientific Summary

## Background

Surgical wounds healing by secondary intention (SWHSI) are open wounds which heal from the base up. Healing by secondary intention may be planned (e.g. due to infection) or unplanned (e.g. where a wound has been closed but then opens (dehisces) either fully or partially). SWHSI may remain open for many months, are prone to infection and may prolong or require further hospital stays, adversely affecting patients’ quality of life and incurring substantial NHS costs.

The lack of available research evidence regarding SWHSI at the start of this programme meant that clinicians and patients lacked evidence regarding SWHSI management, what treatment options were most effective and were best value for money. The lack of basic data regarding the frequency, characteristics, current treatments, healing trajectory and impact meant it was difficult to plan new primary research.

## Objectives

The overall aim of the programme was to derive a better understanding of the nature, extent, costs, impact, and outcomes of SWHSI, effective treatments and the value and nature of further research. The objectives were as follows:

Workstream 1: To describe the number, characteristics, current treatments, impacts, and health outcomes of patients with SWHSI.

Workstream 2: To use all available research data to estimate the cost-effectiveness of current treatments for SWHSI, identified in Workstream 1, and to assess whether investment in future research on treatments for SWHSI was likely to be worthwhile and if so what research would offer best value for money.

Workstream 3: To determine the impact of SWHSI on patients, specifically their perspectives and experiences of living with a SWHSI, of wound management and relevant wound outcomes, and to determine NHS health care professionals’ views of SWHSI treatments and outcomes to measure treatment effects.

Workstream 4: To determine the feasibility of conducting further primary research on SWHSI through a pilot, feasibility randomised controlled trial (RCT).

## Methods and Results

Workstream 1

An inception cohort approach was used to enable accurate assessment of time to healing and treatment use. Given the lack of information on patient numbers and care locations, the cohort study was preceded with a cross-sectional survey which enabled point prevalence of treated SWHSI to be assessed.

Our cross-sectional survey, conducted in East Yorkshire UK, obtained 200 responses, with the majority of responses received from community or district nurses (n=77, 41.2%) followed by research nurses (n=44, 23.5%). Data from 187 patients were analysed, giving an estimated point prevalence of treated SWHSI of 4.1 per 10,000 population (95% CI: 3.5 to 4.7). Most patients had only one SWHSI (87.7%) and the most common surgical procedure resulting in SWHSI was for pilonidal sinuses/abscesses (15.0%). Half of SWHSI were planned (47.6%) and the median wound duration at the point of survey was 28 days (95% CI: 21 to 35). Most patients (98.4%) were receiving active treatment, most commonly wound dressings (93.4%), and care was frequently provided in community settings (58.3%).

Our cohort study, conducted in eight primary, secondary and community care sites in Yorkshire and Humber, UK, recruited 396 participants; with 393 included in the analysis (three participants were subsequently ineligible). Participants were followed up for a minimum of 12 and a maximum of 21 months to collect key clinical outcome data (including healing, surgical site infection, hospital readmission, treatments received, and changes to study involvement), quality of life and pain assessments. The median age of participants was 55 years (range 19 to 95), 69.5% of participants were overweight or obese, and 28.5% were current smokers. The most common comorbidities were cardiovascular disease (38.4%), diabetes (26.2%), and peripheral vascular disease (14.5%). Most patients had only one SWHSI (91.0%), had no previous history of SWHSI (72.0%) and the SWHSI was planned (60.1%) with the most common site being the abdomen (33.6%), reflecting that colorectal surgery was the most commonly represented surgical speciality (39.7%). The most common treatment was hydrofibre dressings (65.9%) and 29.3% participants reported receiving negative pressure wound therapy (NPWT) during the study.

In our cohort study, data indicated that SWHSI healed for 81.4% participants (n=320) with a median time to healing of 86 days (95% CI: 75 to 103). Area greater than the baseline median (6cm2) (p<0.01), surgical wound contamination level as determined at the point of surgery (p=0.04) and surgical site infection at any point (p<0.01) were significant predictors of prolonged time to healing. Quality of life remained constant during the study whilst pain severity, interference, and SF-12 scores improved over time.

Workstream 2

Econometric models were applied to cohort data collected in Workstream 1 to assess the clinical and cost-effectiveness of NPWT, when compared with standard dressings; no published research data could be identified to complement the cohort data in the model. The lack of RCT data on the relative effects of NPWT in SWHSI therefore resulted in much of the economic modelling being based on observational data. A Bayesian approach to inferences was used, computed using Monte Carlo Markov chain simulation. Time to healing was modelled using two approaches: ordinary least squares with imputation using an instrumental variable regression to adjust for unobservable confounding (Model A); and a two stage model using logistic regression followed by linear regression. Instrumental variables were identified to adjust for unobservable confounding (Model B).

Model A identified that NPWT participants were expected to take longer to heal than those who did not receive NPWT – on average 73 days longer (95% Credible Interval (CrI): 33.8 to 112.8). This was maintained when interaction terms (treatment and SWHSI history) and expert opinions on censoring of healing times were included. Model B identified that NPWT participants were estimated to have lower probability of healing (Odds Ratio (OR) 0.59 (95% CrI: 0.28 to 1.12) and time to healing for participants treated with NPWT was an additional 46 days (95% CrI: 19.6 to 72.5). Conclusions were similar in both approaches when adjusted for unobservables.

Cost-effectiveness estimates indicated that NPWT was expected to be less cost effective than standard dressings (associated incremental Quality Adjusted Life Years (QALYs) of -0.012 (SE 0.005) (Model A – Observables), -0.008 (SE 0.011) (Model A – Unobservables), -0.007 (Model B – Observables) and -0.027 (SE 0.017) (Model B – Unobservables). There was little decision uncertainty in this result.

Workstream 3

Semi-structured qualitative interviews were conducted with 20 patients (with experience of a SWHSI), five surgeons, and seven nurses using topic guides. Interviews were audio recorded, transcribed, and analysed using a ‘*Framework*’ approach.

Patients reported that unplanned SWHSI resulted in feelings of alarm, shock, disbelief, and disgust. Patients with previous experience of a SWHSI expected slow healing whilst patients without previous SWHSI experience often had unrealistic expectations of time to healing. Patients were ever-hopeful that a new or untried treatment might accelerate or achieve wound healing, and there was a willingness to try any procedure or treatment to achieve this, even if it was unpleasant or lacked high level evidence of efficacy. The main SWHSI treatments experienced were negative pressure wound therapy (NPWT), debridement, dressings, and skin-grafting. Patients would have liked more information in relation to the rationale for using different treatment methods and approaches.

Prolonged or multiple hospital admissions were not uncommon and many patients reported feeling unsupported at the point of hospital discharge due to a lack of available information regarding follow-up care and infection management. Most patients received home visits from district, community or general practice nurses during their wound healing. Patients acknowledged that the nurses tried to attend to all needs during the visit but felt that nurses had limited time to devote to each visit.

Wound related symptoms had a negative impact on daily life, physical and psychosocial functioning, and well-being. Limited physical mobility was frustrating and disrupted normal activities and patients felt unable to socialise due to concerns about their self-image. Disruption of roles and responsibilities within the family unit was common and patients reported feeling burdensome and dependent. This appeared particularly difficult for younger male participants who were often the main earner in the family.

Surgeons and nurses agreed a number of factors were associated with delayed healing including surgical (e.g. reason for surgery, procedure type), patient comorbidity, systemic infection, medication, mobility, and treatment compliance factors. In many instances, it was difficult to identify any specific reason for impaired wound healing. Specific wound factors reported to be associated with healing included wound size, presence of wound infection, slough and/or granulation tissue and condition of the wound edges. Nurses also emphasised psycho-social and practical issues that might impact on patients’ quality of life, such as family support and patients’ potential for self-care of the wound.

The majority of patients, operated on by general surgeons, had their wound care passed to nurses following discharge. Plastic and vascular surgeons were more likely to continue to care for *‘their’* patients through follow-up in specialist clinics*.* Surgeons relied on nurses to make appropriate dressing choices, which were influenced by wound, patient, and dressing specific factors. Surgeons or Tissue Viability Specialists often initiated decisions regarding the use of NPWT as knowledge and expertise regarding NPWT amongst general nurses was often limited. Tissue Viability Specialists were a frequent point of reference for nurses regarding the management of complex, non-healing open surgical wounds.

Surgeons reported that use of NPWT was increasing and that complex, cavity wounds (e.g. extensive abdominal wounds) were ideally suited to benefit from NPWT. NPWT was generally perceived as a cost-effective and transformative treatment, particularly for patients with hard to heal wounds. Surgeons noted the lack of research evidence relating to NPWT but felt that their own and colleagues’ experiences supported its use.

Workstream 4

A pilot, feasibility RCT was designed to test the methods and the feasibility of conducting a larger RCT to assess clinical and cost effectiveness of NPWT compared to Usual Care (no NPWT). In total 41 participants were recruited from two secondary and one community care NHS trust in the north of England. Forty participants were subsequently included in the analysis (one participant was randomised in error). Using a 1:1 ratio, participants were allocated to one of two groups; NPWT (n=19, 47.5%) and Usual Care (no NPWT) (n=21, 52.5%). Participants were recruited over nine months, and followed up for three months. An intention to treat analysis was conducted.

The proposed primary clinical outcome for a larger trial (time to wound healing) was assessed along with other clinical and feasibility outcomes, including: recruitment and retention rates, time to treatment start, duration of and changes to NPWT, clinical events, resource use data, documentation acceptability and feasibility of blinded outcome assessment.

Of the 248 patients screened for eligibility, 186 (75.0%) were ineligible (including the patient randomised in error) and 22 (8.9%) were eligible but non-consenting. Common reasons for ineligibility included having previously received NPWT on the SWHSI (n=45, 18.1%), having received NPWT in theatre for surgery resulting in the SWHSI (n=7, 2.8%), or both (n=24, 9.7%). Randomised participants received a median of 8 (NPWT) and 7 (Usual Care) post-randomisation assessments. Participant questionnaire response rates were equal to or greater than 78% at all time points.

Two of the 19 participants allocated to NPWT (10.5%) did not receive NPWT, 10 (52.6%) received NPWT within 24 hours and 14 (73.7%) within 48 hours. The most common reason for delay was the machine being unavailable (n=6, 85.7%). Participants received NPWT for a median of 18 days (range 0 to 72). Five Usual Care participants (23.8%) received NPWT at a median of 4 days after randomisation (range 0-17).

Ten wounds (25.0%) were deemed to have healed during the study and17 participants (42.5%) experienced a wound infection. The mean total cost for NPWT was £9,490 (SD £7,346) and for Usual Care was £1,153 (SD £1,806). A substantial proportion of NPWT costs were attributed to hospital stays (£7,710 (SD £7,557).

Of those providing a response (n=31), 28 participants (90.3%) found completing study questionnaires to be straightforward. Half of the eight nurse respondents (n=4) found the case report forms to be straightforward and the majority (n=6, 75.0%) found the frequency of clinical assessments to be manageable. There were mixed opinions regarding processes for identifying potential participants.

Blinded assessment of wound healing, by up to three reviewers, agreed with unblinded, nurse healing assessment in 95.0% of cases. Treatment allocation was correctly identified in 37.5% (n=15) cases; nine participants to NPWT and six to Usual Care.

## Conclusions

This research has provided new information regarding the nature, extent, costs, impacts, and outcomes of SWHSI, insights into uncertainty around current treatment effectiveness and the value and nature of future research in this area.

The cross-sectional survey, of 187 patients in Hull and East Yorkshire, UK, has provided an estimate of treated SWHSI prevalence of 4.1 per 10,000 population (95% CI 3.5 to 4.7) and inception cohort data has provided the first detailed analysis of SWHSI patients, treatments and wound healing trajectories. The heterogeneity of the SWHSI population, wide distributions of SWHSI sites, surgeries resulting in SWHSI and treatments used, and predictors of slower SWHSI healing (wound area, surgical wound contamination as determined at the point of surgery, and surgical site infection at any time) have also been identified as a result of this work.

Qualitative interviews identified the devastating effect SWHSI may have on patients’ quality of life. Patients were focused on complete wound healing and were willing to try any treatment that promised this. Healing is therefore a crucial outcome for future research into SWHSI treatments.

Cost-effectiveness models using the observational cohort data demonstrated, with little uncertainty, that NPWT is less effective and more costly than standard dressings. Should a lack of confidence in these conclusions from observational data mean that a future RCT is considered necessary, the design of this trial should be informed by this programme of work.

Recruitment to a RCT to assess clinical and cost-effectiveness of NPWT for patients with SWHSI has been identified to be possible. This is therefore encouraging for future research which we suggest should focus on enhancing evidence for clinical and cost-effective SWHSI treatments, identifying factors predicting time to healing, assessing interventions to improve patient quality of life and potential improvements which could be made to SWHSI care pathways.

## **Trial registration**

Pilot, feasibility RCT registration: ISRCTN12761776.

## **Funding**

This project was funded by the NIHR Programme Grants for Applied Research (RP-PG-0609-10171).

**Word Count: 2356**

# Plain English Summary

Surgical wounds healing by secondary intention (SWHSI) are open wounds which are left to heal from the base up. At the start of this work, there was little information on these wounds, their management, impact on patients and which treatments offered best value for money. The overall aim of this research was therefore to describe, characterise, and identify the nature and impact of SWHSI and the current evidence for effective treatments.

We found that:

* SWHSI are very common and they affect approximately 4 people per 10,000 adults in the general population.
* Patients may have their wound for a long time and this has an impact on their well-being and daily life.
* Patients are often shocked when they first see their wound and are concerned about what others think of it.
* Several factors are associated with delayed wound healing (e.g. wound infections and wound size).
* Wound dressings are often used as the first treatment but sometimes a vacuum device called negative pressure wound therapy (NPWT) is used. Health professionals are using this treatment more frequently.
* Our study looked at how NHS patients receiving NPWT fared when compared with patients receiving standard dressings. Our study was not experimental — health professionals and patients chose the treatments they received.
* Using specialised analysis methods, we found that NPWT was less effective and did not offer value for money compared with standard wound dressings. It is possible that these findings are due to differences between the people receiving the different treatments rather than the treatments themselves.
* As a result, definitive evidence about the comparative effects of NPWT and standard dressing may still be required in the form of a large randomised clinical trial; our small pilot study has shown that such a study is possible.
* Further studies are required to assess other SWHSI treatments and to improve patient well-being and care.

**Word Count:** 314 words

# Synopsis

# Introduction

More than 10 million surgical operations are conducted every year in the NHS with the majority of these involving a wound created by surgical incision.[1](#_ENREF_1)Most incised surgical wounds heal by primary intention, where the wound edges are closely apposed and sutured, clipped or glued together. However not all surgical wounds heal in this way: some wounds are left open after surgery and heal from the bottom up by the formation of granulation tissue (known as healing by secondary intention). The healing of surgical wounds by secondary intention may be planned (e.g. after significant tissue loss where primary closure is not possible or in the presence of infection). Alternatively healing by secondary intention may be unplanned when a primarily closed wound opens or “dehisces” (full or partial separation of wound edges). These surgical wounds healing by secondary intention (SWHSI), also called “open surgical wounds”, may remain open for many months, are prone to infection, may prolong hospital stays and necessitate further hospital admissions and surgeries (delayed primary closure) or skin-grafting,[2](#_ENREF_2) all adversely affecting patients’ quality of life and incurring substantial NHS costs.

## Prevalence of surgical wounds healing by secondary intention

Whilst SWHSI are thought to be relatively common, when we planned this research there were few national or international data regarding their epidemiology. Two published studies estimated that SWHSI constituted approximately 28% of all prevalent surgical wounds.[3](#_ENREF_3), [4](#_ENREF_4) From data collected in Hull and East Yorkshire, UK, Srinivasaiah *et al*. (2007) reported 136 open surgical wounds and 74 dehisced surgical wounds, from a total population of 590,000 – a point prevalence of 0.36 per 1000 population.[4](#_ENREF_4) Further UK cross-sectional data from Bradford, UK reported 111 wounds that were classed by study authors as open surgical wounds and a further 88 that were classed by study authors as having broken down post-surgery.[3](#_ENREF_3) However, the size of the underlying population and hence point prevalence for these wounds was not reported. A population-based estimate of the prevalence of SWHSI alongside in-depth investigation of their origin, natural history, typical treatments, and impact on patients and health services was needed.

## Details of patient and wound characteristics

Previous research on wound prevalence by Vowden *et al*. and Srinivasaiah *et al.* focused on all wounds rather than specific wound types.[3](#_ENREF_3), [4](#_ENREF_4) When we began this research there was no high quality information (national or international) describing: patients with SWHSI (age, sex, comorbidities, concomitant medications, surgical speciality); wound characteristics (site, size location, aetiology, whether the wounds were planned to be left open before surgery, frequency of wound infection); SWHSI treatments or healing rates in general and for specific patient groups (e.g. those with diabetes). Robust time to healing data were also limited and reports frequently presented inaccurately analysed data.[5](#_ENREF_5), [6](#_ENREF_6), [7-10](#_ENREF_7) The generalisability of the existing research was also limited as many trials reported time to healing rates in relation to subpopulations of SWHSI patients and treatments: one trial of perineal wounds and foam dressing;[5](#_ENREF_5)two trials of pilonidal sinus wounds and Silastic dressing;[7](#_ENREF_7), [8](#_ENREF_8) one trial of below knee amputation wounds and plaster cast with silicone sleeve or elastic compression.[10](#_ENREF_10) The lack of systematic data describing SWHSI and their treatment and outcomes was matched by a lack of knowledge about the impact of SWHSI on patients’ quality of life or daily functioning, as well as the impact of these wounds on the use of health care resources. This, in combination, made it almost impossible to assess the impact of SWHSI and their treatments on patients, or to plan new research studies to assess the clinical and cost-effectiveness of potential new or alternative treatments or interventions.

## The treatment of surgical wounds healing by secondary intention

Management of SWHSI often involves daily or more frequent dressing changes, sometimes with packing of the wound cavity. Many different dressing options are available, from simple dressings such as gauze (which can be painful to remove) to more modern options such as foam, hydrocolloid and alginate dressings. Wounds may also be treated by debridement (the removal of foreign material and devitalised tissue) or skin-grafting. When this research was conceived, the type and frequency of treatments being used for SWHSI was not known. Randomised controlled trials (RCT) in SWHSI patients are infrequent and often poorly designed, underpowered, utilise surrogate outcomes and often report limited or incorrectly analysed healing data making interpretation of these data incredibly difficult. For example, a multicentre RCT comparing the effects of zinc oxide with placebo mesh on secondary healing pilonidal wounds was underpowered, recruiting only 64 participants (33 zinc, 31 placebo) and whilst it did not detect a difference in median healing times (54 days, interquartile range 42-71 days for zinc and 62 days, interquartile range 55-82 days for placebo, p=0.32), this may have been due to the lack of power. In the same study fewer post-operative antibiotics (a surrogate marker of wound infection) were prescribed in the zinc oxide group (n=3) than in the placebo (n=12) group, p=0.005. [11](#_ENREF_11)

In terms of evidence of effectiveness of different treatment options, Vermeulen *et al*. (2004) explored the relative effects of dressings and topical agents for SWHSI in a systematic review.[12](#_ENREF_12) They found only 13 RCTs, all of which were small, of poor quality and often conducted over ten years prior. There was no evidence to indicate that the choice of dressing or topical treatment offered any benefit in terms of wound healing time, but the data were sparse. A systematic review conducted to inform National Institute for Health and Care Excellence (NICE) clinical guidelines on surgical site infection investigated the effects of topical antiseptics and antibiotics (including impregnated dressings) on the risk of wound infection in SWHSI.[13](#_ENREF_13) The four included studies were small and provided generally uncertain evidence on a range of uncommon treatment options. The guidelines recommend that: Eusol and gauze, or moist cotton gauze, or mercuric antiseptic solutions should not be used to prevent surgical site infection in the management of SWHSI.[13](#_ENREF_13)

Increasingly more advanced and costly wound treatments have been extensively adopted into clinical practice with inadequate supporting evidence. One example is negative pressure wound therapy (NPWT), a device that applies a carefully controlled negative pressure (or vacuum) to the dressing, removing tissue fluid away from the treated wound area into a disposable canister.[14](#_ENREF_14) The canister is removed and replaced either when it becomes full or at least once a week. The device is generally used as part of the SWHSI treatment pathway rather than to the point of healing and can be administered and removed by both nurses and surgeons.

## Cost of treating surgical wounds healing by secondary intention

SWHSI can be large and may produce a significant volume of exudate, which can be difficult to manage, and frequent, time consuming, dressing changes are common. In addition, SWHSI must also be protected from infection and trauma during healing. It has been suggested that SWHSI are at high risk of post-operative infection, with the wound providing an ideal environment for bacterial proliferation, which may be associated with delayed healing.[15](#_ENREF_15) These factors, and the possible need for further surgery, suggest the costs of treating patients with SWHSI could be substantial. The lack of available epidemiological evidence in relation to SWHSI had, however, made it difficult to ascertain the healthcare and social costs of treating these wounds.

## Surgical Wounds Healing by Secondary Intention – the patients’ perspective

The lack of systematic data describing SWHSI, their treatment and outcomes was matched by a scarcity of knowledge about the impact of SWHSI on patients’ quality of life. Little was known regarding patients’ perspectives and experiences of living with SWHSI, their views, expectations, and concerns regarding management and outcomes.

## Surgical Wounds Healing By Secondary Intention – the clinicians’ perspective

A variety of clinicians including surgeons, tissue viability nurses, and general practice nurses are all commonly involved in the management of patients with SWHSI. As previously stated there is a dearth of high-level evidence to guide the management of these patients, particularly regarding the clinical and cost-effectiveness of different treatments or interventions. Greater clarity is required regarding assessment of these wounds, and the factors, which influence decisions regarding management decisions.

## Summary

In summary, this research programme was undertaken recognising that SWHSI may be common and costly, but that there was a need for further exploration of the extent, nature, outcomes, and impact of these wounds. The lack of international epidemiological data regarding these patients seriously impairs the development of new research studies in this area. There was also huge uncertainty regarding SWHSI management. Options ranged from inexpensive simple dressings to the more complex and costly NPWT, but accurate data regarding the frequency of use of specific treatments was non-existent. Additionally, all treatment options for SWHSI lacked robust, supportive evidence bases in terms of clinical and cost-effectiveness and the impact on patients’ quality of life. As a result, clinicians and patients were uninformed about how to care for SWHSI, and specifically which treatment options were most effective and offered the best value for money. The need for research to fill these evidence gaps was also highlighted by the UK National Institute for Health and Clinical Excellence guidance.[13](#_ENREF_13)

Given the number of treatment options available, it is important that patients, carers, and health professionals are involved in trial design, including the selection of significant outcome measures, and that research is conducted through sufficiently powered trials to detect significant differences in healing rates between treatments. However, the enormous cost of conducting the trials required to fill the evidence gaps means that a rush to undertake such studies, before obtaining additional key intelligence, would be hugely inefficient. There were several important unknowns: information about the natural history and epidemiology of SWHSI; which treatments were being used most commonly and thus should be evaluated; whether the decision uncertainty associated with various treatments justifies an expensive trial; and whether a trial is feasible. Additionally, little was known about which outcomes matter to patients with SWHSI and what the desirable treatment characteristics are from the perspective of the staff treating them. We have undertaken research to generate vital data regarding an important, costly and hugely under researched health problem. The research findings will aid in planning service delivery and future research including economic modelling and primary studies.

# Aims

We aimed to characterise and quantify SWHSI, their outcomes and impact and to begin to identify effective SWHSI treatments. The core aims of the research were achieved via four interdependent workstreams. The link between the four workstreams is shown in Figure 1.

*Workstream 1*: Aimed to describe the number, characteristics, current treatments, impacts, and health outcomes of patients with SWHSI. This was achieved using an initial prevalence survey and a subsequent inception cohort of patients with SWHSI to collect naturalistic data regarding treatments used, rates of healing, adverse events, and quality of life changes.

*Workstream 2*: Aimed to use all available research data to estimate the cost-effectiveness of current treatments for SWHSI as identified in Workstream 1 and was completed using evidence synthesis and decision analytic modelling. If assessments of cost-effectiveness suggested there was decision uncertainty, i.e. uncertainty about which treatment offers best value to the NHS, we would extend analyses to assess whether investment in future research on treatments for SWHSI was likely to be worthwhile and if so what research would offer best value for money.

*Workstream 3*: Aimed to determine the impact of SWHSI on patients, specifically their perspectives and experiences of living with a SWHSI, of wound management and relevant wound outcomes. In addition this Workstream aimed to determine NHS professionals’ views about SWHSI treatments and important outcomes to measure treatment effects. This was achieved through qualitative interviews with both patients and NHS professionals.

*Workstream 4*: Aimed to determine the feasibility of conducting further primary research on SWHSI through a pilot, feasibility randomised controlled trial.

This monograph describes the results of our findings from all four workstreams. Publications arising from this research programme are listed in section

**Figure 1: Overview of the whole research programme and its inter-relationships**

**Cross-Sectional Survey**

**Aims**

**To aid the design of the cohort study, by identifying:**

* **The number of patients with SWHSI (point prevalence)**
* **Patient characteristics**
* **The NHS settings in which patients were receiving treatment**
* **Numbers of SWHSI planned or occurring due to wound breakdown**

**Cohort Study**

**Aims**

* **Further investigate clinical characteristics of patients with SWHSI from inception of the wound**
* **Delineate clinical outcomes of patients over life time of the wound**
* **Describe treatments received**
* **Assess SWHSI impact on patient quality of life**

**Cost-Effectiveness Analysis**

**Aims**

* **Estimate the cost-effectiveness of NPWT vs dressings for healing of SWHSI (using data from the Cohort study)**

**Pilot, Feasibility Randomised Controlled Trial**

**Aims**

* **To test the methods and feasibility of a full RCT of negative pressure wound therapy (NPWT) compared with Usual Care (no NPWT) for SWHSI**

**Qualitative Research**

**Aims**

**To explore through qualitative interviews:**

* **Patient perspectives and experiences of living with SWHSI**
* **Elicit patient views regarding SWHSI management and outcomes**
* **NHS professional views and experiences regarding treatment choices for SWHSI**

**Value of Implementation Analysis**

**Aims**

* **Assess whether future investment in research on treatments for SWHSI is likely to be worthwhile and if so what research offers best value for money**

Workstream 1 Workstream 2

Workstream 3 Workstream 4

# Patient and Carer Involvement

Involvement of patients and carers was identified at the outset as a priority for this research.

In Workstream 1, two patient representatives contributed to the design of documentation for the cohort study and provided their perspective on study processes, questions, and data interpretation through attendance at associated Workstream meetings. A dedicated section of the meeting was devoted to patient feedback and the meeting was followed by an informal discussion between the research lead, a study research nurse, and the patient representatives. Where possible, any comments received from the patient representatives were incorporated into relevant study documentation or procedures. A newsletter to inform participants about the progress of the research was initiated by the patient representatives who assisted in the design and review of this document.

In Workstream 3, the input of patient and carer representatives was crucial in the design and piloting of the interview topic guide and the interpretation of the findings arising from the qualitative interviews, including review of the main study findings and input into the writing of the results. A summary of the results of the qualitative work was subsequently sent to participants, following review by the patient representatives.

Patient and carer involvement for this programme of work culminated in the development of a ‘*Patient User Group’*, convened at the start of Workstream 4. This group was developed, following experiences in Workstream 1, to increase the number of patient representatives involved and so reduce any burden on the two initial representatives involved. Ten patients or carers with experience of SWHSI were invited to attend the inaugural meeting in March 2015, with five representatives subsequently attending. This resulted in a diverse group with a mix of age, gender, SWHSI history, and previous research experience. A further two meetings were convened during Workstream 4 to provide comment on patient-facing documentation, study procedures and to discuss the interpretation of the results of the pilot, feasibility randomised controlled trial. As in Workstream 1, where possible, any comments received from the patient representatives were incorporated into study documentation or procedures. One member of the group was subsequently recruited to act as a patient and public representative for the Workstream 4 Management Group meetings, and provided a patient perspective on the trial processes and documentation and made substantial contributions. This patient representative also contributed to and reviewed the summary of Workstream 4 for this report and the associated papers arising from this Workstream. In addition, a lay representative was also included in the Workstream 4 Data Monitoring and Ethics Committee (DMEC) to provide patient input on data quality, patient safety and to advise on any issues arising during the trial.

The inclusion of patient and carer representatives has been instrumental in shaping this research programme and will undoubtedly be beneficial in shaping future research in this area. The mix of patients and carers providing input to the individual Workstreams and in the Patient User Group provided the research programme team with a diverse range of experiences to draw upon and consider when making decisions in relation to this research programme. Given the number of patient and public members involved in the various stages of this programme, there was naturally a range of views noted with regards patient and carer experiences, study procedures and documentation however in the vast majority of cases there was a consensus of opinion with regards progression of this research.

# Workstream 1: Cross-sectional survey and cohort study of surgical wounds healing by secondary intention

The dearth of national and international clinical and research information regarding the prevalence, patient characteristics, and treatments for surgical wounds healing by secondary intention (SWHSI) meant that we did not know the extent and nature of these wounds, how and where they were managed, or the associated outcomes. To enable accurate assessment of time to healing and treatment use, we planned an inception cohort study to address key uncertainties. An inception cohort approach was essential to allow accurate assessment of SWHSI duration. Planning the cohort study was difficult however as there were no data regarding *where* most SWHSI occurred, for example: were most SWHSI left open in theatre or did they subsequently break down in hospital or in the community? We needed basic information regarding the numbers of patients with SWHSI and their location in order to put adequate resources in place for the inception cohort study. We therefore preceded the cohort study with a cross-sectional survey. This approach facilitated the gathering of initial intelligence to support subsequent work, and in addition the use of a cross-sectional design also allowed us to estimate a point prevalence estimate for SWHSI. The cross-sectional survey has been published (See Appendix 1).[16](#_ENREF_16)The cohort study has been submitted for publication (See Appendix 2).

# Cross-Sectional Survey

## Objectives

The cross-sectional survey aimed to capture information to aid the design of the cohort study. This included:

i) The number of patients with SWHSI (point prevalence), their characteristics, and the NHS settings where they were receiving treatment.

ii) The proportions of SWHSI planned prior to surgery and those which occurred as a result of wound breakdown (dehisced) after surgery.

Information was also collected on typical durations of SWHSI, the types of surgery preceding the SWHSI and the treatments received by patients.

## Summary

### Methods

The cross-sectional survey was conducted over a two week period (Spring 2012) in primary, secondary and community care settings in Hull and the East Riding of Yorkshire, UK. We asked healthcare professionals to identify patients on their caseload who had at least one SWHSI i.e. *a wound deliberately left open due to infection, swelling, contamination or empty tissue space, a wound initially closed but subsequently dehisced or a wound arising from surgical debridement.* Where patients had multiple SWHSI, the largest wound was deemed to be the ‘*reference SWHSI*’. Detailed data were collected including; patient and wound characteristics, health care provider, clinical and surgery details, and treatment events (See Appendix 3). As this survey was limited to secondary use of routinely collected information, Research Ethics Committee approval was not required.[17](#_ENREF_17) Approval was however obtained from associated NHS Trusts, prior to commencement of data collection.

Data analysis was conducted using IBM SPSS software version 21 (International Business Machines Corporation, New York, USA). Categorical variables were summarised as frequencies and proportions whilst continuous variables were summarised as medians and associated 95% confidence intervals and ranges. The usual resident regional population aged 20 years and over, as taken from the 2011 census, was used as the denominator when calculating point prevalence.[18](#_ENREF_18)

### Results

Following removal of duplicate cases (identified through age, ethnicity and wound characteristics), data were analysed for 187 patients with a SWHSI. In total, 62% of patients were male, 95.2% were of white British ethnicity, and the median age was 58.0 (range 19-90) years, as detailed in Table 1.

Table 1 – Cross Sectional Survey Patient Demographics

|  |  |
| --- | --- |
| **Gender** |  |
| Male (n) | 116/187 (62.0%) |
| Female (n) | 62/187 (33.2%) |
|  |  |
| **Age (years)** |  |
| Median (95% CI) | 58.0 (55 to 61) |
| Minimum - Maximum | 19.0 – 90.0 |
| Missing (n) | 3/187 (1.6%) |
|  |  |
| **Ethnicity** |  |
| White British (n) | 178/187 (95.2%) |
| Asian Indian, Asian Other, Black Other, Other Mixed Background, White Other, White and Asian and Not Specified (n) | 7/187 (3.7%) |
| Missing (n) | 2/187 (1.1%) |
|  |  |
| **Number of SWHSI per patient** |  |
| 1 | 164/187 (87.7%) |
| 2 | 16/187 (8.6%) |
| 3 | 4/187 (2.1%) |
| 4 | 1/187 (0.5%) |
| Missing | 2/187 (1.1%) |

We estimated the point prevalence of treated SWHSI as 4.1 per 10,000 population (95% CI: 3.5 to 4.7) using the resident regional population value as the denominator.[18](#_ENREF_18) The observed maximum number of SWHSI per patient was 4 (1/187, 0.5%) with the majority of patients (164/187, 87.7%) having only one SWHSI. Patients were more frequently treated in community than in secondary care settings (109/187, 58.3% compared with 56/187, 29.9%), with the remaining patients treated within primary care (8/187, 4.3%), other care settings (2/187, 1.1%). There were 12 patients (12/187, 6.4%) for whom treatment location was not recorded.

We found almost half of the SWHSI were planned to heal by secondary intention (n=89, 47.6%) and 77 (41.2%) were primarily closed wounds that had subsequently dehisced. A further six wounds (3.2%) were surgically opened, six (3.2%) arose for other reasons (surgical debridement (n=2, 1.1%), sutures removed and left open to heal (n=1, 0.5%), skin-graft failure (n=1, 0.5%), non-healing wound (n=1, 0.5%) and necrotising fasciitis requiring debridement (n=1, 0.5%)) and for nine patients (4.8%) the information was not known or was missing. The median time from surgery to wound breakdown was 9 days (95% CI: 7 to 10).

In addition, we found that the median duration of wounds at the point of survey was 28 days (95% CI: 21 to 35). Fully dehisced SWHSI had the longest median duration (35 days, 95% CI: 15 to 150) and those with long wound durations were most frequently treated within primary care (median duration 112 days, 95% CI: 21 to 469) and community settings (median duration 35 days, 95% CI: 28 to 56 days) (Table 2).

Table 2 – Duration of SWHSI within different patient treatment settings

|  |  |  |  |
| --- | --- | --- | --- |
| Wound duration (days) | Treatment Setting | | |
| Community | Secondary Care | Primary Care |
| N | 89/109 | 56/56 | 7/8 |
| Median (95% CI) | 35.0 (28 to 56) | 14.5 (6 to 21) | 112.0 (21 to 469) |
| Minimum to maximum | 1-560 | 1-238 | 21-896 |
| Missing (%) | 20 (18.3%) | 0 (0) | 1 (12.5%) |

a Wound duration refers to the number of days elapsed between formation of the SWHSI and survey data collection.

In total, we identified 43 different surgical procedures that preceded the development of a SWHSI. The most common surgical procedures were for pilonidal sinuses/abscesses (28/187, 15.0%), lower limb amputations (19/187, 10.2%) and laparotomy with bowel resection (19/187, 10.2%). As detailed in Table 3, the most common surgical specialties associated with SWHSI were colorectal (80/187, 42.8%), plastic (24/187, 12.8%) and vascular (22/187, 11.8%) surgery.

Table 3: SWHSI categories according to type of surgical specialty.

|  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- |
| **Surgical specialty** | **Wound category** | | | | | | |  |
| Planned  (*n*) | Partially dehisced1  (*n*) | Fully dehisced1 (*n*) | Surgically opened1 (*n*) | Other  (*n*) | Not known  (*n*) | Missing (*n*) | Total  (*n*) |
| Colorectal | 51 | 16 | 8 | 1 | 1 | 2 | 1 | 80 |
| Plastics | 5 | 10 | 5 | - | 4 | - | - | 24 |
| Vascular | 14 | 3 | 4 | - | - | 1 | - | 22 |
| Orthopaedic | 4 | 3 | 2 | 2 | - | 1 | 2 | 14 |
| Upper GI | 2 | 7 | 2 | 1 | - | - | 1 | 13 |
| Cardiothoracic | 2 | 6 | - | 1 | - | 1 | - | 10 |
| Urology | - | 3 | 3 | - | - | - | - | 6 |
| Obstetrics and Gynaecology | 2 | 2 | - | 1 | - | - | - | 5 |
| Other2 | 5 | - | 1 | - | - | - | - | 6 |
| Breast | - | 2 | - | - | - | - | - | 2 |
| Missing | 4 | - | - | - | 1 | - | - | 5 |

1These wounds were initially closed surgically before they dehisced or were surgically opened to become surgical wounds healing by secondary intention.

2Other details: Pressure sore requiring surgical debridement (*n* = 2) and *n* = 1 for each of the following: sutures removed in OPD clinic and wound now left open to heal by secondary intention; skin graft which did not take; non-healing wound; necrotising fasciitis requiring surgical debridement.

At the time of the survey, most patients (184/187, 98.4%) were receiving active treatment for their wound. Dressings were the most common single treatment being received by 169 (93.4%) patients. Eleven (6.1%) patients were receiving negative pressure wound therapy (NPWT); 10 in secondary care and one in the community setting. One patient (0.5%) was receiving larval therapy.

### Conclusions

This cross-sectional study is the first to characterise SWHSI patients and their wound origin, duration and treatment.

This study provided initial data on wound and treatment characteristics, for which there were limited data when the research programme was conceived. Identifying common surgical specialities (within secondary care) which lead to SWHSI, that almost 50% of SWHSI were planned, and that the most common treatment location was the community, helped us to plan recruitment strategies (i.e. identification of planned SWHSI in advance of surgery) and time frames for both the cohort study and the subsequent pilot, feasibility randomised controlled trial (RCT) (Workstream 4) and will also help to inform research studies in the future.

A total of 43 surgical procedures preceding SWHSI were identified, with common associated surgical specialities being colorectal, plastic, and vascular surgeries. SWHSI occur in a wide range of specialties however there are specific populations where SWHSI more frequently occur and so these may be appropriate as the focus of further research.

Data collected in relation to wound duration at the point of the survey has enabled us to estimate the duration of follow-up required to capture healing events. Again, this information helped to inform our design of the cohort study and pilot, feasibility RCT (Workstream 4).

When this research programme commenced, we had identified the need for a rigorous population-based estimate of SWHSI prevalence. This study has provided a population-based estimate of treated SWHSI prevalence which has suggested that these wounds are relatively common. Given the prevalence observed, this therefore supports the need for further research into SWHSI epidemiology and treatments.

# Cohort Study

## Objectives

Following the cross-sectional survey, we conducted a prospective, inception cohort study with the following objectives:

i) To investigate the clinical characteristics of patients with SWHSI from the point of inception of the wound.

ii) To clearly delineate the clinical outcomes of patients with SWHSI over the lifetime of their wound with a particular focus on time to wound healing and associated determinants.

iii) To describe the types of treatments received by those with SWHSI.

iv) To assess the measurable impact SWHSI have on patients’ quality of life.

## Summary

### Methods

The cohort study was conducted over a 21-month period (18.02.2013 to 30.11.2014) in primary, secondary and community care settings at eight study sites across Yorkshire and Humber, UK. Prior to commencement of the study, approval was obtained from Yorkshire and Humber – Humber Bridge Research Ethics Committee (Reference: 12/YH/0350) and from the associated NHS Trusts.

Patients were eligible for inclusion if they had a SWHSI, defined as ‘*an acute (< 3 weeks duration) open wound, resulting from surgery and requiring treatment, which was healing from the bottom up by the formation of granulation tissue*’. Where patients had multiple SWHSI, the largest wound was deemed to be the ‘*reference SWHSI*’ and detailed data collected for this one wound. Healthcare professionals in primary, secondary and community care settings initially identified and screened patients for eligibility. Clinical areas identified as having a high prevalence of SWHSI were targeted for recruitment, including colorectal and vascular surgical wards. Patients meeting the eligibility criteria were approached for informed consent by a Research Nurse before any data collection. A formal sample size calculation was not required for this study though it was anticipated that 443 participants could be recruited over a six-month period.

Data, including patient, surgery and wound information, quality of life and a wound photograph (used to assess wound features) were collected at baseline. Participants were followed up every one to two weeks for a minimum of 12 and a maximum of 21-months to collect key clinical outcome data (including healing either through participant self-reporting or clinician observation (defined as *‘complete epithelial cover in the absence of a scab (eschar)’*); key clinical events such as surgical site infection (in accordance with Health Protection Agency guidance on surgical site infection surveillance) or hospital admission;[19](#_ENREF_19) ; SWHSI treatments received; and any changes to a participant’s study involvement including death. To ensure accurate data collection, healing status was further verified through a home visit to a sample of patients (10 – 20%).Participants also completed quality of life (SF-12 and EQ-5D-3L)[20](#_ENREF_20), [21](#_ENREF_21) and pain (Brief Pain Inventory (BPI)[22](#_ENREF_22)) assessments via postal questionnaires at three-monthly intervals for a minimum of 12 and a maximum of 21-months.

Data analysis was conducted using Stata version 13 (Stata Corporation, College Station, Texas, USA). Summary statistics for all variables were generated. Association with healing was examined for pre-specified variables and multivariate logistic regression analyses conducted. Kaplan-Meier curves and Cox proportional hazards model analyses were used to examine time to event data. SF-12, [20](#_ENREF_20) EQ-5D-3L,[21](#_ENREF_21) and BPI [22](#_ENREF_22) data were summarised with SF-12 [20](#_ENREF_20) data subsequently analysed using linear mixed models.

### Results

396 patients were recruited to the cohort study from primary and acute care settings in Yorkshire, UK, with 393 participants included in data analysis (three patients were found to be ineligible following recruitment and so were excluded from the analysis). Just over half of participants were male (n=222, 56.5%) with a median age of 55 years (range 19-95 years) and 69.5% of the study population were classed as overweight or obese (31.3% and 38.17% respectively). Current smokers made up 28.5% of participants (i.e. were currently smoking or had quit within the last year).

The most common co-morbidities we observed were cardiovascular disease (n= 151, 38.4%) followed by diabetes (n=103, 26.2%) and peripheral vascular disease (PVD) (n=57, 14.5%). The majority of participants had no previous history of SWHSI (n=93, 72.0%), had only one SWHSI (n=358, 91.0%) and their surgical wound had been planned to heal by secondary intention (n=236, 60.1%). The median area of the reference SWHSI at baseline was 6cm2 (range 0.01-1200cm2). SWHSI location varied, however the most common sites were the abdomen (n=132, 33.6%), foot (n=59, 15.0%) and leg (n=58, 14.8%), linking the commonly represented surgical specialities of colorectal (n=136, 39.7%) and vascular (n=82, 20.9%). At baseline, 164 patients (41.7%) were receiving hydrofibre dressings and 89 (22.7%) were receiving NPWT. Further details of baseline demographics (patient, wound and surgery) and treatments received are presented in Table 4, 5, 6 and 7.

Table 4 – Cohort Patient Baseline Characteristics

|  |  |
| --- | --- |
| **Variable** | **Patients (n=393)** |
| **Age** (years): median (range) | 55.0 (19.0 – 95.3) |
| **Gender** | **n (%)** |
| Male | 222 (56.5%) |
| Female | 171 (43.5%) |
| **BMI**: mean (SD) | 28.9 (6.6) |
| **History of SWHSI** | **n (%)** |
| Yes | 93 (23.7%) |
| No | 283 (72.0%) |
| Don’t know | 17 (4.3%) |
| **Tobacco use** (%) | **n (%)** |
| None in last 10 years | 219 (55.7%) |
| None current but in last 10 years | 62 (15.8%) |
| Current (<1 pack/day) or quit in last year | 84 (21.4%) |
| Current (>1 pack/day) | 28 (7.1%) |
| **Baseline comorbidities** | **Patients (n=286)\*** |
|  | **n (%)** |
| Cardiovascular disease (CVD) | 151 (38.4%) |
| Diabetes | 103 (26.2%) |
| Airways (e.g. Asthma) | 69 (17.6%) |
| Arthritis | 65 (16.5%) |
| Peripheral vascular disease (PVD) | 57 (14.5%) |
| Cancer | 51 (13.0%) |
| Orthopaedic (e.g. fractures) | 27 (6.9%) |
| Stroke | 20 (5.1%) |
| Auto-immune | 19 (4.8%) |
| Neurological | 11 (2.8%) |
| Other | 31 (7.9%) |
| **Medications Used** | **Patients (n=272)+** |
|  | **n (%)** |
| Anti-coagulants/anti platelets | 196 (49.9%) |
| Vasodilator | 111 (28.2%) |
| NSAIDs | 66 (16.8%) |
| Corticosteroids | 11 (2.8%) |
| Immuno-suppressant | 9 (2.3%) |
| Cytotoxic | 5 (1.3%) |

* N is less than total sample – 107 patients without associated comorbidity

+ N is less than total sample – 121 patients did not report medication use

Table 5 – Cohort Wound Baseline Characteristics

|  |  |
| --- | --- |
| **Variable** | **Patients (n=393)** |
| **Number of SWHSI:** median (range) | 1 (1-6) |
| **Area (cm2):** median (range) | 6 (0.01 – 1200) |
| **SWHSI Location** (%) | **n (%)** |
| Abdomen | 132 (33.6%) |
| Foot | 59 (15.0%) |
| Leg | 58 (14.8%) |
| Peri-anal | 34 (8.7%) |
| Back | 19 (4.8%) |
| Natal cleft | 16 (4.1%) |
| Buttocks | 16 (4.1%) |
| Breast | 7 (1.8%) |
| Arm | 5 (1.3%) |
| Perineum | 5 (1.3%) |
| Head | 3 (0.8%) |
| Hand | 2 (0.5%) |
| Neck | 2 (0.5%) |
| Missing | 35 (8.9%) |
| **Aetiology** (%) | **n (%)** |
| Planned | 236 (60.0%) |
| Dehisced | 141 (35.9%) |
| Surgically opened | 16 (4.1%) |
| **Tissue Involvement** (%) | **n (%)** |
| Full thickness | 235 (59.8%) |
| Muscle, tendon or bone exposed | 120 (30.5%) |
| Organ exposed | 1 (0.3%) |
| Unsure | 35 (8.9%) |
| Missing | 2 (0.5%) |
| **Infection at Baseline** (%) | **n (%)** |
| Yes | 79 (20.1%) |
| No | 314 (79.9%) |
| **Antibiotics Used** (%) | **n (%)** |
| Yes | 182 (46.3%) |
| No | 211 (53.7%) |
| **Dressing** (%) | **n (%)** |
| Hydro-fibre/spun hydrocolloid | 164 (41.7%) |
| Other | 129 (32.8%) |
| Wound contact | 114 (29.0%) |
| NPWT | 89 (22.7%) |
| Foam | 36 (9.2%) |
| Alginate | 27 (6.9%) |
| Silver containing | 23 (5.9%) |
| Iodine | 19 (4.8%) |
| Soft polymer | 19 (4.8%) |
| Hydrocolloid | 10 (2.5%) |
| Superabsorbent | 7 (1.8%) |
| Cavity foam | 4 (1.0%) |
| Hydrogel | 1 (0.3%) |
| Silver sulfadiazine | 1 (0.3%) |
| **Treatment Environment** (%) |  |
| Hospital inpatient | 229 (58.3%) |
| Home | 88 (22.4%) |
| GP | 55 (14.0%) |
| Hospital outpatient | 11 (2.8%) |
| Other | 8 (2.0%) |
| Missing | 2 (0.5%) |

Table 6 – Surgery Baseline Characteristics

|  |  |
| --- | --- |
| **Variable** | **Patients (n=393)** |
| **Sub speciality** (%) | **n (%)** |
| Colorectal | 156 (39.7%) |
| Vascular | 82 (20.9%) |
| Other | 50 (12.7%) |
| Plastics | 33 (8.4%) |
| Orthopaedic | 17 (4.3%) |
| Obstetrics and Gynaecology | 13 (3.3%) |
| Surgical debridement | 11 (2.8%) |
| Upper GI | 7 (1.8%) |
| Urology | 7 (1.8%) |
| Cardiothoracic | 7 (1.8%) |
| Neurosurgery | 3 (0.8%) |
| Thoracic | 3 (0.8%) |
| Breast | 2 (0.5%) |
| Trauma | 1 (0.3%) |
| Oral and maxillofacial | 1 (0.3%) |
| **Surgery Type** (%) | **n (%)** |
| Emergency | 236 (60.1%) |
| Elective | 135 (34.4%) |
| Missing | 22 (5.6%) |
| **Contamination Level** (%) | **n (%)** |
| Dirty | 247 (62.9%) |
| Contaminated | 65 (16.5%) |
| Clean-contaminated | 51 (13.0%) |
| Clean | 26 (6.6%) |
| Missing | 4 (1.0%) |

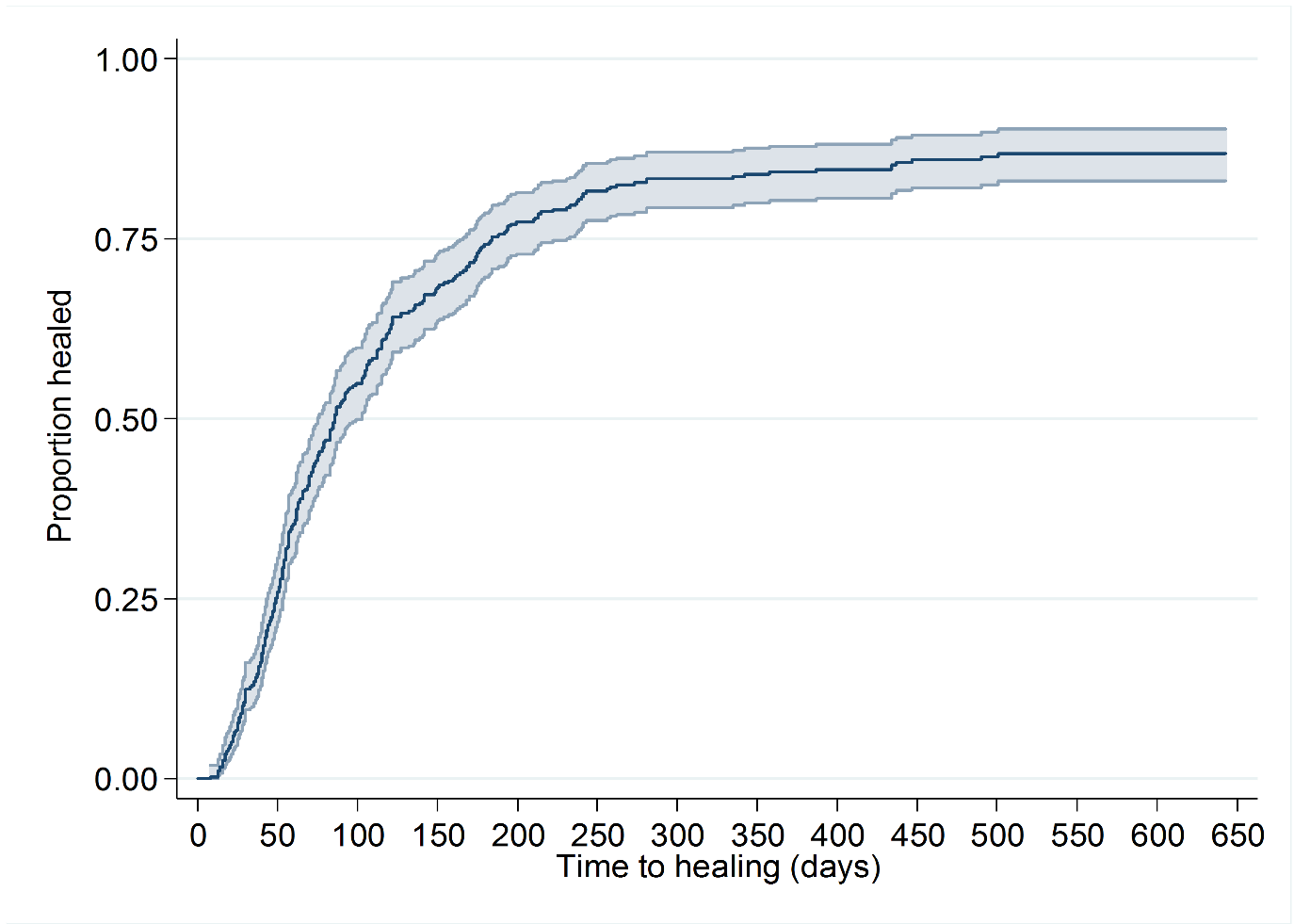
Table 7 – Cohort Treatment Dressings Received at Any Time

|  |  |
| --- | --- |
| **Variable** | **Patients (n=393)** |
| **Treatment Dressings Received (at any time)** (%) | **n (%)\*** |
| Hydrofibre | 259 (65.9%) |
| Basic wound contact dressing | 212 (53.9%) |
| Other | 196 (49.9%) |
| NPWT | 115 (29.3%) |
| Foam | 113 (28.8%) |
| Silver containing dressing | 89 (22.7%) |
| Soft polymer dressing | 73 (18.6%) |
| Iodine containing dressing | 71 (18.1%) |
| Alginate dressing | 49 (12.5%) |
| Hydrogel | 23 (5.9%) |
| Hydrocolloid | 22 (5.6%) |
| Superabsorbent | 21 (5.3%) |
| Cavity | 12 (3.1%) |
| Polyhexamethylene Biguanide (PHMB) dressing | 8 (2.0%) |

Mean length of participant follow-up was 499 days (SD 127.4), with a range of 13 – 651 days (median 528 days). Sixty six (16.8%) participants were not followed-up for the entire study duration; 31 withdrew, 29 died, and six were lost to follow-up. Where the reference SWHSI was situated on a limb, this was amputated for 3.3% of participants (n=13), of whom 61.5% had experienced an infection during follow-up (n=8) and 76.9% had diabetes (n=10). Infections were experienced by 32.1% of study participants (n=126). Hospital admissions were reported for 97 participants (24.7%), of which 66 participants (68.0%) returned to the operating theatre. Thirty six cases (38.1%) of hospital admissions were related to SWHSI.

Our data indicated that the reference SWHSI healed for 81.4% of participants (n=320) during the study. Agreement between patient self -report and nurse assessment of healing status verification was relatively high (77.8% at six-months, 74.2% at 12-months). Disagreements were present for four participants; three patients had healing confirmed during a visit; however paperwork was not completed to this effect and one participant was not healed at the verification visit, but healed shortly afterwards. The median time to healing for all cohort participants was 86 days (95% CI: 75 to 103) as presented in Figure 2. When we assessed time to healing against baseline participant and wound characteristics in a Cox proportional hazards model, baseline wound area above median (p<0.01) and surgical wound contamination level, as determined at the point of surgery (p=0.04) were significant predictors of prolonged time to healing (See Appendix 4). Infection at any point was also found to be a significant predictor of prolonged time to healing (p<0.01).

Figure 2: Cohort Study: Kaplan-Meier curve of time to healing in days



The most commonly received treatment throughout the study was hydrofibre dressings (with 65.9% (n=259) of participants receiving this treatment at least once). Nearly a third (n=115, 29.3%) of participants received NPWT at some point during the study.

Health utility scores captured by the EQ-5D measure, [21](#_ENREF_21) (where 0 corresponds to death and 1 to perfect health) had a mean of 0.5 (SD 0.4) at baseline increasing to a mean of 0.6 (SD 0.4) at six-months and 0.6 (SD 0.4) at 12-months. Further details are provided in Table 8.

Table 8 – Cohort EQ-5D Utility scores by time point and healing status

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
| **Time point** | **Overall** | **Healed** | **Not Healed** | **P value** |
| Baseline (N) | 383 | 311 | 72 |  |
| Mean (SD) | 0.5 (0.4) | 0.5 (0.37) | 0.4 (0.42) | 0.07 |
| 3 months (N) | 258 | 223 | 35 |  |
| Mean (SD) | 0.6 (0.4) | 0.6 (0.38) | 0.6 (0.33) | 0.58 |
| 6 months (N) | 219 | 191 | 28 |  |
| Mean (SD) | 0.6 (0.4) | 0.6 (0.37) | 0.5 (0.34) | 0.08 |
| 12 months (N) | 185 | 166 | 19 |  |
| Mean (SD) | 0.6 (0.4) | 0.6 (0.35) | 0.6 (0.38) | 0.31 |

Pain, measured as BPI scores for pain severity (where 0 = no pain and 10 = pain as bad as you can imagine) and pain interference (where 0 = does not interfere and 10 = completely interferes),[22](#_ENREF_22) reduced slightly over time. Mean pain severity reduced from 3.7 (SD 2.54) at baseline to 3.0 (SD 3.0) by 15-months; similarly mean pain interference scores reduced from 4.2 (SD 2.54) at baseline to 3.1 (SD 3.17) at 15-months. Further details are provided in Table 9.

Table 9 – Cohort BPI scores by time point and healing status

|  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- |
|  | **BPI - Pain Severity** | | | | **BPI - Interference** | | | |
| **Time point** | **Overall** | **Healed** | **Not Healed** | **p value** | **Overall** | **Healed** | **Not Healed** | **p value** |
| Baseline (n) | 385 | 313 | 72 |  | 390 | 318 | 72 |  |
| Mean (SD) | 3.7 (2.54) | 3.6 (2.53) | 4.0 (2.53) | 0.28 | 4.2 (3.12) | 4.2 (3.14) | 4.4 (3.05) | 0.63 |
| 3 months (n) | 257 | 220 | 37 |  | 260 | 223 | 37 |  |
| Mean (SD) | 3.3 (2.63) | 3.3 (2.70) | 3.4 (2.17) | 0.83 | 3.8 (3.12) | 3.7 (3.13) | 4.3 (3.08) | 0.30 |
| 6 months (n) | 210 | 182 | 28 |  | 214 | 186 | 28 |  |
| Mean (SD) | 3.4 (2.67) | 3.3 (2.71) | 3.9 (2.38) | 0.22 | 3.8 (3.18) | 3.7 (3.20) | 4.6 (2.97) | 0.13 |
| 12 months (n) | 179 | 161 | 18 |  | 179 | 161 | 18 |  |
| Mean (SD) | 3.4 (2.66) | 3.3 (2.70) | 4.0 (2.32) | 0.29 | 3.6 (3.18) | 3.5 (3.20) | 4.3 (2.97) | 0.36 |

Quality of life was measured using the SF-12 and presented as SF-12 Physical (PCS) and Mental Component (MCS) scores.[20](#_ENREF_20) Baseline PCS mean scores were 33.1 (SD 10.7) and MCS mean scores were 42.2 (SD 12.35). At 15-months follow-up the PCS mean score was 40.8 (SD 13.46) and the MCS mean score was 48.3 (10.73). Further details are provided in Table 10. A linear mixed model, adjusting for duration of SWHSI, baseline SWHSI area and location, participant age, and baseline SF-12 subscale score, found follow-up time point, baseline score, age and SWHSI duration to be significant predictor of PCS score (p<0.001 in all cases) and MCS score (p=0.03 for time point, p<0.01 for age, baseline score and SWHSI duration).

Table 10 – Cohort SF-12 Physical and Mental Components by Time point

|  |  |  |
| --- | --- | --- |
| **Time point** | **Dimensions (overall population)** | |
| **PCS** | **MCS** |
| Baseline | n=390 | N=390 |
| Mean (SD) | 33.1 (10.17) | 42.2 (12.35) |
| 3 months | n=255 | n=255 |
| Mean (SD) | 37.7 (13.15) | 45.1 (11.69) |
| 6 months | n=223 | n=223 |
| Mean (SD) | 39.2 (12.91) | 45.1 (12.13) |
| 9 months | n=210 | n=210 |
| Mean (SD) | 39.4 (12.89) | 46.4 (11.28) |
| 12 months | n=187 | n=187 |
| Mean (SD) | 38.8 (13.11) | 47.2 (11.58) |
| 15 months | n=147 | n=147 |
| Mean (SD) | 40.8 (13.46) | 48.3 (10.73) |
| 18 months | n=78 | n=78 |
| Mean (SD) | 39.4 (13.52) | 47.3 (11.12) |

### Conclusions

This prospective inception cohort study in patients with SWHSI is the first we have identified. Broad patient groups (patients undergoing abdominal colorectal surgery, lower limb vascular surgery, and a mixed group of other procedures and specialities) were identified which were similar to those identified in our cross-sectional survey. This information flags populations of clinical relevance as well as those likely to be the focus of further research.

The median time to healing for these wounds of approximately three-months is new information, which highlights the extended period of time that patients might expect to cope with open surgical wounds. There was high variability with time to healing ranging from 8 days to 1 year and 4-months (prior to censoring) and 5 days to 1 year and 7-months (following censoring). The chronicity of these wounds is crucial for patients and carers to appreciate in order for them to have realistic expectations regarding wound healing. The cohort also highlights the high number of adverse events that occur in SWHSI patients, with wound infection and readmission to hospital (with the associated care costs) being particularly common. This cohort study data clearly demonstrated that SWHSI pose a distinctive management challenge which was previously unsupported by high-level evidence.

Adjusted analyses provide further initial insights into possible patient and wound ‘*risk*’ factors that might have a detrimental impact on healing including wound infection at any point, baseline wound area and higher levels of surgical wound contamination, as determined at the point of surgery. The predictive baseline factors may be important for the stratification of randomisation or adjustment for prognostic factors in future trials however it should be noted that there are many other covariates which are associated and correlate with these predictors. The SF-12 data indicate that, at baseline, SWHSI patients have quality of life limitations comparable with patients with congestive cardiac failure; however they were significantly younger.[23](#_ENREF_23) This therefore demonstrates the potential impact SWHSI have on patient quality of life; however, as the improvements in SF-12 scores during the study demonstrate, quality of life may be improved by time or wound healing. The research to date is therefore building a picture of a relatively common wound type which takes a prolonged time to heal, negatively impacts quality of life and puts patients at high risk of infection and other adverse events.

The common treatments for SWHSI, in the centres involved in this cohort who were treating SWHSI patients across Yorkshire and Humber, UK, were dressings and NPWT. There is currently limited and generally low quality evidence on how effective dressings are in terms of wound management and promoting optimal clinical outcomes in a cost-effective way.[14](#_ENREF_14) A recent Cochrane systematic review found only two randomised controlled trials with a total of 69 participants that had investigated the relative effectiveness of NPWT on SWHSI, both reporting limited outcome data which prevents any firm conclusions to be made.[14](#_ENREF_14) Given that all SWHSI in this cohort were receiving dressings and/or NPWT, further research to explore clinical and cost-effectiveness of these treatments in one or more of the common surgical groups identified seems warranted and so was considered appropriate for further assessment in Workstream 2.

The prospective and observational design of this study allowed us to follow patients over time and to collect the important natural history, treatment, and outcome data presented here. Whilst we tried to maintain a representative sample, due to the need for consent, the subset recruited might differ in some systematic way to the wider SWHSI patient population. Comparison of the cohort and the cross-sectional survey data may be useful here since the survey data were captured away from the patient’s bedside, did not require consent, and thus may provide a more epidemiologically complete overview of the SWHSI population. In terms of patient epidemiological, wound and surgery data, the populations in the survey and cohort appear similar; however, the findings from the survey may have influenced specific areas for focused recruitment into the cohort study (e.g. sub-speciality specific hospital wards). Some patient groups, where wound problems are recognised nationally, seem under-represented in the cohort study (e.g. post Caesarean section wounds where dehiscence rates as high as 6% have been reported).[24](#_ENREF_24)

The cohort study was conducted in a single geographical area (two large centres in Yorkshire, UK) and therefore the patient groups and the treatment availability observed may not be reflective of national or international patient populations or treatment availability. However we have no reason to suspect that there are huge differences between these surgical patients and those elsewhere, particularly given the breadth of our inclusion criteria.

We also note that our analyses exploring the impact of factors on time to healing is based on our observational dataset and thus these cannot be assumed to be causal relationships. Thus, firm conclusions regarding factors that may affect healing cannot be drawn. However, we are able to report the associations found between observed covariates and healing, and reflect on them. From the outset of the study, there was careful consideration regarding measured study variables, with the aim of capturing important data including factors that had the potential to be prognostic in relation to healing. We consulted widely with clinical experts and extensively scoped the literature with the aim providing the most comprehensive analysis possible.

The further research conducted as part of this research programme (Workstreams 2, 3 and 4) focused on further investigation of interventions which may offer clinical and cost-effective treatment options for SWHSI (Workstream 2) as well as more detailed exploration of patients’ experiences of living with SWHSI and health professionals’ view of delivering care to patients with these challenging wounds.

# Workstream 2: Using evidence from observational research to estimate the value of negative pressure wound therapy in the healing of surgical wounds healing by secondary intention

Following characterisation of surgical wounds healing by secondary intention (SWHSI) patients and their treatment in Workstream 1, the evidence gap regarding the cost-effectiveness of SWHSI treatments remained. Data collected in Workstream 1 indicated that a variety of interventions are used when treating and managing SWHSI. Whilst the majority of participants in the cohort study received dressings throughout follow-up, 29.3% (115/393) received a significantly more expensive technology: negative pressure wound therapy (NPWT).

NPWT devices apply a carefully controlled negative pressure (or vacuum) to a dressing creating an air tight seal and removing tissue fluid away from the treated wound area into a disposable canister.[14](#_ENREF_14) The canister is removed and replaced either when it becomes full or at least once a week. The device is generally used as part of the SWHSI treatment pathway rather than to the point of healing and can be administered and removed by both nurses and surgeons. It has been claimed that NPWT speeds-up wound healing by removing excess fluid, increasing tissue perfusion and removing bacteria.[25](#_ENREF_25) However, despite a recent Cochrane systematic review having identified two randomised controlled trials investigating the relative effectiveness of NPWT on SWHSI,[14](#_ENREF_14) it could not draw any conclusions as the outcome data reported on both studies was very limited.

Given the current level of clinical use on SWHSI, the cohort data collected in Workstream 1 have here been used to evaluate the cost-effectiveness of NPWT for the healing of SWHSI (the clinical outcome of wound treatments most valued by patients,[26](#_ENREF_26) and the value of a future RCT. From this work, a manuscript highlighting methodological challenges of analysing observational evidence in this context has been submitted for publication (See Appendix 5). The current chapter presents the clinical implications of the research.

## Objectives

1. To estimate the cost-effectiveness of NPWT versus wound dressings for the healing of SWHSI using cohort data from Workstream 1.
2. To assess whether investment in further research on treatments for SWHSI is likely to be worthwhile.

## Summary

### Methods

In this Workstream, we evaluated whether, after adjustment, the effects of NPWT on time to healing suggested this health technology is clinically and cost-effective when compared with standard dressings. For clinical effectiveness we used wound healing as the outcome and for cost-effectiveness we quantified the impact of differences in time to healing on Quality-Adjusted Life Years (QALY). This approach assumed that no mortality differences existed and, thus, any improvements in health-related quality of life (HRQoL) were associated with accelerated time to healing only. We also noted that any additional HRQoL improvements that may have arisen from treatment (independent of healing status) were expected to be transient and to not significantly impact on HRQoL (which is a multi-dimensional concept that includes domains related to physical, mental, emotional, and social functioning). For this reason, such effects were not considered here.

We hypothesised that NPWT could be cost-effective by reducing healing time, improving HRQoL, and reducing treatment costs (via reduced healing time). We envisaged that if the total costs of treatment were higher with NPWT than for comparator treatments, NPWT would only be cost-effective if the incremental costs to QALY gains fell below the standard NICE £20,000 to £30,000 per QALY threshold.

Specifically, the cost-effectiveness analysis used cost per QALY gained as the cost-effectiveness outcome. A one year time horizon was considered and an NHS perspective adopted. Formally, we aimed to quantify the impact of NPWT in expected time to healing. The difference in QALY between the interventions was a function of the expected time to healing and the EQ-5D index score while healed/unhealed, the latter estimated by the multilevel model described above. Incremental disease costs were calculated in an analogous way to incremental QALYs, making use of the cost estimates derived in the multilevel two-part modelling approach described above (See Supplementary material in Appendix 5). Treatment related costs considered that patients received some form of treatment up to healing. The daily costs associated with the ‘*Non-NPWT group*’ were based on average costs of dressings in participants who had received other treatments and were calculated by multiplying this cost by the difference in time to healing. For patients receiving NPWT, an average daily cost of NPWT was applied to the mean time on NPWT treatment on the cohort study. In the remaining time patients were assumed to use dressings, with a daily cost equal to patients in the ‘*Non-NPWT*’ group.

The cohort data were analysed for evidence regarding the various aspects of treatment and wound healing including the impact of treatment (NPWT vs. dressings) on the time to healing, and the impact of this SWHSI healing on disease specific costs and HRQoL, as is presented in Figure 3. To estimate the effect of treatment on healing, we attempted to control the confounding (and selection bias) inherent when using observational data in this context. We adjusted for observed confounding (i.e. for characteristics observed within the cohort study sample that determine time to healing and may have differed between the groups). We also attempted to account for any potential confounding from unobserved sources.

Figure 3: Time to healing: descriptive Kaplan-Meier curve



HRQoL was assessed in the cohort study using the EQ-5D index score, obtained through a self-reported questionnaire comprising five domains; mobility, self-care, usual activities, pain and discomfort and anxiety and depression.[21](#_ENREF_21) Participants were also asked to complete a resource use questionnaire quarterly. This questionnaire was developed for this study to allow costing of NHS resources specifically due to the SWHSI and included collection of number of contacts with GPs, nurses and doctors in NHS institutions or the patient’s home as well as the number of nights spent as an inpatient between study follow-up time points. The costing used national sources and 2014 prices.[27](#_ENREF_27)

Analyses required the application of econometric models to the cohort data. A Bayesian approach to inferences was utilised, computed using Monte Carlo Markov chain simulation using WinBUGS version 1.4.3 (Medical Research Council Biostatistics Unit, Cambridge, UK).[28](#_ENREF_28)

#### Identification of external evidence to supplement cohort data

To evaluate the existence of any external evidence to complement the cohort data, we also conducted the following range of systematic literature searches.

We conducted Cochrane systematic reviews of randomised controlled trials evaluating the treatment of SWHSI with any recognised form of NPWT. [14](#_ENREF_14), [29](#_ENREF_29)

Using the general review methods and with the support of an information specialist and an expert systematic reviewer, we conducted systematic searches and identification of the following studies:

* Any cohort studies evaluating the use of NPWT for SWHSI
* Any EQ-5D or related health utility data for people with SWHSI
* Any previous modelling work for the treatments of SWHSI which might inform the planned work.

#### Details of the search strategies used are detailed in Appendix 6.

#### EQ-5D Index Scores and Disease Specific Costs

A multilevel (or panel data) approach was used to model both EQ-5D index scores and quarterly costs that accounted not just for between-participant variation, but also for within-participant variation across the quarterly observations. A time-dependent indicator of whether the participant had healed or not at each time-point was used to capture the effect of healing. Changes from baseline EQ-5D index scores were modelled using a standard multilevel model based on the Normal distribution (random intercept). For cost data, due to a high proportion of zero observations and the typical skewness associated with these data, a two-part model was used: the first part being a multilevel logistic regression (to explain the probability of observing zero costs over time), and the second a mixed Gamma model with log-transformed costs (to evaluate the expected value of the non-zero observations). Both parts were multilevel models to account for the repeated observations per participant.

We calculated the average daily cost of NPWT as £31.78 (according to centre specific costings). For dressings, a unit cost of £2.39 per day was calculated (based on the mix of dressings used within the cohort data). The duration of NPWT treatment was evaluated from the cohort data (mean 37 days, SD 64.6) and was assumed to be independent of time to wound healing, as this treatment is rarely used up to the point of wound healing. NPWT patients were assumed to receive only dressings for the remainder of time unhealed.

Results indicated that healing was associated with a small (but statistically significant) increase in EQ-5D index score (mean 0.055; SE 0.02). Cost data, as presented in Table 11, indicated that healing significantly reduced quarterly wound-related costs (mean £865, SE £112).

Table 11: EQ5D index score and disease-related costs - regression analysis

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
| Model |  | Mean , £ | 95% CrI | |
| Expected EQ5D unhealed | | 0.091 | 0.036 | 0.146 |
| Expected EQ5D healed | | 0.091+0.055  = 0.146 | 0.098 | 0.193 |
| Difference in EQ5D attributed to healing | | 0.055 | 0.015 | 0.094 |
| Expected costs unhealed | | 1124.45 | 916.9 | 1359.1 |
| Expected costs healed | | 258.91 | 208.1 | 317.7 |
| Difference in costs attributed to healing | | 865 | 674.2 | 1126.5 |

#### Relative effectiveness (time to healing) of NPWT and dressing-treated wounds

Based on the cohort data, we took two different approaches to modelling the time to healing, and assessed robustness of our conclusions to the approach taken.

Modelling strategy ‘A’ - Ordinary Least Squares with Imputation: Modelling strategy ‘A’ used ordinary least squares (OLS, or linear regression) to describe time to healing. OLS methods do not deal with censoring, and 73 participants did not heal within the study follow-up period. To generate a complete dataset on time to healing the censored observations on time to wound healing were imputed assuming their follow-up time plus an additional quantity: either 1 day (i.e. participants were conservatively assumed to have healed the day after they were censored) or expected healing time (data elicited from three experienced clinicians and pooled (See Supplementary material in Appendix 5). Note that by attributing an additional time to healing, elicited by clinical experts, to patients that have been censored in the study we are also extrapolating beyond the study follow-up. Such extrapolation is required to allow achieving an unrestricted estimate of the effects of NPWT on mean time to healing, required for cost-effectiveness analysis.

Modelling Strategy ‘B’ - Two-Stage Model: A second, more complex, modelling strategy (modelling strategy B) was also implemented, which explicitly considered the unhealed participants. Instead of OLS, it used a two-step modelling approach: a logistic regression estimated the probability of healing within the follow-up for each treatment, followed by linear regression which estimated the expected time to healing for the population that healed within follow-up. This strategy reflected the possibility of there being a group of ‘long term non-healers’ and allowed exploration of different determinants of the probability of healing and of time to wound healing conditional on having healed in the adjustment for observables.

In terms of adjustment for observed confounding, and in the absence of evidence on determinants of healing in this patient group, a comprehensive variable selection process was undertaken using the cohort data sample. It aimed to identify predictors of treatment assignment with NPWT, predictors of healing and treatment effect modifiers. The selection criterion was based on goodness of fit (using the deviance information criteria at a widely used cut-off of five Deviance Information Criterion points).[30](#_ENREF_30) All the predictors identified were used as adjustment covariates in the regression model for time to healing.

To account for unobservable confounding, instrumental variable (IV) regression was used. This method uses a variable (the instrument), which is associated with treatment assignment but not with outcome (except for any indirect effect on treatment assignment), to adjust for unobservable confounding. A range of instruments focused on the decisions of health professionals to use NPWT (i.e. use of NPWT on previous patient treated, perceptions of NPWT as effective treatment, likelihood of NPWT use for patients, desire to use NPWT more frequently, perceptions of NPWT as affordable and value for money, and company representative input) were considered (See Supplementary material in Appendix 5). The selection of instruments was based on frequentist tests aimed at assessing aspects of validity and relevance (See Supplementary material in Appendix 5). Previous treatment used by the treating health professional was the best performing instrument.

The IV model used two regressions (two stages). The first stage regressed treatment allocation by the instrument and the set of relevant predictors of outcome (logistic regression) to predict the probability of each individual participant being assigned to NPWT. The predictions were then used as a covariate in the second stage regression(s) which, again, conditions on the set of relevant predictors of outcome. Inferences were obtained using a Bayesian framework so that uncertainty over predictions of treatment allocation was fully considered. Any external evidence located (from previous research) was to have been used as prior evidence to update the data obtained from the cohort.

#### Cost-effectiveness of NPWT

The cost-effectiveness analysis uses cost per QALY gained as the cost-effectiveness outcome. A one year time horizon was considered and an NHS perspective adopted. Formally, we aimed to quantify the impact of NPWT in expected time to healing. The difference in QALY between the interventions is, therefore, a function of the expected time to healing and the EQ-5D index score while healed/unhealed, the latter estimated by the multilevel model described above. Incremental disease costs were calculated in an analogous way to incremental QALYs, making use of the cost estimates derived in the multilevel two-part modelling approach described above (See Supplementary material in Appendix 5). Treatment related costs considered that patients received some form of treatment up to healing. The daily costs associated with the ‘*Non-NPWT group*’ were based on average costs of dressings in participants who had received other treatments and were calculated by multiplying this cost by the difference in time to healing. For patients receiving NPWT, an average daily cost of NPWT was applied to the mean time on NPWT treatment on the cohort study. In the remaining time patients were assumed to use dressings, with a daily cost equal to patients in the ‘*Non-NPWT*’ group.

### Results

#### Identification of external evidence to supplement cohort data

We screened 1477 citations from the literature searches and found no existing health utility data collected from patients with SWHSI that could be used. Neither did we find any relevant published models exploring either the clinical or cost-effectiveness of treatments for SWHSI. In terms of relative effects for NPWT compared with alternative treatments on healing, we located four potentially relevant randomised controlled trials and no observational data.

Of the four trials, two explored the use of NPWT compared with standard dressings to treat foot wounds in patients with diabetes.[31](#_ENREF_31), [32](#_ENREF_32) One trial included 162 adult patients who had undergone a transmetatarsal amputation of the foot.[31](#_ENREF_31) It was not clear from the study whether the wounds had been left open following surgery. A second trial included 342 adult patients who had undergone debridement of a foot wound and were randomised to receive NPWT or dressings (predominantly hydrogels and alginates).[32](#_ENREF_32) Whilst it was not clear whether the debridement of these wounds was surgical, we were advised by local clinicians that it was likely to be. Both trials of NPWT in foot wounds reported time to healing data; however, the data appeared to include wounds that had been closed by surgery following treatment with NPWT or dressings. The two trials were considered to be at high risk of performance bias since unblinded health professionals had made key decisions regarding the treatment of wounds, such as closure surgery. This issue has been noted previously and the validity of combining wounds closed by secondary intention and those closed by surgery questioned.[33](#_ENREF_33) The potential for high risk of bias in these studies, combined with the fact that the data from these trials related to only a sub-set of the heterogeneous group of patients of interest, meant that we felt that the relative healing data could not be reasonably combined with the adjusted estimates of the cohort data.

Two further trials were identified.[34](#_ENREF_34), [35](#_ENREF_35) The first study with 20 participants compared NPWT with an alginate dressing in the treatment of open, infected groin wounds.[34](#_ENREF_34) The second study, with 49 participants, compared NPWT with a silicone dressing in the treatment of excised pilonidal sinus.[35](#_ENREF_35) No useable healing data were reported in either trial. For this reason, these studies did not provide relevant evidence to complement the cohort data.

#### Effectiveness results when adjusting for observables

Modelling strategy A: Ordinary Least Squares with Imputation

Relevant associations found with predictors of treatment assignment with NPWT, were: wound area >25cm2, skin and subcutaneous tissue loss (a measure of tissue involvement), and inpatient (vs. outpatient) management. Relevant associations found with predictors of healing were: inpatient (vs. outpatient) management and previous history of SWHSI. The data also suggested that history of SWHSI could be a relevant treatment effect modifier. Predictors of treatment assignment and predictors of healing were used to adjust all regressions within modelling strategy A.

In the model where treatment effect modifiers were not considered, and censored observations were assumed to heal one day after follow-up, participants treated with NPWT were expected to take longer to heal than those who did not receive NPWT – on average 73 days longer (95% Credible Interval (CrI): 33.8 to 112.8) (See Table 12). The addition of the interaction term between treatment and SWHSI history indicated that NPWT was still expected to increase time to healing compared with the use of dressings alone, but the magnitude of effect differed between the groups (181 days in participants with history of SWHSI compared with 42 days in patients without history of SWHSI). Results were similar when elicited expert opinion was used to impute censored healing times, however the point estimates were even less favourable for NPWT (requiring on average, 114 days additional days to wound healing compared to the use of standard dressings) and uncertainty was significantly increased.

Table 12: Effectiveness results. Complete dataset.

|  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- |
| Model ID | model 0 | model 1 | model 2 | model 3 | model 4 |
| Instrument used, *z*: | none | none | none | previous treatment | previous treatment with interaction |
| Equation: | TTH | TTH | TTH | (stage 2)  TTH | (stage 2)  TTH |
| Adjustment covariates: | none | observables | observables + interaction | observables | observables + interaction |
| Area (>25cm2), *x1* |  | 18.0 | 21.1 | 23.8 | 36.2 |
|  | [-23.1, 58.0] | [-20.3, 62.1] | [29.8, 43.7] | [-23.7, 56.3] |
| Treatment location, *x2* |  | 45.3 | 43.8 | 48.9 | 55.3 |
|  | [11.3, 79.2] | [9.9, 76.8] | [3.0, 63.8] | [10.8, 70.8] |
| Tissue involvement, *x3* |  | 31.9 | 26.6 | 33.8 | 37.2 |
|  | [-1.5, 65.0] | [-5.3, 58.7] | [-8.0, 73.1 | [-2.0, 50.6] |
| History, *w* |  | 7.5 | -29.3 | 7.2 | -10.3 |
|  | [-28.4, 42.9] | [-71.5, 12.1] | [-29.5, 44.6] | [-61.4, 7.4] |
| NPWT, *t* | 108.0 | 73.2 | 41.9 | 56.9 | 9.1 |
| [73.6, 142.2] | [33.8, 112.8] | [-1.1, 84.1] | [-71.7, 192.8] | [-120.2, 55.9] |
| NPWT x History, *w.t* | -- | -- | 138.7 | -- | 69.4 |
| -- | -- | [56.9, 221.8] | -- | [-67.5, 118.0] |
| Constant | 116.8 | 81.4 | 92.7 | 81.1 | 86.7 |
| [97.9, 135.2] | [53.3, 110.0] | [64.5, 120.8] | [52.3, 109.1] | [56.7, 97.0] |
| Observations | 393 | 372 | 372 | 372 | 372 |

Imputation using minimum date of healing ; TTH = Time to healing

+ Tissue involvement, skin and subcutaneous tissue loss (*vs* skin loss)

++ Treatment location: inpatient (*vs* outpatient)

Modelling strategy B: Two Stage Model

This modelling approach explicitly modelled the probability of healing within follow-up, and in addition to the predictors of treatment assignment mentioned above, it identified associations with BMI and wound location foot (vs. other locations). For those healing within follow-up, time to healing was associated with surgery type (colorectal vs. other surgeries), wound duration and diabetic foot wounds. No evidence of relevant interaction terms was found. As detailed in Table 13, results indicated that participants treated with NPWT were estimated to have lower probability of healing than those who did not receive NPWT (Odds Ratio (OR) of healing with NPWT was 0.59 (95% CrI: 0.28 to 1.12). The expected time to healing of NPWT treated participants who healed, compared with participants treated with dressings alone, was an additional 46 days (95% CrI: 19.6 to 72.5).

Table 13: Time to healing - Extended modelling approach.

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
| Model ID | model b0 | | model b1 | |
| Equation | (stage 2A)  P[heal] (OR) | (stage 2B)  TTH | (stage 2A)  P[heal] (OR) | (stage 2B) TTH |
| Type of regression model | Logit | OLS | IV, Logit | IV, OLS |
| Adjustment | none | none | adjustment set | adjustment set |
| Area (>25cm2), *x1* | -- | -- | 0.52 | 27.7 |
| -- | -- | [0.24, 0.99] | [0.6, 54.5] |
| Treatment location+, *x2* | -- | -- | 0.52 | 30.9 |
| -- | -- | [0.22, 1.04] | [9.2, 52.3] |
| Tissue involvement++, *x3* | -- | -- | 0.50 | 11.4 |
| -- | -- | [0.25, 0.91] | [-8.1, 30.9] |
| BMI, *v1* | -- | -- | 1.04 | -- |
| -- | -- | [1.00, 1.09] | -- |
| Location – foot, *v2* | -- | -- | 0.34 | 30.1 |
| -- | -- | [0.16, 0.64] | [9.2, 52.3] |
| Surgery type, *v3* | -- | -- | -- | 13.1 |
| -- | -- | -- | [-6.1, 32.4] |
| SWHSI duration, *v4* | -- | -- | -- | 2.3 |
| -- | -- | -- | [0.6, 4.0] |
| Diabetic feet, *v5* |  |  |  | 42.8 |
|  |  |  | [9.1, 76.3] |
| NPWT, *t* | 0.35 | 69.0 | 0.59 | 46.0 |
| [0.20, 0.57] | [48.2, 89.1] | [0.28, 1.12] | [19.6, 72.5] |
| Constant, γ*1* | 6.56 | 82.0 | 6.98 | 36.9 |
| [4.70, 9.37] | [71.9, 92.1] | [1.62, 29.55] | [12.4, 61. 3] |
| Observations | 393 | | 354 | |

OR = Odds ratio; TTH = time to healing;

+ Treatment location: inpatient (vs outpatient);

++ Tissue involvement, skin and subcutaneous tissue loss (vs skin loss)

#### Effectiveness results when adjusting for observables and unobservables

Overall conclusions were similar using modelling strategies A and B, and treatment effect estimates adjusted for unobservables were broadly consistent with the results we observed when adjusting only for observables. Participants treated with NPWT were predicted to take longer to heal, albeit with a high level of uncertainty in the estimates – e.g. modelling strategy B, second stage regression: 46 days longer (95% CrI: 19.6 to 72.5 days).

#### Cost-effectiveness of NPWT

The results for healing, utilities and costs were combined to generate cost-effectiveness estimates for NPWT. Evidence relating to the additional days until healing after censoring for unhealed patients within the follow-up period was elicited from three experts and used in an extended analysis; the results of which are shown in Table 14. Irrespective of the adjustment made (either on observables or unobservables) the results indicated that treatment with NPWT was expected to be less effective and a more costly use of NHS resources than treatment with standard dressings alone. Associated incremental QALYs of -0.012 (SE 0.005) (Model A – Observables), -0.008 (SE 0.011) (Model A – Unobservables), -0.007 (Model B – Observables) and -0.027 (SE 0.017) (Model B – Unobservables). There was little decision uncertainty in this result. When losses arising from the displaced healthcare resources were added to the direct health effects (by valuing 1 QALY at £20, 000), the health consequences of using NPWT were evaluated at -0.111 (Model A – Observables), -0.095 (Model A – Unobservables), -0.087 (Model B – Observables) and -0.183 (Model B – Unobservables) .

Table 12: Elicited evidence on additional time to healing from follow-up for censored patients

|  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- |
|  | Elicited | | Fitted values for parameters of a Gamma distribution | | | | |
|  | 50th percentile, days | 90th percentile, days | Shape,  1st and 3rd quartiles | Scale,  1st and 3rd quartiles | Mean, days  1st and 3rd quartiles | 50th percentile, days  1st and 3rd quartiles | 90th percentile, days  1st and 3rd quartiles |
| Expert 1 | 1044 | 3234 | 1.12 | 1290 | 1445 | 1031 | 3322 |
| Expert 2 | 496 | 679 | 15.3 | 33.1 | 506 | 495 | 683 |
| Expert 3 | 180 | 3650 | 0.23 | 5222 | 1201 | 176 | 3176 |
| Pooled using formal synthesis (95% CrI) |  |  | 1.79  (0.03, 54.5) | 615  (241, 1615) | 1038  (29, 39065) | 559  (0, 28011) | 1820  (15, 37161) |

Data and analyses of the cohort study indicates, with little uncertainty, that treatment with NPWT is less effective and a more costly than treatment with standard dressings alone.

#### Value of a future RCT

Whilst there is uncertainty in the incremental cost and QALY estimates, our analyses consistently indicate there is little uncertainty in the optimal decision, i.e. the probability of treatment with NPWT being considered cost-effective to the UK NHS was close to 0. This means that conducting a future study in order to reduce the associated uncertainty (in the costs and QALYs) would not change the optimal decision and therefore there is no value in conducting such a study for this purpose. For this reason, the VoI analyses originally planned were redundant: the value of information is zero.

Negative Pressure Wound Therapy is currently widely used in clinical practice. The results from the observational study may contradict beliefs with regards the effectiveness of NPWT, but given that our findings have been derived from observational research there is the potential for unresolved confounding to affect the results and reduce confidence in them and the associated conclusions drawn. This lack of confidence may lead decision makers and funders to justify calls for definitive evidence from an RCT. The value of conducting such research, to obtain definitive evidence, will be looked at next.

The value of an RCT to promote implementation was here calculated using a “value of implementation” approach.[36](#_ENREF_36) This assumes that the results of our research provide the best available evidence on the clinical and cost-effectiveness of NPWT, and that the adjustments made for confounding returned unbiased estimates. Data from the cross-sectional survey conducted within this research programme (Workstream 1) indicated a prevalence of treated SWHSI of 4.1 per 10,000 population (95% CI: 3.5 to 4.7). Using the observed median duration of wounds (28 days), the daily incidence of SWHSI was estimated to be approximately 0.0146. Therefore, across England and Wales (population of 57,408, 654 as per ONS 2014 mid-year estimates),[37](#_ENREF_37) we would expect 305,000 patients with SWHSI per year. Cohort study data indicated that 29.3% (115 out of 393) of incident patients used NPWT and so we would expect over 89,000 patients with a SWHSI receiving NPWT per year. Using this information, the value of implementation approach indicated, should definitive RCT evidence correspond with the findings of the modelling of observational data, that successful cessation of NPWT in clinical practice would have direct health benefits that would sum up to between 719 and 2427 QALYs. When displaced healthcare benefits were included (by valuing a QALY at £20,000) the value of a definitive trial increased, to approximately 8,500 to 16,400 QALY per year (conditional on the findings of a future trial and their successful implementation).

### Conclusions

This work compared the clinical and cost-effectiveness of NPWT in healing of SWHSI, relative to dressings using advanced methods of adjustment for the potential selection effects expected with observational data. The initial publication from this stream of work (See Appendix 5) covers methodological aspects of this research; thus here we aimed to discuss the clinical implications of our results.

Results show that NPWT users in the cohort took longer to heal, and this result (which did not reach conventional levels of statistical significance) sustains even after adjustment for differences in potential prognostic factors between the groups. A number of limitations of the data and methods of analyses were also tested (such as alternative assumptions on censoring); none leading to different conclusions. Across all analyses, treatment with NPWT for SWHSI was not effective or cost-effective, and there was little uncertainty over this result. Our treatment effect findings are derived from modelling of observational data, and our results (and our interpretation of these) assume that inferences obtained (after adjustment) are unbiased. However even extensive adjustment of observational data does not negate the potential for unresolved confounding to affect the results and the risk of this can reduce confidence in conclusions drawn from observational data. Definitive evidence from a RCT may be the only way to overcome this lack of confidence.

It is also important to emphasise that we evaluated the causal effects of NPWT on the *healing of SWHSI*. Wound infection at baseline was explored in our analyses and was not found to be associated with either treatment allocation or wound healing. However, NPWT may have further direct effects on HRQoL (independent of healing), for example, in prevention of wound infection or assisting with wound management. These other effects are likely to be less significant in magnitude and in duration as NPWT is typically used for only a short duration of time. If future research further explores the effectiveness of NPWT on infection (prevention or treatment), it is important that this research is designed to also explore effects on healing.

There are other important clinical conclusions to be drawn from our analyses. Firstly, patients treated with NPWT in the cohort study differ from those that were not; that is, there was significant selection into treatment with NPWT in the cohort study. Trying to understand how clinicians allocate treatment with NPWT was, however, difficult. Wound area, level of tissue involvement, and being an inpatient (rather than outpatient) seemed to have contributed to decisions on whether to use NPWT, but do not fully explain these treatment decisions.

Secondly, in adjusting for selection effects it was important to consider relevant predictors of healing. However, given the absence of epidemiological research, there was no a priori evidence on what could predict healing in this patient group. The associations found within our work used a pre-defined process of model selection and indicated that being an inpatient (rather than outpatient) and having a history of SWHSI may be relevant prognostic characteristics for healing. However, the sample of patients included in the cohort was very heterogeneous – for example, there was a range of anatomical sites for the SWHSI with the most frequent being the abdomen (33.6%) and foot and leg wounds (30%); an approximately equal share of dehisced vs. planned open wounds (60% vs. 40%, respectively), and an approximately equal share of wounds with superficial vs deeper tissue involvement (59% with skin involvement only and 41% with skin and subcutaneous tissue involvement). If determinants of healing differ across different subpopulations, then a more homogeneous sample would have meant it was easier to identify these.

Thirdly, our analyses of the cohort data suggests the existence of a subpopulation of ‘hard to heal’ patients –  time to healing for those who healed (mean 99 days) was very different to the mean follow-up for those who did not heal (mean 416 days). Those who did not heal within follow-up also differed from those who did, and our explorations indicate that BMI and foot wound location are associated with a lower probability of healing. Further research could continue to explore characteristics of ‘*hard to heal*’ patients who present with the biggest burden of disease and thus have a larger capacity to benefit from treatments.

Finally, our research also suggests that individuals with a history of SWHSI treated with NPWT are expected to take even longer to heal than those who did not have a history of SWHSI. Whilst we are not clear of the clinical plausibility of such an effect, future research on NPWT could explore the evidence for such treatment effect interaction.

The findings from this Workstream have informed the final phase of work in our research programme, a pilot, feasibility RCT assessing NPWT compared with standard dressings.

# Workstream 3: Qualitative interviews to explore patient and clinician perspectives regarding surgical wounds healing by secondary intention

The absence of available literature meant that when we began this programme there was limited knowledge about patient experience of surgical wounds healing by secondary intention (SWHSI) or their impact. There was also a lack of research about patient and professional opinions regarding wound management, treatment options and relevant outcomes in relation to measuring treatment effectiveness. These key elements were explored through qualitative interviews with both patients and health professionals (surgeons and nurses). A paper detailing findings from the patient interviews has been published (See Appendix 7) [38](#_ENREF_38). A paper detailing findings from the clinician interviews has been submitted for publication (See Appendix 8).

## Objectives

To explore, using qualitative interviews;

1. Patients’ perspectives and experiences of living with a SWHSI and to elicit their views regarding management and desirable outcomes.
2. NHS professionals’ views and experiences concerning treatment choices for SWHSI.

## Summary

### Methods

The purpose of this qualitative research was to explore the daily, lived experiences of patients with SWHSI and to understand health care professionals’ perspectives of managing these wounds. The topic guide developed for use with patients (See Appendix 9) comprised a few key questions to encourage in-depth exploration of how a SWHSI might impact on every aspect of patients’ lives. Patient advisors were asked to comment on the content and clarity of the patient topic guide prior to its use. During interview, individual patients were encouraged to identify and speak freely about any issue related to their SWHSI that affected them. The clinicians’ topic guide (See Appendix 10) similarly encouraged clinicians to fully express their own perspectives, with the topic guide acting as a flexible tool to guide the discussion.

Patients and clinicians were recruited from both acute and community nursing services in two settings in the North of England; one a large city with an economically and ethnically diverse population and high levels of deprivation, the other a smaller sized city, also with high levels of deprivation and ethnic diversity.

Patients were eligible to participate if they had a surgical wound considered to be healing by secondary intention by the referring clinician, were aged 18 years or older and able to give informed consent. Patients were purposively sampled to include those who had SWHSI, which were slow to heal or non-healing, and to ensure representation across gender, age, duration of wound and surgical discipline (e.g. general, vascular, orthopaedic surgery). We aimed for ethnic diversity within the patient sample and for a range of patients from both acute and community treatment settings. Potentially eligible patients were identified and approached regarding study participation by a member of their usual healthcare team. Clinicians were purposively sampled from amongst those with responsibility for caring for patients with SWHSI, and a range of clinicians from community and acute settings were selected for participation.

The backgrounds of the two researchers involved in the study differed; one was a registered nurse with extensive experience of applied health services research, while the other had a background in social sciences research. The two researchers, who were co-located in the same office, held regular, informal meetings during data collection, to discuss any differences and ensure consistency of approach. No significant differences were identified in the data collected by the two individuals.

Semi-structured interviews were conducted in patients’ homes and at the clinicians’ place of work. Interviews with patients lasted approximately one hour; interviews with surgeons ranged from 30 to 45 minutes; and those with nurses from 60 to 75 minutes. All interviews were audio recorded and fully transcribed, before being analysed for thematic content using ‘*framework*’ approach (See Appendix 11).[39](#_ENREF_39) Interviews continued until no new information was forthcoming.[40](#_ENREF_40) After familiarisation with the data set, and initial identification of themes, a coding framework was developed to allow for linkage between participants and their responses and comparison across the full dataset. This coding framework was modified during the initial phases of data analysis to accommodate new responses from patients. Interpretation relied on the abilities of the analysts to determine meaning, salience and connection.[41](#_ENREF_41) The input of patient advisors was sought during the analytic process, and advisors were asked to contribute to reflections on the meaning and interpretation of the data arising from the interviews.

The study received research ethics approval from Yorkshire and The Humber – Leeds Central Research Ethics Committee (Reference: 11/YH/0313) and written, informed consent was obtained from all patients prior to participation in the interviews.

### Results

#### Patient Interviews

Twenty patients with SWHSI participated in the qualitative interviews. The mean age of patients was 53 years (range: 19-76), with an almost equal split in gender (11 women and nine men), 19 patients were of white British ethnicity and one of south Asian ethnicity. The surgical procedure preceding the SWHSI was abdominal surgery (11 patients), vascular surgery (five patients), orthopaedic surgery (two patients) and excision of pilonidal sinus and drainage of abscess (one patient each respectively). The median duration of SWHSI was 5.5-months (range: 1.5 – 60). Further details of the sample are presented in Table 15.

Table 15 - Study participants’ (patient) socio-demographic details

|  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- |
| **ID** | **Gender** | **Age** | **Employment**  **status** | **Wound type** | **Wound duration**  **(months)** | **Co-morbidities**  **(self-reported)** |
| P1 | Female | 58 | Unemployed  Registered disabled | Dehisced abdominal wound; had had multiple operations | 6 | Diabetes  Crohn’s disease |
| P2 | Female | 73 | Retired | Dehisced wound on upper thigh after bypass graft | 2 | Diabetes |
| P3 | Female | 19 | Unemployed since surgery | Dehisced wound on leg after open fracture | 3 |  |
| P4 | Female | 65 | Retired | Open surgical wound following amputation of toes | 12 | Diabetes |
| P5 | Male | 30 | Employed | Dehisced wound in groin after infection | 3 |  |
| P6 | Male | 32 | Unemployed since surgery | Open surgical wound after abdominal surgery | 2 |  |
| P7 | Female | 44 | Employed | Open surgical wound after drainage of abscess in axilla | 1.5 |  |
| P8 | Male | 52 | Unemployed since surgery | Dehisced abdominal wound | 24 |  |
| P9 | Male | 76 | Retired | Non-healing abdominal wound following surgery for bowel cancer | 60 |  |
| P10 | Male | 64 | Early retirement due to work injury | Open surgical wound following amputation of toes; had had skin graft | 5 |  |
| P11 | Male | 45 | Unemployed since surgery | Dehisced wound due to infection after surgery for Crohn’s disease | 3 | Crohn’s disease  Necrotising fasciitis  Pyoderma |
| P12 | Female | 72 | Retired | Dehisced abdominal wound | 8 |  |
| P13 | Female | 54 | Employed | Dehisced abdominal wound | 1.5 |  |
| P14 | Female | 47 | Unemployed since surgery | Dehisced abdominal wound | 4 |  |
| P15 | Female | 46 | Unemployed since surgery | Dehisced abdominal wound | 9 | Crohn’s disease |
| P16 | Female | 76 | Retired | Dehisced abdominal wound | 10 |  |
| P17 | Male | 44 | Unemployed | Open surgical wound following partial amputation of foot | 24 | Diabetes |
| P18 | Male | 65 | Employed | Non-healing abdominal wound | 2 |  |
| P19 | Male | 25 | Employed | Slow to heal wound following treatment for pilonidal sinus | 30 |  |
| P20 | Female | 71 | Retired | Dehisced wound following spinal surgery | 9 | Rheumatoid arthritis |

Six emerging themes were identified through the interviews: initial reactions, wound symptoms, expectations of wound healing, psychosocial impact, service provision and SWHSI treatment.

##### *Initial Reaction*

Unexpected SWHSI (i.e. following emergency surgery or a dehisced wound) resulted in feelings of alarm, shock, disbelief and disgust amongst patients. This was most significant in patients whose SWHSI resulted in the exposure of their internal organs. These patients frequently reported that they had presumed that their wound would be stitched closed and they were shocked and confused when this had not occurred. Where wounds were extensive, patients indicated their fear that the wound ‘*would never heal’*, to the extent where they could often recall the specific dimensions of their wound at various points in time.

In contrast, elective SWHSI (e.g. from an elective partial foot amputation in a diabetic patient) resulted in less shock and alarm in relation to the initial appearance and immediate impact of their wound. These patients frequently viewed surgical intervention as a means of respite from pain, as well as offering a reduced risk of limb loss. Given the planned nature of these wounds, pre-operative discussion with clinicians regarding their post-operative surgical wound was much more common in this group of patients, which is likely to have helped to manage patient expectations.

##### *Wound Related Symptoms*

Wound related symptoms were reported as having a negative impact on daily life, physical and psychosocial functioning and sense of well-being. Frequently reported symptoms included: pain and reduced mobility; leakage; smell; difficulties with personal hygiene; reduced appetite; disrupted sleep; lack of energy and low mood; skin problems; and side-effects from wound related medication (such as analgesia).

The limited physical mobility (and especially being unable to drive) was particularly frustrating for patients and disruptive of normal activities. In addition, patients felt unable to socialise as they believed the wound smell and exudate might be offensive to others.

##### *Healing Expectations*

The majority of patients with open abdominal wounds feared their wound would never heal. Patients reported frequently feeling disappointed, dismayed and frustrated with the slow healing process of their SWHSI and lack of, or delayed, healing also resulted in increased anxiety about future surgery for some patients. These feelings were intensified when patients had experienced healing delays due to infection. Many of those who had experienced previous SWHSI expected healing to be a slow process whilst patients without previous SWHSI often had unrealistic expectations of time to healing. Patients’ expectations often conflicted with information provided by health professionals. Comments from health care professionals regarding the wound and its prospects of healing often had profound implications for patients. Positive remarks were a morale boost, whilst negative remarks frequently adversely affected the patients’ general outlook. Where conflicting information was provided, this was identified as a cause of confusion and consternation.

Patients were ever-hopeful that a new or untried treatment might accelerate or achieve healing of the wound, and they often looked to tissue viability nurses, regarded as experts in their field, to provide a solution for their unhealed wound. There was a willingness among patients to undergo almost any procedure or treatment if it might promise accelerated healing, even if it was unpleasant.

##### *Psychosocial Impact*

SWHSI were frequently found to have a devastating effect on the lives of patients and their families, particularly following emergency surgery or if associated with a large cavity. Patients reported feeling uncertain and anxious following their surgery, particularly in relation to wound healing, physical health, financial concerns and relationships with others.

Patients felt that they had become isolated, withdrawn from society and confined to their homes whilst their SWHSI was healing. Patients receiving negative pressure wound therapy (NPWT) as a SWHSI treatment reported feeling unable to leave the house due to the pump and tubes associated with the device and concerns about their self-image in public. Feelings of isolation were particularly acute in patients who were incapable of driving after surgery, especially if they were the only car driver in the family. Disruption of established roles and responsibilities within the family unit was common and patients often reported feeling burdensome and dependent. Anxiety was also extremely common and often multifaceted.

The financial impact associated with SWHSI was severe for some patients and their families, causing high levels of stress. The uncertainties and restrictions associated with SWHSI appeared particularly difficult for younger male participants who were often the main earner in the family. Family members were also affected as they tried to balance maintaining the household income and acting as a carer for the patient. Out of pocket expenses in relation to transport to clinic appointments were troublesome for several patients, particularly for those who were unwilling to use public transport to attend appointments due to concerns about wound odour and who preferred to pay for private taxis.

Most participants described support from partners, family members, friends and neighbours as crucial, whether that support was practical (e.g. with transport and shopping) or emotional (helping them to adapt and adjust to living with their wound). Some older patients were however reluctant to ask their offspring for assistance, preferring to try to manage independently if they could.

Living with a SWHSI had a profound impact on patients’ mental well-being. Almost a quarter of patients indicated they had become depressed as a result of factors associated with their SWHSI. This was sometimes associated with acceptance of the diagnosis of the condition (e.g. Crohn’s disease) that had resulted in their SWHSI. Other patients did not report feeling depressed but did acknowledge periods of low mood as a result of their experience of living with a SWHSI.

##### *Service Provision*

Patients were managed in a variety of settings including acute hospital and community settings, where district, community or general practice nurses predominantly gave patient care. Reported impressions of care were wide ranging, from *“brilliant”* to *“rubbish”.*

Prolonged or multiple hospital admissions were common. Duration of hospital admission ranged from an overnight stay (abscess drainage) to nine-months (spinal surgery). Patients indicated that timely provision of information and regular contact with surgeons (especially those who had performed the operation) and nurses during this time was important and valued. Comments from surgeons regarding general progress and wound healing were highly important to patients. Positive comments generated reassurance whilst brusque and hurried interactions led to patients feeling unheard, dismissed and angry.

Several patients reported that their wound dressings had not been changed as frequently as they thought necessary whilst in hospital and a majority reported their care on the wards was less than satisfactory. Significantly, many patients reported feeling dissatisfied and unsupported at the point of hospital discharge due to a lack of available information relating to follow-up care and risks, symptoms and management of infection. Following discharge from hospital however, only a minority of patients felt unsupported.

All patients expressed views about the district, community and general practice nursing service with the majority having received home visits by district, community or general practice nurses during their healing pathway. It was widely perceived that the district, community or general practice nurses had limited time to devote to visits, leaving patients feeling that visits were rushed, although there was acknowledgement that the nurses had tried to attend to all needs during the visit. Patients also indicated that the unpredictability of visit timings caused substantial frustration and inconvenience, and for three patients, care via a general practice or treatment centre nurse was preferred, due to convenience and on-going continuity of care.

With specific regard to district, community or general practice nursing services, patients were particularly troubled by a lack of continuity of care; with some patients claiming that they would *‘never see the same nurse twice in a row’.* Patients became anxious when they received conflicting information regarding the condition and likely healing and management of their wound, particularly if the information given was at variance to that provided by their surgeon.

##### *SWHSI treatment*

The main wound treatments experienced by study participants were (i) NPWT, (ii) debridement, (iii) dressings, and (iv) skin-grafting.

Eleven patients had experience of NPWT, which they generally viewed as an effective treatment. The majority of patients receiving NPWT had undergone bowel or abdominal surgeries; however patients also experienced NPWT for foot and orthopaedic surgical wounds. Perceived advantages of NPWT included reduced dressing change frequency compared with ‘*traditional*’ dressings, and a reduced risk of wound infection. Patients did however note that NPWT dressing changes were painful when sponge or foam, rather than gauze, were used. Patients with prior experience of NPWT reported that some district, community and general practice nurses lacked appropriate knowledge, experience and expertise in NPWT and in some instances required guidance from the patient in its application. Perceptions concerning lack of nursing expertise in the use of this therapy were linked to feelings of anxiety by some patients. Several patients reported they were disinclined to go out of the home with NPWT *in situ*, due to it being cumbersome or due to embarrassment about the equipment, and when they did leave the house they felt a need to somehow disguise the device. Patients also reported delay in discharge from hospital due to difficulty associated with obtaining NPWT within the community setting and they expressed the view that this treatment was more easily administered within a hospital environment as opposed to community settings.

Six patients had undergone wound debridement and described this as an extremely painful procedure. The rationale for, and potential effectiveness of, debridement was often poorly communicated to patients.

Three patients underwent skin-grafting as a method of promoting healing, with a further two participants having discussed the possibility of a skin-graft for their SWHSI. Views regarding the desirability of skin-grafting were mixed, due to fears of infection and/or graft failure.

Patients reported they would have liked more information from clinicians about the rationale for using different treatment methods and approaches, including different dressings, and they described nurses as rarely ‘singing from the same hymn sheet’ when selecting dressings.

#### Clinician Interviews

Five surgeons and seven nurses participated in the qualitative interviews; two general surgeons, two vascular surgeons, one plastic surgeon, three tissue viability nurses, one general surgery nurse, two district nurses and one community staff nurse. Further details of the sample are presented in Table 16 and17.

Table 16 - Study participants’ (nurses) demographic details

|  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- |
| **ID** | **Gender** | **Age** | **Qualifications** | **Role** | **Specialist training** |
| 1 | F | 49 | RN; BA (Hons) nursing practice; post graduate certificate nursing studies; community/specialist practitioner. | Tissue Viability Nurse Specialist  *(specialist assessment; care planning; evaluation; prescribing; liaison with surgeons; supporting nurses)* | Diploma in wound care and ulcer management. |
| 2 | F | 46 | RN; BSc (Hons) health and social care; diploma in nursing. | Clinical Nurse Specialist  *(education; training; support for colleagues)* | No specialist training.  Has experience of working within the tissue viability team. |
| 3 | F | 42 | RN; BSc (Hons); district nursing qualification. | Tissue Viability Nurse Specialist  *(assessment of complex surgical wounds; instigation and monitoring of negative pressure wound therapy)* | No specialist training. Experience; reading relevant research; ‘peer shadowing’. |
| 4 | F | 44 | RN | Senior nurse working on acute general surgery ward caring for patients with abscess/fistulas /wound dehiscence | Had training from employees of commercial company in use of NPWT. |
| 5 | F | 39 | RN; district nursing qualification | Senior treatment room nurse (7 treatment rooms city wide) | Study days; experience; leg ulcer management course. |
| 6 | F | 38 | RN; district nurse | District Nurse  Link nurse tissue viability | Link nurse tissue viability and related study sessions. |
| 7 | F | 52 | RN | Community Staff Nurse  General wound care | Wound management course. |

Table 17 - Study participants’ (surgeons) demographic details

|  |  |  |
| --- | --- | --- |
| **Surgeon** | **Specialty** | **Study site** |
| Surgeon 1 | General surgeon | Site 1 |
| Surgeon 2 | Vascular surgeon | Site 1 |
| Surgeon 3 | General surgeon | Site 2 |
| Surgeon 4 | Plastic surgeon | Site 1 |
| Surgeon 5 | Vascular surgeon | Site 2 |

Six themes were identified in the interview data: factors influencing SWHSI development, devolving care to nurses, multifaceted assessment, NPWT for specific types of SWHSI, presumed cost-effectiveness and dressing selection by nurses.

##### *Factors influencing SWHSI development*

Surgeons and nurses identified that the main types of SWHSI encountered were extensive cavity wounds (e.g. from abdominal or pilonidal sinus surgery); open wounds on the feet of diabetic patients and wounds associated with lymph node removal (e.g. in the axilla and groin). Abdominal surgery wounds were regarded as being most likely to heal slowly or not to heal and were thought to be most likely to dehisce.

Both surgeons and nurses broadly agreed that there were a number of factors that predicted slow or no healing. These included surgical factors (e.g. emergency surgery, reason for surgery, type of procedure, or presence of a foreign body), patient co-morbidities or factors (e.g. obesity, diabetes, cancer, arterial and/or vascular disease, impaired immune system or Crohn’s disease, nutritional status, smoking status and age), infection, medication, restricted mobility, and lack of treatment compliance. It was however noted that in many instances it was difficult to identify any specific reason for impaired wound healing.

Wound healing was sometimes viewed as completely unpredictable: a wound was said to sometimes progress well, stop healing for a period with no obvious explanation and then re-commence healing. It was suggested that a pause in healing might occur following removal of NPWT. Over-granulation was also mentioned as a factor that could delay the final stages of wound healing.

##### *Devolving care to nurses versus “looking after our own”*

Surgeon involvement with the wound management of individual patients was related to wound related factors as well as the patient’s general condition and the nature of the surgery. The two general surgeons included in the study indicated that usually their patients’ wound care was passed on to nurses following discharge. However, the two vascular and one plastic surgeon interviewed said that they were more likely to continue to have personal involvement in wound care for *‘their’* patients through follow-up in specialist clinics, which they described as *“looking after our own”.*

Surgeons and/or tissue viability nurse specialists generally initiated the decisions to use NPWT. Ward, district and community nurses indicated that there was limited knowledge and expertise about use of NPWT amongst general nurses working in both acute and community nursing settings. Tissue viability nurses reported that they were often regarded as the first port of call for expert advice in relation to complex non-healing wounds and use of NPWT.

##### *Assessment is multifaceted and complex*

Factors cited by the surgeons as associated with wound healing were: the size of the wound; presence of wound infection, slough and/or granulation tissue; whether the wound appears to have healed superficially, but remains unhealed at a deeper level; level of exudate; the condition of the wound edges; the patients’ general condition, including nutritional state and ability to mobilise; signs of over-granulation; whether the wound seems ‘*static*’ and/or appears to be colonised and blood supply at the wound site. Nurses described similar factors as affecting wound healing. They also emphasised psychosocial and practical issues that might impact on patients’ quality of life, such as level of family support and patients’ potential for self-care of the wound. Tissue viability nurses, for example, commented that they would adopt a holistic approach to assessment by gathering background information about the history of the wound, as well as other relevant details about the patient’s physical, social and psychological status.

Only one nurse mentioned using a wound-specific assessment tool - the TIME (Tissue, Infection, Moisture and wound Edge) tool during the initial wound assessment.[42](#_ENREF_42)

##### *Perceived advantages and disadvantages of NPWT*

NPWT was favoured for a variety of reasons. Surgeons reported that the use of NPWT was increasing and that complex, cavity wounds (e.g. extensive abdominal wounds) were ideally suited to benefit from NPWT. It was perceived that NPWT controlled exudate, contained and limited contamination (reducing infection risk), supported resolution of infection, promoted growth of granulation tissue, hastened wound healing, and was liked by patients because it was convenient, promoted mobility, enhanced quality of life, shortened hospital stay and reduced the number of required dressing changes. Clinicians generally perceived NPWT as a cost-effective and transformative treatment, particularly for patients with hard to heal wounds.

One tissue viability nurse did however express strong reservations about the perceived “*espoused universal benefit*” of NPWT, noting that it was not necessarily *‘the answer to everything’* and inappropriate for some patient groups*.* This view was supported by some surgeons and nurses who indicatedthat NPWT was an inappropriate treatment for some types of wound, particularly in patients following abdominal surgery who might be at risk of developing fistulae, as well as some patients who were unable to cope with the device. The same tissue viability nurse felt NPWT was sometimes “*oversold*” to patients, raising expectations unrealistically. This nurse also commented that longer-term healing of SWHSI could be impeded by the use of NPWT due to the use of foam, rather than gauze dressings, which, they suggested, could result in the formation of less *‘robust’* granulation tissue. Further disadvantages, perceived by surgeons, included its lack of suitability for some patients who might be unable to cope with the equipment due to frailty or impairment; limited availability in the community; high cost; and the need for staff (predominantly nurse) training in its application. Disadvantages from a patient perspective mentioned by nurses were anxiety and disruption to sleep, and restrictions, even with ‘*portable*’ devices, when mobility increased in the time following surgery.

##### *Presumed cost-effectiveness*

Three surgeons noted the lack of research evidence relating to NPWT but felt that their own and colleagues’ experiences supported its use. These surgeons perceived NPWT use as increasingly widespread and safe. They viewed NPWT as a cost-effective treatment option on the basis that patients with complex wounds could be discharged from hospital sooner, required less input from district, community or general practice nurses (in terms of dressing changes) once back in the community, and could return to work more quickly.

One surgeon was of the opinion that there was currently sufficient evidence to support the use of NPWT and referred to various studies (small scale, mainly case series) apparently demonstrating its effectiveness. This surgeon, the strongest advocate of NPWT amongst those interviewed, asserted that the advent of NPWT had *‘changed practice considerably’.*

##### *Dressing selection usually devolved to nurses by surgeons in the study*

Surgeons’ knowledge concerning dressings was, by their own admission, limited, resulting in reliance on nurses to make appropriate dressing choices. The nurses described how wound, patient and general factors influenced wound management decisions. Nurses felt they had adequate information to support wound management decisions for most routine SWHSI, with choices determined by local guidance (formularies and protocols), that purported to be evidence based, alongside an appreciation of the need for cost-effective treatment decisions, patient preference and likely concordance, and inclusive of the views of colleagues.

Nurses also commented that if they were uncertain about how to manage a complex, non-healing open surgical wound, they would contact tissue viability nurse specialists for advice and guidance. The tissue viability nurses noted that in these situations they were able to draw on each other’s knowledge and experience in dealing with difficult to heal wounds, through their involvement in close knit clinical teams and other wound-focussed clinical networks.

*Similarities and differences between responses from surgeons and nurses*

Surgeons and nurses were in broad agreement about the types of wounds likely to be slow to heal/non-healing, and their symptom burden. During interview, tissue viability nurses focussed more than surgeons on describing the possible psychosocial and financial consequences for patients of experiencing a SWHSI. Tissue viability nurses explained that they had more time than surgeons to explore the range of impacts of a SWHSI on the lives of individual patients and their family members; in their interviews, surgeons tended to focus mainly, though not exclusively, on clinical aspects of patients’ surgical wounds and healing.

Tissue viability nurses reported their own first-hand experiences of the challenges of managing patients’ hopes and expectations for healing; they suggested that sometimes patients appeared ill-informed about likely healing projections after discharge from hospital; and they said that sometimes there appeared to be a ‘mismatch’ between surgeons’ and patients’ expectations for healing (patients holding unrealistic expectations).

Six of the seven nurses interviewed were in agreement with the study surgeons’ views that NPWT is effective in the management of SWHSI, particularly in the management of wound exudates, due to the good dressing seal that can be obtained, and the potential for reduced likelihood of infection, resulting in perceived speedier healing of the wound. Reservations expressed by the seventh nurse related to the use of gauze rather than foam in the application of NPWT (she thought use of gauze caused less pain to patients), and the possibility of patients with an abdominal SWHSI developing an intestinal fistula connected to use of NPWT, a concern also noted by the general surgeons. Surgeons and nurses both commented that NPWT was not a suitable treatment for the very frail (who could find the equipment difficult to manage) and/or for patients with cognitive impairment.

During interview, surgeons were more likely than nurses to talk about perceived cost-effectiveness of NPWT in relation to length of hospital stay, reporting that use of NPWT allowed patients to be discharged from hospital sooner than with use of conventional dressings; surgeons also pointed to a reduced need for dressing changes by community based nurses, which they perceived as beneficial in terms of reducing these nurses’ workload and accrual of savings to the NHS. Variability in community and district nurses’ expertise in application of NPWT, and the need for more widespread training in its application, were reported more frequently by nurses than surgeons, who appeared to be less aware of these issues.

### Conclusions

This is the first study investigating patients’ and clinicians’ views about the management and treatment of SWHSI, and patients’ experiences of living with this condition. Findings from our study therefore lay the groundwork for further research in this important aspect of healthcare about which so little is known. For example, understanding more about what matters to patients helps to ensure appropriate outcomes are captured in future trials.

Patients’ initial reactions to their SWHSI were of shock and disbelief, and the visual reminder following surgery of a ‘*violated*’ body intensified these feelings, particularly for patients with large abdominal cavity wounds. Having a SWHSI impacted substantially on daily living and this impact was particularly important for those patients with children or in employment, who constitute a younger demographic than seen in previous wound research associated with other wound types. As healing progressed, patients were concerned with both their own reaction to the wound and the reactions of others. The long healing process for many patients, characterised by a reduced quality of life and a constant need for treatment and care concurs with previous evidence in relation to patients with other wound types or ulceration.[43-50](#_ENREF_43) It is worth emphasising however that SWHSI patients are typically much younger than patients with leg or pressure ulcers and frequently have major caring and employment responsibilities: Cullum *et al*. reported a mean age of 79.65 years (SD 11.32) for venous leg ulcer patients,[26](#_ENREF_26) a difference of 25 years when compared with the mean age observed in Workstream 1 (54.1 years (SD 18.2). Wound care experiences amongst patients varied greatly but most patients were willing to try any treatment that promised healing. Understanding the ‘*lived experience’* of patients is crucial for clinicians to provide effective management and improve patient quality of life. Establishing a therapeutic relationship and listening to patient concerns is vital to meeting patient’s physical, emotional and psychosocial needs during the wound healing process. The provision of additional information for patients in relation to the rationale of treatment choices is also an important element for consideration with regards future treatment delivery.

Clinicians had varying levels of knowledge in relation to wound care treatment options. Nurses were frequently responsible for dressing choice decisions, made on the basis of wound condition, clinical experience and recommendations. A treatment frequently favoured by clinicians was NPWT. The lack of robust evidence for this treatment option was noted by several of the study clinicians however, for many, individual experiences of its use were deemed to sufficiently demonstrate the effectiveness of this treatment.[14](#_ENREF_14)

The use of purposive sampling enabled us to obtain a diverse range of views from both patients and clinicians. It is noted however that only a limited number of interviews were conducted with clinicians. Therefore further research may be warranted to build upon these findings.

Generalisability in qualitative research involves thinking through what kind of relationship the study findings have with other populations and settings, and unpacking exactly what inferences can be drawn from the data analysis.[39](#_ENREF_39) Our study yielded ‘*rich*’ data that captured a wide ranging, yet in-depth, picture of significant issues relating to patients’ and clinicians’ views and experiences of SWHSI. The study findings therefore promote and enhance understanding of the impact of a SWHSI on patients’ lives, as well as describing the challenges faced by clinicians in managing these wounds, thereby adding to the evidence base by ‘*sensitising*’ readers, including the research community, to new ways of thinking about SWHSI. Our study findings may be considered transferable to the ‘*parent populations*’ of patients with surgical wounds healing by secondary intention, and the clinicians looking after them; however, decisions concerning broader extrapolation of the findings must take into account any study-specific contextual factors that may limit applicability.[39](#_ENREF_39)

# Workstreams 1 – 3: Overall Conclusions

Workstreams 1 to 3 have substantially contributed to the evidence base and understanding of surgical wounds healing by secondary intention (SWHSI), providing data about patient characteristics, wound origins, durations, and treatments, alongside patient and clinician views of living with and treating SWHSI.

Workstream 1 has identified the prevalence of treated SWHSI and has provided extensive data on populations of clinical relevance for inclusion in further research. The median time to healing we observed in this Workstream highlights the extended period of time that patients might expect to cope with open surgical wounds. This Workstream has also highlighted the distinctive management challenge posed by SWHSI.

Workstream 2 has identified that negative pressure wound therapy (NPWT) is not a clinically or cost-effective treatment for SWHSI. However, because this uses observational research, even with adjustment, there is still the potential for unresolved confounding to affect the results so reducing confidence in them. This lack of confidence may justify calls for definitive evidence from a RCT, which would be more likely to effect a change in clinical practice should the evidence support one.

Workstream 3 has provided the first evidence of clinicians’ and patients’ views about the management and treatment of SWHSI, and patients’ experiences of living with this condition. The impact of SWHSI on patients was evident in all interviews and the understanding of patient experiences will assist in providing effective management of this condition. The work conducted in Workstream 3 has provided the necessary groundwork for further research in this area.

Interviews with clinicians identified increasing use of NPWT and illustrated the strength of support for NPWT amongst clinical staff, despite the lack of research. Surgeons and nurses perceived NPWT as safe and cost-effective, however we have been unable to identify existing, or derive new, evidence to support this. Given the increasing use and perceived effectiveness of this treatment, it is crucial that further, robust evidence is obtained to support, or refute, the estimates derived from observational data in Workstream 2.

In addition to the need to establish clinical and cost-effectiveness of treatments such as NPWT, the findings from Workstreams 1, 2 and 3 suggested that further research is necessary to understand the epidemiology of SWHSI, prognostic factors for healing, and the clinical and cost-effectiveness of other treatment options. The findings of Workstreams 1, 2 and 3 helped formalise key components of the design of Workstream 4 for this research programme which comprised a pilot, feasibility RCT, required to assess feasibility of RCT assessment of NPWT versus Usual Care (no NPWT), prior to a larger study being conducted.

# Workstream 4: A pilot, feasibility randomised controlled trial of negative pressure wound therapy compared with Usual Care

The results of Workstream 2 indicated that NPWT was, with little uncertainty, not clinically or cost-effective. This conclusion was however based solely on observational data, which, even with extensive adjustment, may be subject to unresolved confounding, leading to a lack of confidence in the finding. A randomised controlled trial (RCT) may therefore be justified, to enable definitive, high level, evidence regarding the clinical and cost-effectiveness of NPWT to be generated.

Given the difficulties in recruitment identified in previous studies of NPWT,[51](#_ENREF_51), [52](#_ENREF_52) we conducted a pilot, feasibility study to assess the feasibility of conducting a larger RCT of this treatment. The study was registered with ISRCTN (ISRCTN12761776) and the protocol has been published (See Appendix 12).[53](#_ENREF_53) The results of this study have been published (See Appendix 13) and the findings relating to nurse participation in the pilot, feasibility study have been submitted for publication (See Appendix 14).

## Objectives

1. To test the methods and feasibility of a full RCT of NPWT compared with Usual Care (no NPWT) for SWHSI.

Specifically to determine:

1. Likely recruitment rate, including potential participants’ willingness to be randomised and if this depends on wound location and other factors.
2. Clinicians’ willingness and ability to recruit and randomise participants.
3. Testing of inclusion and exclusion criteria.
4. Fitness for purpose of data collection methods including across and between care settings.
5. Ability of sites and clinicians to supply NPWT to participants in a timely fashion, irrespective of care settings, and assess any training requirements.
6. Ability of community staff to manage participants randomised to NPWT.
7. Suitability of method of outcome ascertainment.
8. Adequacy of duration of follow-up.
9. Rates of withdrawal from treatment, response rates to questionnaires; attrition from the trial and likely rates of missing data for outcomes.
10. Other methodological issues including feasibility of blinded outcome assessment and whether trial documentation is acceptable to NHS nurses collecting data.
11. Feasibility of collecting data for and conducting of economic analyses in a larger trial (through exploratory analyses)

## Summary

### Methods

The pilot, feasibility RCT was conducted over a 10-month period (20.11.2015 to 30.09.2016 – Recruitment: 20.11.15 to 30.06.16, Follow Up 20.02.16 to 30.09.16) in acute and community settings at three study sites in Leeds and Hull, Yorkshire, UK. Prior to study activity commencing, approval was obtained from Yorkshire and Humber – Leeds East Research Ethics Committee (Reference: 15-YH-0307) and from the associated NHS Trusts.

Patients were eligible for inclusion if they were aged 18 years and over and able to give full informed consent; were receiving care from Hull and East Yorkshire Hospitals NHS Trust, Leeds Teaching Hospitals NHS Trust or Leeds Community Healthcare NHS Trust; had a SWHSI which could be reasonably treated with NPWT and wound dressings; had a SWHSI which was considered ready for NPWT (i.e. *minimum 80% viable tissue or thin layer of slough requiring no further debridement*); and were receiving adequate nutrition (as assessed by the senior nurse responsible for nursing care). Patients were ineligible for inclusion if they had: limited life expectancy, active systemic infection, inadequate haemostasis or risk of bleeding, chronic wounds (e.g. pressure or foot ulcers) which were non-surgical in origin but had been surgically debrided, or had wound characteristics which precluded the use of NPWT (e.g. unclear undermining, necrotic or malignant tissue, eschar, exposed blood vessels, organs, anastomotic sites or nerves). Patients were also excluded if they had previously or were currently receiving NPWT on their SWHSI (including applications whilst in theatre for the surgery resulting in the SWHSI), if the wound was located where a vacuum seal could not be obtained, if they had participated in a research study in the previous four weeks, or were unwilling to have wound photographs taken.

Healthcare professionals initially identified and screened patients for eligibility. Those meeting eligibility criteria were approached with further details of the study by a clinical or research nurse (subject to patient consent to approach) prior to study consent being obtained. As the main aim of this study was to determine the feasibility of conducting a larger trial, rather than to detect a treatment effect, a formal sample size calculation was not required. We aimed to randomise 50 patients over a seven-month recruitment period.

Baseline data were collected including: participant, surgery and wound information; wound dimensions (measurements and wound tracing) and a photograph; pain assessment (using a visual analogue scale (VAS) and the Brief Pain Inventory (BPI))[22](#_ENREF_22) and quality of life data (SF-12and EQ-5D-3L).[20](#_ENREF_20), [21](#_ENREF_21) Since this was a feasibility trial, a primary outcome was not defined; rather, a range of feasibility (e.g. recruitment rate, time to intervention delivery) and clinical (e.g. time to wound healing) outcomes were collected to inform a future definitive trial. Participants were followed-up for a maximum of three-months unless they withdrew consent, died or became lost to follow-up. Clinical outcomes were collected prospectively on a weekly to fortnightly basis at follow-up assessment visits conducted by the research nurses including: wound dimensions and photographs, healing status (defined as ‘*complete epithelial cover in the absence of a scab (eschar)*’); infection; hospital admission; return to operating theatre and treatment changes. Participants also completed self-report postal questionnaires (EQ-5D-3L,[21](#_ENREF_21) BPI, [22](#_ENREF_22) SF-12[20](#_ENREF_20) resource use and pain via a VAS) at two weeks, one-month and three-months post randomisation. Where consent was provided, participants were also contacted by text message on a weekly basis and asked to provide a numeric rating of their wound pain in the previous week. Where participants failed to respond, one further message was sent before text message data collection discontinued. Where participants’ wounds were reported to have healed during the study, text messaging data collection ceased at the point of wound healing.

Information concerning acceptability of study participation was collected from participants using Likert scales. Data relating to acceptability of documentation and training requirements for NPWT were initially collected from research nurses using a Likert scale. Qualitative interviews were then completed with the research nurses to ascertain additional information regarding acceptability of the study processes, documentation, and delivery.

Participants were allocated (1:1) to the intervention (NPWT) or Usual Care (no NPWT), using random permuted blocks with stratification by wound area (<28cm2, ≥28cm2). Allocations were concealed through a central randomisation service at the University of York.

The study intervention (NPWT) was delivered using NPWT devices that were in use in the acute and community services in Hull and Leeds were selected for use in this study, which included V.A.C® (KCI), Renasys® (Smith and Nephew), and PICO® (Smith and Nephew) devices. The NPWT treatment delivery, for example device type, pressure cycles, dressing change and canister emptying frequency, application and removal of the device, and treatment duration were as per the standard practice at the time to ensure the pragmatic nature of the pilot, feasibility study was maximised. This was therefore decided by the clinical care team in conjunction with the participant and nurse, with the only stipulation made for NPWT use was that use must be clinically appropriate.

The control group participants received usual care (wound dressings, no NPWT), with dressing type and frequency of change left to the discretion of the clinical care team. As there is no evidence to suggest that any one dressing is more clinically or cost effective than another [12](#_ENREF_12), types of dressings were not stipulated for the trial.

Due to the nature of the intervention it was not possible to blind participants or healthcare professionals to trial treatment; however, the feasibility of blinded outcome assessment of healing was assessed within the trial using study photographs. Initially it was proposed that blinded review of healing would be completed for every participant photograph obtained but this was reduced during the study to review of the final photograph only due to time and resource constraints. Assessment of blinding to treatment allocation was conducted through review of photographs taken at week 1 follow up.

Data analysis was conducted using Stata version 13 (Stata Corporation, College Station, Texas USA) using the principles of intention to treat and two-sided statistical tests at the 5% significance level, where appropriate. Summary statistics for all variables were generated by trial arm and overall. Time to healing was defined as the number of days from randomisation to date of healing. Data were right censored at the date of the final assessment visit for participants not deemed to have healed. Time to healing was assessed using Kaplan Meier curves, recognising that the study was not powered to detect a treatment effect. A Cox proportional hazards regression was used to investigate the impact of covariates (contamination level of surgery, wound infection, wound size, SWHSI history, and location). Cost-effectiveness was explored using total mean resource use cost and mean quality adjusted life year (QALY) per trial arm.

To understand improvements to trial processes, to support research nurses in conducting a larger RCT in this area, qualitative interviews with eight research nurses were completed. Interviews were audio recorded and fully transcribed before being analysed for thematic content using a ‘*Framework*’ approach.[39](#_ENREF_39), [54](#_ENREF_54) Interpretation of the findings enabled linkage between individual nurses and their responses to account for variation between the type of study site (acute or community).

Prior to analysis, wound tracings were measured using Mouseyes Software to obtain perimeter and area estimates.[55](#_ENREF_55) Both adjusted (length x width x ∏)[56](#_ENREF_56) and unadjusted (length x width) wound area (cm2) measurements were calculated using ruler measurements obtained at clinical follow-up visits.

### Results

#### Recruitment and Participation

Recruitment to the study commenced on 20th November 2015 and continued until 30th June 2016. Delays in study set up, beyond the control of the research team, impacted on recruitment rate in the early stages of the trial; there was only one recruiting site active until the two remaining sites were opened to recruitment in February and March 2016 respectively. The overall target recruitment rate for the study was seven participants per month and following successful opening of all three recruitment sites, the study achieved this target in the final four months of recruitment (Figure 4). The flow of participants through the trial is shown in Figure 5.

Figure 4: Cumulative target and actual participant recruitment



Figure 5 – Pilot feasibility randomised controlled trial: CONSORT diagram

Screening

Number of patients screened (n=248)

Ineligible (n=185):\*

  no SWHSI (n=1); aged <18 (n=1); receiving care out of area (n=2); cannot be treated with NPWT or wound dressings (n=29); not receiving adequate nutrition (n=5); limited life expectancy (n=5); systemic infection (n=7); already receiving/received NPWT on SWHSI (n=68); received NPWT in theatre for surgery resulting in SWHSI (n=31); inadequate haemostasis and/or at risk of bleeding (n=4); unclear undermining in wound cavity (n=13); necrotic tissue or eschar present (n=5); wound involves exposed blood vessels, organs, anastomotic sites and/or nerves (n=11); wound situated where vacuum seal cannot be obtained (n=13); unwilling to have photographs taken (n=5); participated in research in last 4 weeks (n=2); does not have capacity to consent (n=12); other reason (n=48)

\*reasons not mutually exclusive

Did not consent (n=22):

  does not want NPWT (n=5); does not want to participate in research (n=3); preference for NPWT (n=3); preference for standard treatment (n=3); did not want to delay discharge (n=2); wound close to healing (n=2); other health issues (n=1); no reason given (n=3).

Randomised in error (n=1)

  patient had previously received NPWT on the current SWHSI

Randomisation

Randomised (n=41)

Allocation

**Allocated to Usual Care (n=21)**

**Allocated to NPWT intervention (n=19)**

 Received allocated intervention (n=17)

 Did not receive intervention (n=2)

Application of NPWT would have delayed patient’s discharge from hospital (n=1); patient discharged into care of community practice nurses so unable to get onto NPWT (n=1)

Follow Up

**Returned/expected**

**Week 2** (n=15/19)

**Month 1** (n=15/19)

**Month 3** (n=16/19)

**Returned/expected**

**Week 2** (n=18/21)

**Month 1** (n=16/20)

Withdrew from trial (n=1)

**Month 3** (n=15/19)

Withdrew from trial (n=1)

Analysis

## alysis

**Analysed (n=21)**

**Analysed (n=19)**

Of 248 patients screened for eligibility, 75.0% (n=186) were ineligible (including one participant found to be randomised in error). The most common reason for ineligibility was that the patient was receiving or had previously received NPWT on their current SWHSI (n=45/248, 18.1%), had NPWT applied whilst in theatre (n=7, 2.8%), or both (n=24, 9.7%). Twenty two participants were eligible but did not wish to consent to study participation; the most common reason for declination was not wishing to receive NPWT (n=5/22, 22.7%). Reasons for ineligibility were largely distributed across the observed wound locations, with exception of ‘*receiving inadequate nutrition’,* which was only reported for 5 patients with abdominal wounds*,* and ‘*presence of exposed vessels or organs’* which was reported for 11 abdominal and two leg wounds only.

Forty one of the 248 screened patients (16.5%) were randomised to the pilot, feasibility RCT with 40 participants included in the study analyses (one patient was found to be ineligible following randomisation and so was withdrawn from study data collection and analysis). Of those correctly randomised, 19/40 (47.5%) were allocated to NPWT and 21/40 (52.5%) to Usual Care.

The mean age of participants was 57.8 years (SD 14.4) and just over half (n=22, 55.0%) were male. Participants were, on average, overweight (mean BMI: 29.1, (SD 5.7)), 60% (n=24) were diabetic and 10 (25.0%) reported being a current smoker. The most common location of the wound in recruited participants was the foot (n=24, 60.0%) of which 19/24 (79.2%) were due to toe or foot amputation, two (8.3%) were due to incision and drainage, two (8.3%) occurred following debridement (of amputation site n=1, of non-chronic ulcer n=1), and the cause of the remaining foot wound was unknown. Usual Care participants had had their wound for a median of 12 days and over a third (n=8/21, 38.1%) had a wound infection at baseline. NPWT participants had had their wound for a median of seven days and 26.3% (n=5/19) of participants had a wound infection at baseline. Baseline characteristics are summarised in Table 18.

Table 18 – Pilot feasibility randomised controlled trials: Baseline characteristics of randomised participants by treatment group

|  |  |  |  |
| --- | --- | --- | --- |
|  | **NPWT**  **(N=19)** | **Usual Care**  **(N=21)** | **Total**  **(N=40)** |
| **Age, years**  N, Mean (SD)  Median (min, max) | N=19  58.8 (15.1)  62 (33, 88) | N=21  56.9 (13.9)  55 (35, 86) | N=40  57.8 (14.4)  58.5 (33, 88) |
| **Sex, n (%)**  Male  Female | N=19  11 (57.9)  8 (42.1) | N=21  11 (52.4)  10 (47.6) | N=40  22 (55.0)  18 (45.0) |
| **Body Mass Index (BMI)**  N, Mean (SD)  Median (min, max) | N=19  29.2 (5.6)  28.6 (20.9, 39.9) | N=21  29.0 (6.0)  29.3 (13.7, 39.9) | N=40  29.1 (5.7)  28.7 (13.7, 39.9) |
| **Diabetic, n (%)**  Yes | N=19  12 (63.2) | N=21  12 (57.1) | N=40  24 (60.0) |
| **Peripheral Vascular Disease (PVD), n (%)**  Yes | N=19  7 (36.8) | N=21  7 (33.3) | N=40  14 (35.0) |
| **Tobacco use, n (%)**  None  Ex-smoker  Current (≤1 pack a day)  Current (>1 pack a day) | N=19  13 (68.4)  1 (5.3)  2 (10.5)  3 (15.8) | N=21  10 (47.6)  6 (28.6)  4 (19.1)  1 (4.8) | N=40  23 (57.5)  7 (17.5)  6 (15.0)  4 (10.0) |
| **History of SWHSI, n (%)**  Yes  No  Don’t know | N=19  5 (26.3)  11 (57.9)  3 (15.8) | N=21  5 (23.8)  15 (71.4)  1 (4.8) | N=40  10 (25.0)  26 (65.0)  4 (10.0) |
| **Wound area, cm2**  <28cm2  ≥28cm2  Median (min, max) | N=19  10 (52.6)  9 (47.4)  18.2 (0.2, 122.5) | N=21  11 (52.4)  10 (47.6)  20.4 (2.3, 93.2) | N=40  21 (52.5)  19 (47.5)  19.3 (0.2, 122.5) |
| **Wound duration, days**  N, Median (min, max) | N=19  7 (0, 27) | N=21  12 (1, 142) | N=40  7 (0, 142) |
| **Wound infected, n (%)**  Yes  No | N=19  5 (26.3)  14 (73.7) | N=21  8 (38.1)  13 (61.9) | N=40  13 (32.5)  27 (67.5) |
| **Wound location, n (%)**  Foot  Abdomen  Leg  Breast  Groin  Buttocks  Peri-anal area | N=19  11 (57.9)  3 (15.8)  3 (15.8)  1 (5.3)  0 (0.0)  0 (0.0)  1 (5.3) | N=21  13 (61.9)  3 (14.3)  1 (4.8)  1 (4.8)  2 (9.5)  1 (4.8)  0 (0.0) | N=40  24 (60.0)  6 (15.0)  4 (10.0)  2 (5.0)  2 (5.0)  1 (2.5)  1 (2.5) |
| **Type of surgery, n (%)**  Elective  Emergence | N=18  12 (66.7)  6 (33.3) | N=21  18 (85.7)  3 (14.3) | N=39  30 (76.9)  9 (23.1) |
| **Contamination level of surgery, n (%)**  Clean  Clean/contaminated  Contaminated | N=19  6 (31.6)  9 (47.4)  4 (21.1) | N=21  2 (9.5)  12 (57.1)  7 (33.3) | N=40  8 (20.0)  21 (52.5)  11 (27.5) |

#### Data Collection Methods

Twenty six participants (of 40, 65.0%) consented to data collection via text messaging; twenty (76.9%) subsequently provided at least one response (NPWT: n=10, Usual Care: n=10). Response rates to text messaging varied throughout the trial ranging from 57.7% of those receiving a text in the week following randomisation to 100% of those receiving a text in week 12. Participants who responded to text messaging tended to be younger than those who did not respond (mean age 51 vs 60 years), and non-responders were predominantly male (85.7%). All non-responders had a foot wound, had at least one comorbidity and over half of those who did not respond to text messaging had been allocated to the control arm (57.1%). A range of wound locations were observed in those participants who did respond to text messages (for example foot wounds comprised 36.8%) and 78.9% of participants had one or more comorbidities. Participants who responded to text messaging were almost evenly split between the intervention and control groups (52.6% vs. 47.4%, respectively).

Wound area (cm2) was collected by ruler measurement and wound tracing at each follow-up visit. Ruler measurements were found to overestimate the true area as obtained using wound tracings (mean difference: 7.0, SD 9.1) even when an adjustment of ‘*Π/4’* was used. Wound area decreased in both treatment groups throughout the trial.

The movement of patients from acute to community settings did not substantially affect follow-up completion. In the majority of cases follow-up continued as planned, however qualitative interviews with the study nurses noted that on occasion it was impossible to assess the wound at follow-up visits. This was primarily due to community healthcare professionals (e.g. district, community or general practice nurses) either having already attended and redressed the wound or not attending at the agreed time for the visit, meaning research data could not be collected in full.

#### NPWT supply

Nineteen participants (of 40, 47.5%) were allocated to receive NPWT; however two participants (of 19, 10.5%) did not receive the allocated intervention (one as NPWT would have caused delay in discharge, and one because all NPWT devices were in use in the community with other patients at that time). Approximately three quarters of allocated participants (n=14/19, 73.7%) received NPWT within 48 hours of randomisation. Seven participants (of 19, 36.9%) did not receive NPWT within 24 hours of randomisation with the primary reason for delay being lack of device availability (n=6, 85.7%). Participants received NPWT for a median of 18 days (range: 0 to 72) with eight participants discontinuing NPWT due to wound improvement. One participant recommenced NPWT following their initial cessation. Two participants (of 19, 10.5%) ceased NPWT therapy on the day they received it due to failure to maintain a seal. Twenty one participants (of 40, 52.5%) were allocated to Usual Care, of which more than half were initially treated with a hydrocolloid dressing (n=11/21, 52.4%), nine with either a silver containing (n=3, 14.3%), iodine containing (n=3, 14.3%), or basic dressing (n=3, 14.3%) and one with a soft polymer dressing (4.8%). Five Usual Care participants (23.8%) switched to NPWT during the trial at a median of 4 days (range: 0 to 17) after randomisation and subsequently remained on NPWT for a median of 31 days (range 19 to 36). The most common reason for treatment cross over was wound deterioration (n=2/5, 40.0%).

#### Withdrawal and Retention

During the trial, two participants (of 40, 5.0%) were fully withdrawn from the study due to amputation of the limb on which the reference wound was situated. The study protocol was revised following these withdrawals to enable continued data collection from participants after amputation, provided they continued to give consent for this study; however, in the event, no further participants underwent amputation.

Participant questionnaire response rates were positive achieving 77.5% or more at all time points and 291 follow-up clinic visits were completed (NPWT median 8; Usual Care median 7) at intervals of between 4 and 33 days after randomisation (NPWT median 7.5 days; Usual Care median 9 days).

#### Blinded outcome assessment

In total 308 photographs were taken as part of the study (38 at baseline, 270 at follow-up visits). Assessments of the final photographs for healing indicated that there was agreement between two reviewers for 29 (of 40, 72.5%) participants (NPWT n=15, 79.0%; Usual Care n= 14, 66.7%), increasing to 38 participants (95.0%) following a third review. Where healing status was recorded by one or more reviewers as ‘*Unsure*’, this was due to poor photograph quality in 50.0% (n=4/8) of cases. For two participants (of 40, 5.0%), blinded outcome assessment of healing provided no consensus, with each reviewer recording a different healing status. The blinded assessors classed eight (of 40, 20.0%) wounds as healed (NPWT n=3, 15.8%; Usual Care n=5, 23.8%) of which, seven (87.5%) were also recorded as healed by the unblinded investigators. Blinded assessors were unsure of healing status, or there was discordance between reviewers, for a further three wounds judged to have healed by the unblinded investigators.

The feasibility of blinding to treatment allocation was assessed using photographs taken at week 1, as the final photograph would not necessarily reflect the originally allocated treatment (given that NPWT is not necessarily used to the point of wound healing). In terms of blinding success, the assessors correctly identified treatment allocation for 15 participants (of 40, 37.5%); nine participants allocated to NPWT and six participants allocated to Usual Care. Allocation to NPWT was incorrectly identified in six cases (15.0%).

#### Documentation Acceptability - Nurses

Half of the eight research nurses who responded (n=4, 50.0%) indicated that they found the questionnaires asked all relevant questions and were straightforward to complete. There were mixed opinions on the ease of participant identification with three nurses agreeing (agree or strongly agree), two nurses remaining impartial (neither agree nor disagree) and three strongly disagreeing. Half of the nurses (n=4, 50%) indicated trial processes were clear, the randomisation process was straight forward and just over half (n=5, 62.5%) found the assessments were straightforward to complete.

Qualitative interviews were subsequently conducted to ascertain further information on responses provided. Five face-to-face and three telephone interviews were conducted with research nurses across the three study sites, which identified key points of feedback on the trial procedures and processes:

* Trial documentation was found to be acceptable, straightforward and in keeping with expectations based on nurses’ prior research experience. Amendments to clarify consistency in interpretation of eligibility criteria, processes for recording of wound depth and general minor amendments to study documentation were however suggested. The nurses acknowledged that the majority of issues encountered with the implementation of this pilot, feasibility RCT were not dissimilar to other new studies.
* Nurses based at the secondary care sites highlighted issues with engagement of consultants due to concerns that randomisation could interfere with their preferred wound management plan. Nurses suggested that direct PI involvement enabled more patients to be successfully screened at the pre-operative stage. Nurses based within the community settings noted that the majority of patients were identified in the acute settings. Randomisation was regarded as an easy process although availability of a 24-hour randomisation service would have been preferred.
* Given the geographical spread of participants at each study site, arranging visits to coincide with a patient’s clinic appointment was the most efficient approach although this was not always viable and often time was wasted waiting for district, community or general practice nurses at home visits. The frequency of follow-up visits was noted as impacting on time available to recruit and the value of continued follow-up beyond wound healing (up to three visits completed post healing) was queried. Access to equipment was generally better in the acute rather than the community setting, although there were occasions when equipment needed to be borrowed by the trial team across both acute and community settings to facilitate patient treatment.
* There was mixed feedback regarding nurses and consultants indirectly involved with the study. At one site there was a perception that if NPWT was involved, some nurses would avoid a study due to a lack of confidence or training in its application, and also the potential for additional work involved. At another site it was reported that negative pressure is widely used and therefore there was a potential bias towards use of negative pressure. It was suggested that additional PI involvement to promote the study, particularly during the set-up phase, would be helpful.
* All research nurses received training in the application of NPWT but as a result of randomisation not all nurses had the opportunity to apply it. Generally there was confidence in the use of NPWT however staff turnover and levels of junior staffing were noted to highlight gaps in training. Nurses reported that for patient safety, patient lifestyle, in particular mobility requirements, should be taken into account during recruitment.

#### Study Acceptability - Patients

Feedback from participants indicated that taking part in the study had matched expectations (n=30/31, 96.8%) and that completing questionnaires had been straightforward (n=28/31, 90.3%) and manageable (29/31, 93.6%).

#### Clinical Outcomes - Healing

Participants were followed for a median of 84 days after randomisation (range: 13 to 105) to assess wound healing. During the study 10 wounds (of 40, 25.0%) were deemed to have healed based on assessment at weekly follow-up; 6 in the NPWT group (31.8%) and 4 (19.1%) in the Usual Care group. Time to healing was summarised using Kaplan Meier curves (See Figure 5). Adjusted Cox Proportional Hazards Models indicated that wound size (p=0.03) and duration of wound (p<0.001) were predictors of time to wound healing, with smaller and longer duration of wounds associated with increased time to healing (Supplementary table 2 of Appendix 13).

Figure 6 – Pilot feasibility randomised controlled trial: Kaplan Meier Curve – time from randomisation to healing

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#### Clinical Outcomes - Infection

During the trial, 17 participants (NPWT: n=6, 31.6%; Usual Care: n=11, 52.4%) experienced an infection. Of these, nine experienced infection at baseline only (NPWT: n=3, 15.8%; Usual Care: n=6, 28.6%); four during follow-up only (NPWT: n=1, 5.3%; Usual Care: n=3, 14.3%); and four both at baseline and during follow-up (NPWT: n=2, 10.5%; Usual Care: n=2, 9.5%).

#### Clinical Outcomes - Hospitalisation

Participants in the NPWT group spent a median of 29 nights in hospital during the trial and participants in the Usual Care group spent a median of 10 nights in hospital.

There were five reported hospitalisations during the trial, all of which were associated with serious adverse events (as detailed below). In four instances (of 5, 80.0%) the participants were subsequently discharged and in one instance (20.0%) the participant was withdrawn from the study (due to amputation) and subsequently deceased and so further information regarding hospital discharge was not collected.

#### Patient reported outcomes

Participant completed questionnaires indicated that pain severity (BPI)[22](#_ENREF_22), interference and VAS wound pain reduced (improved outcome) in the NPWT group between baseline and month 1, but increased again (worse outcome) slightly at month 3 of follow-up. In the Usual Care group, pain interference followed the same pattern as in the NPWT group but VAS wound pain reduced consistently over time, and BPI interference fluctuated between the follow-up time points. There was lower (improved outcome) reported pain severity and interference scores (BPI)[22](#_ENREF_22) and wound pain (VAS) for Usual Care participants at all time points relative to the NPWT group (See Table 19). A total of 20 participants provided at least one weekly text messaging pain score (NPWT: n=10, Usual Care: n=10). Mean scores reduced between week 1 and month 3 (week 1: 4.0, SD 3.0; week 12: 1.6, SD 2.0); however, there was some fluctuation observed in scores during this time (See Appendix 15).

Table 19 – Pilot feasibility randomised controlled trial: Pain scores by randomised group and time point

|  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- |
|  | **NPWT**  **(N=19)** | | **Usual Care**  **(N=21)** | |  | **Total**  **(N=40)** |
| **BPI severity** | **N** | **Mean (SD)** | **N** | **Mean (SD)** | **N** | **Mean (SD)** |
| Baseline | 16 | 4.4 (2.8) | 20 | 2.7 (2.8) | 36 | 3.5 (2.9) |
| Week 2 | 15 | 3.7 (2.8) | 17 | 2.5 (2.5) | 32 | 3.0 (2.7) |
| Month 1 | 14 | 3.5 (3.4) | 15 | 1.9 (2.6) | 29 | 2.7 (3.1) |
| Month 3 | 14 | 4.3 (2.9) | 13 | 2.1 (2.6) | 27 | 3.2 (2.9) |
| **BPI interference** |  |  |  |  |  |  |
| Baseline | 15 | 5.0 (3.5) | 16 | 2.8 (3.6) | 31 | 3.8 (3.6) |
| Week 2 | 15 | 4.5 (3.5) | 17 | 3.3 (3.3) | 32 | 3.9 (3.4) |
| Month 1 | 14 | 4.2 (3.7) | 15 | 2.3 (2.8) | 29 | 3.2 (3.4) |
| Month 3 | 13 | 5.3 (2.8) | 15 | 2.7 (3.4) | 28 | 3.9 (3.4) |
| **VAS wound pain** |  |  |  |  |  |  |
| Baseline | 15 | 51.2 (32.1) | 18 | 34.8 (32.7) | 33 | 42.2 (33.0) |
| Week 2 | 13 | 32.4 (33.4) | 17 | 26.5 (29.3) | 30 | 29.1 (30.7) |
| Month 1 | 13 | 27.1 (31.1) | 14 | 20.7 (26.7) | 27 | 23.8 (28.5) |
| Month 3 | 12 | 30.8 (27.2) | 15 | 13.5 (23.1) | 27 | 21.1 (26.0) |
| **VAS pain at dressing changes\*** |  |  |  |  |  |  |
| Week 2 | 13 | 22.3 (25.5) | 15 | 22.6 (24.5) | 28 | 22.5 (24.5) |
| Month 1 | 13 | 26.5 (32.8) | 14 | 16.4 (24.2) | 27 | 21.2 (28.5) |
| Month 3 | 11 | 18.1 (20.2) | 15 | 12.5 (27.0) | 26 | 14.8 (24.1) |
| \* not measured at Baseline | | | | | | |

There was improvement (i.e. better health status) in the mean SF-12 PCS scores over time in both groups. MCS scores reduced in the NPWT group over time but improved initially in the Usual Care group (between baseline and 1 month) before declining slightly at the month 3 follow-up visit. Further detail regarding these results is presented in Table 20 and Figures 7 and 8 in Appendix 16.

Table 20 - Pilot feasibility randomised controlled trial: Physical and Mental Health Composite Scale scores (PCS & MCS) derived from the SF-12 by randomised group and time point

|  |  |  |  |
| --- | --- | --- | --- |
| **SF-12**  N, Mean (SD)  Median (min, max) | **NPWT**  **(n=19)** | **Usual Care**  **(n=21)** | **Total**  **(n=40)** |
| **Physical Composite Scale (PCS)** | | | |
| **Baseline** | 16, 28.9 (10.6)  28.0 (12.2, 47.9) | 19, 34.9 (11.4)  32.7 (15.5, 53.2) | 35, 32.1 (11.3)  32.4 (12.2, 53.2) |
| **Month 1** | 14, 29.8 (10.1)  28.0 (14.9, 48.9) | 15, 38.8 (12.1)  39.8 (21.4, 55.1) | 29, 34.5 (11.9)  33.2 (14.9, 55.1) |
| **Month 3** | 14, 30.4 (11.9)  26.6 (17.4, 51.0) | 14, 42.8 (8.3)  40.8 (30.5, 57.9) | 28, 36.6 (11.9)  37.5 (17.4, 57.9) |
| **Mental Health Composite Scale (MCS)** | | | |
| **Baseline** | 16, 44.7 (12.6)  44.2 (19.0, 62.4) | 19, 42.2 (11.2)  42.5 (18.8, 56.6) | 35, 43.3 (11.8)  43.4 (18.8, 62.4) |
| **Month 1** | 14, 42.7 (13.8)  40.8 (21.8, 61.7) | 15, 48.6 (11.7)  46.8 (31.7, 67.5) | 29, 45.8 (12.9)  45.0 (21.8, 67.5) |
| **Month 3** | 14, 41.5 (10.9)  41.5 (24.8, 62.3) | 14, 47.1 (12.1)  46.6 (29.8, 64.7) | 28, 44.3 (11.6)  42.1 (24.8, 64.7) |

#### Adverse Events

Adverse event data collection throughout the study identified 28 non-serious (NSAE) and five serious events (SAE). Two SAEs were reported in the NPWT group from one participant and three in the Usual Care group from two participants. All five events were hospitalisations and only one (Usual Care group) was classed as related to the reference wound. Three events (of 5, 60.0%) were said to be possibly or probably related to treatment, all of which were recorded as expected. There were no suspected unexpected serious adverse reactions (SUSARs). The majority of non-serious adverse events related to the reference wound (n=25/28, 89.3%), and were reported as definitely related to treatment (n=19/28, 67.9%). The most common event type was ‘*Other*’ (n=12/28, 42.9%), which included events such as skin irritation (n=3/12, 25.0%) and dressings falling off (n=3/12, 25.0%), followed by ‘*Pump Failure*’ (n=8/12, 28.6%).

#### Economic Outcomes

Usual Care participants reported that they received a mean of 8.0 (SD 14.8) nurse visits at home and had 12.41 visits at the GP surgery (SD 15.04) for their SWHSI. NPWT participants reported a limited number of nurse visits at the GP surgery (mean 1.14, SD 2.24), but additional nurse visits at home (mean 6.78, SD 9.82) and substantial mean inpatient hospital stays (mean 17.5, SD 19.8) and GP visits (mean 1.35, SD 2.70) (See Table 21).

Table 21 – Pilot feasibility randomised controlled trial: Cost effectiveness analyses Mean resource use, based on all available cases

|  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- |
|  | **NPWT (n=19)** | | | **Usual care (n=21)** | | |
| **Type of resource use** | **Mean (SD)** | **Missing (%)** | | **Mean (SD)** | **Missing (%)** | |
| **DOCTOR Hospital outpatient clinic** |  |  |  |  |  |  |
| **Wound related** | 2.73 (3.23) | 5 | 25.0% | 0.76 (1.16) | 8 | 38.0% |
| **Not wound related** | 1.70 (2.00) | 10 | 50.0% | 0.20 (0.63) | 11 | 52.0% |
| **NURSE Hospital outpatient clinic** |  |  |  |  |  |  |
| **Wound related** | 6.66 (10.35) | 5 | 25.0% | 4.07 (10.07) | 8 | 38.0% |
| **Not wound related** | 1.45 (2.39) | 9 | 45.0% | 0 (0) | 11 | 52.0% |
| **Day case visit to the hospital** |  |  |  |  |  |  |
| **Wound related** | 0.33 (0.88) | 8 | 40.0% | 0.21 (0.80) | 7 | 33.3% |
| **Not wound related** | 0.09 (0.30) | 9 | 45.0% | 0 (0) | 9 | 43.0% |
| **Nights stayed as hospital inpatient** |  |  |  |  |  |  |
| **Wound related** | 17.5 (19.8) | 6 | 30.0% | 0.90 (3.01) | 10 | 48.0% |
| **Not wound related** | 14 (22.01) | 10 | 50.0% | 0.54 (1.80) | 10 | 48.0% |
| **GP visit at GP practice** |  |  |  |  |  |  |
| **Wound related** | 1.35 (2.70) | 6 | 30.0% | 0.69 (1.31) | 8 | 38.0% |
| **Not wound related** | 0.54 (1.03) | 9 | 45.0% | 0.83 (1.19) | 9 | 43.0% |
| **GP visit at home** |  |  |  |  |  |  |
| **Wound related** | 0.28 (0.61) | 6 | 30.0% | 0 (0) | 9 | 43.0% |
| **Not wound related** | 0.15 (0.37) | 7 | 35.0% | 0.08 (0.29) | 9 | 43.0% |
| **Nurse visit at GP practice** |  |  |  |  |  |  |
| **Wound related** | 1.14 (2.24) | 6 | 30.0% | 8.00 (14.8) | 9 | 43.0% |
| **Not wound related** | 0.31 (0.75) | 7 | 35.0% | 0.09 (0.30) | 10 | 48.0% |
| **Nurse visit at home** |  |  |  |  |  |  |
| **Wound related** | 6.78 (9.82) | 6 | 30.0% | 12.41 (15.04) | 9 | 43.0% |
| **Not wound related** | 1.91 (3.87) | 8 | 40.0% | 0 (0) | 11 | 52.0% |

Costs associated with NHS and healthcare resource use were calculated on a per contact basis using NHS reference and health and social care costs (See Appendix 17). [57](#_ENREF_57), [58](#_ENREF_58)The associated NHS and healthcare costs were higher for the NPWT group; the mean total cost for the NPWT intervention was £9,490 (SD £7,346) compared to £1,153 (SD £1,806) for patients receiving Usual Care (See Table 22).

Table 22: Total mean costs based on all available cases, up to 3 month follow up

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
|  | **Total mean cost £ (SD)\*** | | | **Incremental Cost £ (NPWT – Usual Care) (95% CI)\*** |
| **Type of resource use** | **NPWT** | **Usual Care** | |
| **Combined Resource Use** | 9,490.00  (7,346.00) | 1,153.00  (1,806.00) | | 8,333.00 (3,311.13; 13,362.96) |
| **DOCTOR Hospital outpatient clinic** | 360.77 | 101.53 |  | 259.24 (1.63; 516.84) |
|  | (427.59) | (153.86) | |
|  | N=15 | N=13 | |
| **NURSE Hospital outpatient clinic** | 472.46 | 288.93 |  | 183.53 (-380.89; 747.96) |
|  | (733.90) | (713.67) | |
|  | N=15 | N=13 | |
| **Day case visit to the hospital** | 240.26 | 154.45 |  | 85.80 (-407.07; 578.69) |
|  | (639.78) | (577.90) |  |
|  | N=12 | N=14 |  |
| **Nights stayed as hospital inpatient** | 6,284.77 | 326.48 |  | 5,958.29 (1,452.14; 10,464.44) |
|  | (7,128.17) | (1,082.81) |  |  |
|  | N=14 | N=11 |  |  |
| **GP visit at GP practice** | 59.71 | 30.46 |  | 29.25 (-45.92; 104.43) |
|  | (119.07) | (57.88) | |
|  | N=14 | N=13 | |
| **GP visit at home** | 25.40 | 0 |  | 25.40 (-5.68; 56.49) |
|  | (54.35) | 0 |  |  |
|  | N=14 | N=13 |  |  |
| **Nurse visit at GP practice** | 12.69 | 88.88 |  | -76.19 (-168.35; 15.98) |
|  | (24.97) | (165.46) |  |
|  | N=14 | N=12 |  |
| **Nurse visit at home** | 158.31 | 289.68 |  | -131.37 (-367.93; 105.19) |
|  | (229.16) | (350.93) |  |
|  | N=14 | N=12 |  |

* Costs expressed in GBP using the price level of 2015 (1 GBP = 1.12 Euro)

NPWT participants reported a mean baseline EQ-5D-3L score of 0.34 (SD 0.10) and Usual Care participants reported a mean baseline score of 0.54 (SD 0.08). At three-months, following adjustment for baseline utility, mean scores had improved over time; NPWT participants: 0.49 (SD 0.35) and Usual Care participants: 0.77 (SD 0.23) (See Table 23 and Appendix 18 and 19).

Table 23 - Summary of EQ-5D utility scores at each time point (all available cases)

|  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- |
| **Utility** | **NPTW (n=19)** | | **Usual Care (n =21)** | | **Unadjusted mean difference**  **(NPTW – Usual Care)**  **(95% CI)** | **Adjusted mean difference\***  **(NPTW – Usual Care)**  **(95% CI)** |
| **Follow up** | **N** | **Mean (SD)** | **N** | **Mean (SD)** |
| **Baseline** | 16 | 0.34 (0.10) | 21 | 0.54 (0.08) | -0.20  (-0.46, 0.05) |  |
| **3 months** | 15 | 0.49 (0.35) | 15 | 0.77 (0.23) | -0.28  (-0.50, -0.06) | -0.05  (-0.31, 0.20) |

*\* The difference at 3 months is adjusted for baseline utility.*

The results show that NPWT had higher total NHS and healthcare costs and also achieved lower quality adjusted life year (QALY) gains than Usual Care (Complete case analysis: -0.007, 95% CI: -0.04 to 0.02), multiple imputation analysis: -0.004, 95% CI: -0.03 to -0.02)).

During the study, 1135 dressing changes were completed (NPWT: n=518; Usual Care: n=617). The average number of dressing changes completed was 27.26 for NPWT participants and 29.38 for Usual Care participants. The majority of dressing changes were completed by district, community or general practice nurses (NPWT: n=253; Usual Care: n=272) or the participant’s clinic nurse (NPWT: n=107; Usual Care: n=167). The distribution of dressing changes by group corresponds to the distribution by group of nursing visits received or attended by participants; nursing visits at home or at the GP clinic were higher for Usual Care participants than those allocated to NPWT.

### Conclusions

This pilot, feasibility RCT provides invaluable information on the feasibility of conducting a large-scale trial of NPWT for treatment of SWHSI and identifies areas of key consideration in the planning of future research.

#### Recruitment, participation and retention

The consistent rate of recruitment, observed following the opening of all sites to recruitment, demonstrates that it is possible to recruit participants to a trial of NPWT versus Usual Care. A full trial would however need to ensure an adequate number of recruiting sites are identified. On the basis of the recruitment rate observed (2 patients per site per month), to recruit 400 participants to a similar trial over an 18-month recruitment period, 11 study sites would need to be opened to recruitment. This example is based upon hypothetical detail and would therefore be subject to revision following full sample size calculations for a larger trial. A larger trial should consider the impact of, and account for in associated sample size calculations, the rates of participants randomised to, but subsequently not receiving NPWT (10.5% of participants in the pilot, feasibility RCT) and rates of cross over to NPWT (23.8% of Usual Care participants in the pilot, feasibility RCT).

Qualitative interviews indicated that nurses perceived the majority of SWHSI patients to be identified within acute care settings, highlighting that the primary source of recruitment in a future RCT may be best achieved in acute care settings. This distribution may however differ between individual localities and so work would be required prior to recruitment to ensure appropriate and effective recruitment strategies and pathways were implemented at individual sites.

Having previously received, or currently receiving NPWT for their SWHSI, was found to be the most frequent reason for patients’ ineligibility to take part in the study. Prior to undertaking a full RCT, it would be necessary to undertake some promotional work with clinical colleagues and research groups in order to fully engage surgeons and nurses within the study site and to ensure consistent and continued referrals into the study. In addition, a future trial should recruit study sites where there is sufficient equipoise with regards to treatment of patients with SWHSI, thus thorough evaluation of potential trial sites will be essential.

Work to engage clinical colleagues and research groups prior to recruitment commencement would also be crucial to allay resistance to trial recruitment from certain clinical groups. Anecdotal evidence from the study sites indicated some resistance to trial recruitment participation from colorectal surgeons, either because NPWT was primarily used for wound management rather than healing, or because a surgeon’s prior experience of NPWT had led them to feel this treatment was inappropriate for use in this patient group. Given the small number sites involved in this pilot, feasibility study, it is impossible to draw firm conclusions on the likely resistance amongst specific clinical groups which may be observed in a larger RCT. Promotional work with clinicians across potential research sites, in advance of study commencement, should however help to minimise any resistance to recruitment in a larger RCT. Where necessary, promotional work may need to be targeted to ensure clinicians from a cross section of surgical disciplines are aware of, and open to recruitment for, a larger trial.

Participant reported questionnaire response rates in excess of 75%, and the limited number of withdrawals observed, also demonstrates that it is possible to retain participants in a RCT of NPWT compared with Usual Care. During the study, only two (5.0%) participants were withdrawn from the trial due to amputation of the limb on which the reference wound was situated. Data collection did not continue for these participants. The trial team subsequently amended the study protocol to reflect that clinical data would cease at the point of amputation but participant reported data could continue to be collected, subject to continued consent. A future trial should ensure the process for continued data collection following amputation is discussed and is clearly defined prior to study recruitment commencing.

#### Data Collection Methods

Assessment of wound measurements indicated that ruler measurements, both with and without adjustment, over-estimate wound size compared with wound tracings. Wound tracings should therefore be chosen over ruler measurement in any future RCT.

We have shown how wound pain data can be successfully collected on a weekly basis using text messaging; however there were limited numbers of participants who responded to this method of data collection and rates of response varied considerably throughout the study. Exploration of participant characteristics in relation to text message respondents and non-respondents indicated that collection of data using this method may be most effective in younger populations; those who routinely responded were on average almost 10 years younger than those who did not respond routinely. The use of text messaging data collection in a larger study should therefore be considered carefully, before implementation, to ensure that use of this method will provide sufficient data for analysis.

#### NPWT Supply

NPWT delivery was largely completed within 48 hours; however three participants did not receive NPWT within this time. Furthermore, two participants did not receive NPWT at all due to delays to discharge and lack of intervention availability. A future RCT would therefore need to establish the availability of NPWT devices with sites from the outset to ensure timely intervention delivery.

Nurses involved in the study reported that they had received sufficient training within their individual institutions to confidently apply NPWT. It was however noted that nursing colleagues were not always confident in using NPWT, which corresponds with findings from Workstream 3 of this research programme. A future trial would therefore need to invest sufficient resource to ensure that NPWT training was provided to all staff that may be providing trial treatment to a participant.

#### Blinded outcome assessment

This pilot, feasibility trial explored the feasibility of blinded outcome assessment in the context of NPWT for SWHSI healing. Blinded and unblinded investigator assessment in relation to wound healing agreed 87.5% of the time and so blinded outcome assessment can be deemed to be feasible and appropriate within a future RCT. Blinded assessment of healing was, however, often hampered by the quality of the wound photograph. A robust photography protocol would therefore be required for a full RCT to facilitate consistency of imaging throughout the study and accurate blinded healing assessment.

It was not possible within this study to blind assess time to healing due to difficulties in transferring the necessary numbers of photographs required to complete this activity. Dependent upon the outcomes included in a larger study, this may warrant further exploration and a robust and tested process for transfer of photographs to blinded assessors for review should be established prior to the study commencing.

It is important to note that assessors correctly identified treatment allocation in approximately one third (37.5%) of cases, when reviewing photographs taken in the first week of the study. Therefore, assessment of time to healing in a larger study may become biased through identification of treatment allocation and so inclusion of this assessment should be carefully considered before implementation.

#### Documentation Acceptability

Participant questionnaires were largely well received and so limited changes would be required for data collection in a larger RCT. The variation in opinions from research nurses involved in the study regarding study documentation and study processes, especially frequency and method of follow-up visits, indicates that further work should be conducted during the design of a larger trial to develop and test data collection processes to ensure fitness for purpose.

#### Clinical events

Given the limited number of participants involved in this study, there were insufficient data to enable any true treatment effect of NPWT to be identified, and this was not the purpose of this study. A full RCT is therefore required to fully assess the clinical and cost-effectiveness of NPWT as a treatment for patients with SWHSI.

The cohort study undertaken before this pilot, feasibility RCT (Workstream 1) estimated that a follow-up duration of 90 days should be sufficient to observe wound healing. However in this pilot, feasibility study only 25% of participants healed which meant that a median time to healing could not be calculated. As a result, a three month follow-up may be inadequate to reliably investigate and compare healing rates; therefore, a longer follow-up should be considered for future trials. The difference in time to healing between this pilot, feasibility study and our cohort study may be explained by the greater proportion of participants with foot and leg wounds in the pilot, feasibility study (usually secondary to diabetes). The complexities associated with wound healing in patients with diabetes,[59](#_ENREF_59) may explain these lower healing rates.

Regional arrangements for the supply of NPWT in community settings may have resulted in between group differences in relation to nights spent as an inpatient. It is however worth noting that this may be due to specific regional arrangements present in the participating sites, rather than being an issue which would manifest in a larger, national study. To ensure that inpatient stay is not distorted by regional arrangements, it is imperative to assess provisions for treatment delivery (e.g. local discharge arrangements and availability of NPWT within community settings) prior to commencing research activity at any study site. Associated with NPWT supply is the aforementioned requirement for training. Nurses noted that clinical colleagues were not always confident in using NPWT and so sufficient resource would be required to ensure full coverage of training across all those who may provide treatment to a participant.

This pilot, feasibility study has clearly demonstrated the feasibility of completing a full RCT to provide definitive evidence in relation to NPWT effectiveness as a treatment for patients with SWHSI. The pilot, feasibility study has also identified key elements of, and recommendations for recruitment, data collection, outcome measurement, trial design, and safety reporting which would need to be considered during the design of a larger RCT to investigate the clinical and cost-effectiveness of NPWT versus Usual Care.

# Conclusions and recommendations

## What do we now know about the SWHSI patient population?

This research programme emerged from clinical uncertainty about the best way of managing surgical wounds healing by secondary intention (SWHSI). There has been very little previous research on open surgical wounds, and what small amount there was focused only on dehisced surgical wounds:[60](#_ENREF_60), [61](#_ENREF_61) we have now shown that these constitute approximately half of all SWHSI. We have studied both dehisced surgical wounds and those intentionally left open after surgery because they present similar challenges for clinical management. We planned this research at a time (2009) when the use of a costly intervention, negative pressure wound therapy (NPWT), was increasing, whilst access to it varied hugely based on clinical setting, local policies, and resources. Prior to this research, little was known about the frequency of SWHSI, the characteristics of the patients who experience them and longer-term outcomes. Without basic information about the frequency and prognosis of a health condition and how patients are affected by it, it is impossible to plan research on treatments.[62](#_ENREF_62) Initially we undertook a cross-sectional survey of the prevalence of treated SWHSI which had the dual purpose of deriving the first population-based estimate of prevalence as well as identifying where and when SWHSI occurred to aid the planning of an inception cohort. The cross-sectional survey (conducted in 2012) was anonymised, completed away from the patient and did not require consent in order to optimise data capture. This survey provides the first estimate of the prevalence of treated SWHSI which we estimate at 4.1 per 10,000 of the population (95% CI: 3.5 to 4.7 per 10,000).[16](#_ENREF_16) There are several things worth noting about this estimate: the prevalence is similar to best estimates of the UK prevalence of leg ulcers (4.4 per 10,000);[26](#_ENREF_26) almost half of SWHSI (48%) were planned (before surgery) to be left open; the wounds had been present for a median of 28 days; the patients were mainly receiving care in primary and community care settings; and 93% of patients were receiving wound dressings (6% had NPWT). Colorectal surgery was the most frequent type of surgery to precede the SWHSI although plastic surgery and vascular surgery were also common.

This survey, although rather basic in design (lacking independent case ascertainment for example, due to resourcing), provided crucial intelligence for planning the cohort study. Our median time from surgery to wound breakdown (in those whose wounds were not intentionally left open) of 9 days accords with previous studies of dehiscence.[60](#_ENREF_60), [63](#_ENREF_63)

Our inception cohort collected data from 393 patients with SWHSI and is the first detailed analysis of this patient population, their wound treatments and healing trajectories. A notable difference between this and the cross-sectional survey (apart from the longitudinal follow-up) was the requirement for informed consent, which may have influenced participation. In total 57% of the cohort were men, the overall median age was 55 years, 70% of the cohort were overweight or obese (higher than the 2015 national average of 63%)[64](#_ENREF_64) and 29% were smokers or had quit in the last 12-months (compared with 19% of the adult population in Great Britain).[65](#_ENREF_65) Common co-morbidities were cardiovascular disease (in 38%), diabetes (in 26%), and peripheral vascular disease (in 14.5%). The wounds of 60% of the cohort participants were planned to be left open before surgery; higher than for the cross-sectional survey where 48% were planned. This probably reflects the relative ease of recruitment of participants to the cohort, when it was known in advance that their wound would be open after surgery.

Our research illustrates, for the first time, the heterogeneous nature of the population of people with SWHSI and of their wounds. Whilst it was anticipated that SWHSI would stem from a range of surgical specialties, the distribution of SWHSI sites is noteworthy (34% abdominal, 15% feet, 15% leg) and anatomical site is very likely to influence the impact of the wound on quality of life (if it influences mobility or ability to drive for example). The clinical specialty under whose auspices the preceding surgery occurred was most commonly colorectal (40%) but also commonly vascular (21%). This information is vital to the planning of future research to ensure that the studies are carried out in the populations most affected. Moreover these subpopulations of people with SWHSI are likely to demonstrate very different healing trajectories from one another (an open wound on the foot in somebody with peripheral vascular disease and/or diabetes is likely to heal differently from a partially dehisced abdominal wound post-appendectomy). Those conducting future trials in this area will need to make decisions about trading off ease of recruitment of a heterogeneous population (with consequent “*noisy*” healing data) versus recruitment from smaller, focused patient populations. This is illustrated by our pilot trial to which we recruited 40 eligible participants, 60% of whom had a SWHSI on the foot (compared with 15% in the cohort study). The nature of those recruited to the pilot trial meant that the time to healing was much longer than for the cohort study and far fewer healing events were observed (only 25% healed) despite the 90 day follow-up period. The reasons for the excess of patients with foot wounds in the pilot trial are unclear but it is likely that they were more readily recruited for some reason. It is possible that the current enthusiasm for NPWT as a treatment for SWHSI meant some health professionals were not in equipoise and were unwilling to randomise thus making it difficult to recruit specific patient sub-groups.

Future trials will therefore need to be carefully planned with a desired population in mind and appropriate, targeted recruitment. The cohort study time to healing data will be invaluable to the planning of new research, particularly in relation to appropriate follow-up time frames.

Exploratory analysis of predictors of healing within the cohort identified larger area, surgical wound contamination classification (as judged at the point of surgery)[66](#_ENREF_66) and infection at any time point as predictors of slower healing. The median time to healing of 86 days (95% CI: 75 to 103) is very similar to that for venous leg ulcers (84 days in typical venous ulcer patients in a recent trial).[67](#_ENREF_67) The typical healing trajectory for people with SWHSI is typically not smooth with episodes of infection and hospital readmission commonplace. The relatively young age of SWHSI patients compared with other patient groups with chronic wounds (e.g. leg and pressure ulcers) is particularly noteworthy. The wide-ranging impact on quality of life was detectable using the generic EQ-5D and SF-12 instruments and was both physical and mental.[20](#_ENREF_20), [21](#_ENREF_21) We heard directly from the patients themselves of the often devastating impact on their lives. Patients often felt isolated and confined to the home with disruption of working and caring responsibilities causing feelings of dependency and burden. There were frequently financial impacts of the SWHSI on the person and their family. The cost to the NHS of a SWHSI had not previously been estimated. We estimated that the mean cost of a SWHSI to health services was £1,060 before the inclusion of treatment costs. Use of NPWT was, on average, estimated to cost an additional £1,323 per month and use of dressings, on average, an additional £441 per month.

## What do we now know about treating SWHSI?

Prior to this research we had no information about treatments that were being used for SWHSI. From our research we have learned that SWHSI treatments fall into three main categories: dressings, NPWT, and further surgery. We observed a plethora of treatments being used for SWHSI however hydrofibre dressings were the most commonly used (66% of patients received these at some time), alongside a high use of NPWT. Whilst the cross-sectional survey identified NPWT use in only 6% of patients, the cohort study indicated that a much larger proportion (29%) were treated with NPWT at some time.

Dressings are the cornerstone of treatment for complex wounds and there are many categories available ranging from simple, basic wound contact dressings to “*advanced*” dressings containing ingredients such as silver [27](#_ENREF_27). However the evidence for the effectiveness of specific dressings and NPWT for SWHSI is sparse and low quality.[12](#_ENREF_12) The most recent systematic review of the effects of dressings for open surgical wounds highlighted the paucity of evidence and a review of the effects of NPWT on open surgical wounds (search date: June 2015) similarly concluded that there is currently no rigorous evidence available and therefore the benefits and harms are unclear.([14](#_ENREF_14)) There is an increasing volume of research regarding NPWT for the primary prevention of surgical site infections in closed surgical wounds however its effects in this context also remain unclear.([68](#_ENREF_68), [69](#_ENREF_69)) There is some evidence of potential benefit of NPWT for foot wounds in diabetes however this evidence is low certainty due to its low quality.[29](#_ENREF_29)

We planned to construct a cost-effectiveness model for NPWT compared with dressings for open surgical wounds using a combination of published and cohort study data. We were unable to populate this model with published data as there were no data reporting time to healing as an outcome in RCTs of NPWT in this patient population. Using the cohort data alone to compare the effects of NPWT and dressings on time to healing effectiveness, and after using different approaches to adjust for confounding, we concluded that NPWT is less effective and a more costly than wound dressings for SWHSI. We had originally intended to conduct a value of information analysis to determine the potential impact of uncertainty on the decision regarding NPWT to treat SWHSI. This analysis would assess the health and cost implications of the wrong decision being made, and thus inform investments in future research to mitigate these uncertainties. However, our analyses showed uncertainty around the decision not to use NPWT was very small. Even with the use of advanced adjustment techniques, such as those applied here, observational data may still affect the conclusions Meta-analyses comparing the findings of RCTs and cohorts designed to answer the same clinical question gives an odds ratio of 1.04 (95% CI: 0.89 to1.21) highlighting the potential for agreement between the designs and the associated uncertainty.[70](#_ENREF_70) The current economic evaluation uses all available evidence on the effectiveness and cost-effectiveness of NPWT thus we argue should be seriously considered. However, the potential for unresolved confounding may limit confidence in the associated conclusions, and therefore this may lead to justified calls for definitive RCT evidence to be obtained.

Interviews with patients and health professionals provided further insights into the use of, and views about, treatments for SWHSI. The wide range of dressings used and inconsistency of use was noted by patients. Sharp, sometimes painful, debridement of SWHSI was also reported by patients despite the lack of high quality evidence to support its use however,[71](#_ENREF_71) debridement was not measured explicitly as a treatment in the cohort study so further data are needed on how widespread sharp debridement is as a treatment for SWHSI. Finally, although our study participants generally viewed NPWT as an effective treatment, they reported various drawbacks, including pain during dressing changes. Some study participants reported feeling too embarrassed to go outside the home with NPWT *in situ*, due to the bulky appearance of the equipment, and their fears that the exudate and odour might be detected by other people. Nurses’ varying levels of expertise in use of NPWT therapy appeared to provoke anxiety in patients. These findings mirror those from other small qualitative interview studies with patients receiving NPWT.[72-74](#_ENREF_72)

## What do we now know about living with a SWHSI?

The interviews with patients together with the cohort health-related quality of life data show the devastating effect that open surgical wounds can have on those affected. For those who did not expect to have an open wound after surgery there were feelings of shock, fear and anxiety: feelings akin to those reported by people who have undergone life-changing trauma.[75](#_ENREF_75) Significantly, the presence of an open wound resulted in the withdrawal of many people from normal employment, leisure and social activities. During interviews participants indicated that their physical and mental resources had become depleted through the dominance of the wound in their lives.

We note the low baseline SF-12 PCS and MCS mean scores for SWHSI patients (mean PCS score: 33.1 (SD 10.17); mean MCS score: 42.2 (SD 12.35)). These values, for people who have recently undergone surgery and who have an open wound, are lower than the mean PCS score reported for an, on average, older venous leg ulcer population (mean PCS score: 38.4 (SD 11.2); mean MCS score: 48.6 (SD 12.0)),[67](#_ENREF_67) and are also lower than mean scores for other patient groups such as those with coronary heart disease and arthritis.[76](#_ENREF_76), [77](#_ENREF_77) However, the SWHSI cohort mean scores are similar to post-operative SF-12 data from 85 participants with mainly closed wounds (mean PCS score: 35.1 (SD 7.8); mean MCS score: 43.5 (SD 12.4) 30 days post-surgery).[78](#_ENREF_78) Thus, it is difficult to separate the impact of surgery from the impact of an open wound on health-related quality of life. In the SWHSI cohort we noted a significant improvement over time in both PCS and MCS scores, suggesting that the SF-12 is responsive to changes in health-related quality of life in this population. Improved quality of life was likely to be the result of recovery from surgery, changes in the underlying condition the surgery aimed to ameliorate or resolve and wound healing. Baseline EQ-5D index score was found to be, on average, 0.43 (SD 0.45). Modelling results indicated that wound healing was associated with a small (but statistically significant) increase in EQ-5D index score (mean 0.055, SE 0.02). This level of improvement is smaller than what has been detected for the healing of other wound types,[67](#_ENREF_67) but this may be due to different estimation methods. This value is also within the range of minimal clinically important differences evaluated across a wide range of conditions.[79](#_ENREF_79), [80](#_ENREF_80)

Whilst baseline health-related quality of life was relatively poor in this SWHSI cohort, pain severity and interference scores of 4 (SD 3) (measured using the brief pain inventory)[22](#_ENREF_22) were indicative of relatively mild pain when compared, for example, with the mean pain severity score of 7.0 (SD 1.8) and pain interference score of 7.6 (SD 2.0) reported for in 440 patients with known chronic, non-malignant pain.[81](#_ENREF_81) Additionally, for the SWHSI cohort mean pain scores reduced, on average, by only one point to 3 by 15-months follow-up. In interviews, some patients discussed pain and its impact but it did not seem to be a key topic of concern and was not an obvious source for the overall poor health-related quality of life observed in those with SWHSI.

Our findings, from exploring living with a SWHSI with patients, illuminate the significance of psychosocial effects, due to diminished sense of self, inability to fulfil social roles and obligations and curtailment of normal social activities, especially when patients’ hopes for healing are not met. Our study also highlights the impact of financial pressures on younger patients whose wound rendered them unfit for work, and their concerns about consequences for their family and implications for employment in the longer term.

From a patient perspective, the aspiration for complete wound healing was a major focus of all those interviewed. Healing was largely equated with return to some semblance of life prior to surgery, and a sign that the body was returning to ‘*normality*’. This focus on healing as a key outcome agrees with previous findings from interviews with 33 patients with a range of complex wounds, including leg ulcers, foot ulcers and surgical wounds.[26](#_ENREF_26) Here most people again said that being healed or ‘*cured*’ was their main goal, as did eight participants with complex wounds who, when responding to the question ‘*what did they most want from treatment?*’, reported that they most wanted the wound to heal.[43](#_ENREF_43)

Health professionals’ management of patient expectations is crucial to the patient experience. We know from our cohort study that whilst the median time to healing was around three-months, some people would live with a SWHSI for significantly longer than this. We heard how comments from health care professionals regarding healing and the condition of their wound had profound impacts on patients. Positive feedback was a boost for morale, and sustained the patient’s hope for healing, while negative remarks adversely affected the patient’s general outlook. Conflicting information led to feelings of confusion and consternation in patients. Even quite casual remarks from health care professionals could have a profound impact, which has been noted in other recent research on patients with complex wounds.[82](#_ENREF_82) Patients’ expectations for wound healing may often appear unrealistic, yet clinicians need to manage these expectations within a framework that allows patients some measure of hope for healing, while avoiding the arousal of ‘false hope’, which may result in feelings of disappointment, disillusionment and distrust that undermine professional-patient relationships.[43](#_ENREF_43) Open, non-healing wounds that endure, such as SWHSI, are associated with the ‘forever healing’ process, characterised by a constant need for treatment and care and a diminished quality of life, as described in patients with venous, diabetic and pressure ulceration.[44](#_ENREF_44), [45](#_ENREF_45), [46](#_ENREF_46), [47](#_ENREF_47), [48](#_ENREF_48), [50](#_ENREF_50), [83](#_ENREF_83) This is challenging for clinicians, who must communicate uncertainty regarding wound progress and likely treatment outcomes without raising false hope, or inducing a ‘spiral of hopelessness’ in patients.[48](#_ENREF_48)

Given the severity of impact that these wounds have on patients’ well-being it is not clear whether psychological interventions may be useful in helping patients with hard-to-heal wounds to accept and adapt to their non-healing wound. Our findings also point to the need for improvements in communication with healthcare professionals concerning the slow healing processes associated with SWHSI, and further research is required to investigate how, when, and by whom, information should be conveyed to patients with these types of wounds. Study (nurse) participants also highlighted the need for patients to receive written as well as verbal information, including information about signs and symptoms of infection, and what action to take should these occur.

## Strengths of the research

A key strength of this research is the new information that has been captured and reported on this SWHSI patient population. Prior to this research we did not know the prevalence of SWHSI, the surgeries involved, how many SWHSI were planned compared to how many formed spontaneously, how costly these wounds are to the health service, how best to treat these wounds and how best we might direct future research on SWHSI. There was also an absence of rigorous data regarding SWHSI management in the UK, how long they took to heal and what the impact of these wounds are on patients and their families. This research has provided this information for one geographical area of the UK (Yorkshire and Humber).

We present data and conclusions that address many of the uncertainties that were faced at the start of the work, which we aimed to address using the methodologies described here. This work should provide a solid foundation for the design and planning of further research in the field.

We have employed robust epidemiological, analytical, and qualitative methodologies as required. By conducting an inception cohort study (as opposed to a prevalence cohort), we were able to obtain accurate estimates of time to event data on outcomes for this SWHSI patient group: we also obtained a full picture of treatments received over the natural history of the wound. Whilst a prevalence cohort would have allowed higher recruitment figures, it would have provided far less clarity on crucial outcomes, such as time to healing. We were unable to rely on retrospective extraction of routinely collected data on wound treatments and outcomes as systematically collected data, especially in the community, are limited. Thus, obtaining robust data, such as we have, requires data collection to be embedded in an appropriately designed primary study from the inception of the wound.

## Limitations of the research

Our cohort study was conducted in only two centres in the UK and we therefore acknowledge that practice may various across different centres, and that the prevalence rates observed may not reflect those observed across the UK.

We have noted previously that the generalisability of findings of the cohort study may have been reduced by the need for consent, which removes some of the patient group from the study group. Our cross-sectional survey findings reassured us however, as there were no major differences in key demographic features although more wounds in cohort participants were planned to be left open before surgery. Those patients treated with NPWT in the cohort study were found to differ from those who were not, therefore indicating potential treatment selection. Interviews with clinicians helped to explore how NPWT may be allocated however this did not provide a definitive explanation for treatment decisions.

The nature of the cross sectional survey may have resulted in some cases of SWHSI not being reported, resulting in an under-estimation of treated SWHSI prevalence. The number of responses received was as we expected, and so we are confident that the numbers of missed wounds was low and not systematic, likely due to publicity of the survey and support provided for nurses to complete study activity.

Within the cohort study, 73 wounds (18.6%) did not heal by the end of the study follow up period. Time to healing was used as the primary outcome given this is an important and recommended outcome in wounds research, however, when using this outcome it is acknowledged that there will inevitably be some participants who do not heal by the end of the follow up time point. We acknowledge that the lack of healing data for these participants may have impacted on the robustness of the findings, however expect this to be minimal given the small number of participants this affected.

To meet the objective of our research programme we opted to take a broad approach and collected data on a wide range of SWHSI. This means we have captured data on the heterogeneity of the wound type but also results in more limited data with which to investigate sub-groups of SWHSI in more detail and this may be the focus of future work.

We present findings on the relative treatment effects of NPWT using observational data, given there was a lack of RCT data available on relative effects of NPWT on SWHSI. It is widely acknowledged that experimental data with groups formed by randomisation provide the least biased estimates of treatment effects. We implemented use of advanced adjustment approaches to try and reduce bias as much as possible for both known (e.g. factors identified as prognostic for wound healing such as wound size, previous wound history or level of tissue involvement) and unknown confounders. However, even with adjustment, there is still the potential for unresolved confounding to affect the results and reduces confidence in them, leading to calls for definitive evidence from an RCT.

The relative treatment effects of NPWT were evaluated only on the *healing of SWHSI* and so could not account for other direct effects on health related quality of life, for example wound management. Again these limitations may benefit from further assessment in a RCT.

The qualitative interviews conducted as part of this research programme, identified a diverse range of views from both patients and clinicians. It is however noted that only a limited number of interviews were conducted with both clinicians (12 clinicians comprising of seven nurses and five surgeons) and patients, which may limit the conclusions drawn. Interviews with both patients and clinicians continued until data saturation was achieved, thus ensuring comprehensive data. Further qualitative research may however be warranted to build upon these findings.

## Implications for practice

Findings from this research indicate that surgical wounds healing by secondary intention are relatively common, at least within the Yorkshire and Humber region, UK (4.1 per 10,000 populations), and such wounds frequently arise following colorectal, plastic or vascular surgery.

Data suggests that wounds will demonstrate different healing trajectories. Wounds with a large area, contaminated wounds (at the point of surgery) and infection at any time were found to predict slow healing. Furthermore, wound location and patient comorbidity may impact upon wound healing trajectory.

This research has identified the vast range of treatments in use for SWHSI, and has identified increasing use of NPWT as a treatment during the wound healing pathway (rising from 6% to 29% over the course of approximately 3 years). Despite increasing use of this treatment within the NHS, RCT evidence supporting the use of this treatment for SWHSI is sparse and of low quality. Our results indicates that NPWT has a negative impact on healing and is not cost-effective. However, as our results are based solely on observational data, and even after thorough adjustment there may be unresolved confounding, the potential for which may limit confidence in the research findings.

## Implications for research

The research here signals the importance, scope, feasibility, and opportunity for further research on SWHSI. As is the case across the wound care field there are few good data on the prognostic factors for healing and which factors may be amenable to treatment to promote better outcomes. NPWT, as with other medical devices in wound care, has been adopted widely with relatively little evidence to support its use. If decision makers and funders call for definitive evidence derived from a RCT, the design of such a randomised controlled trial would need to be carefully considered based on data presented here. The overall population of those with SWHSI is too heterogeneous for inclusion into a single trial and we would suggest future research should focus on specific groups. Whilst people with open surgical wounds after colorectal surgery formed our largest sub-population, careful engagement with colorectal surgeons and patients would be required for a full trial in this patient population given the difficulties and barriers outlined in the pilot trial.

Careful consideration also needs to be given to the outcomes measured in a full trial. We focused in this research on healing, and maintain, based on the findings of patient interviews, that this is a key outcome for future research. However, it is important to note that if NPWT is not cost-effective for healing it may still offer worthwhile advantages for patients and health services, which need to be balanced against disbenefits and costs. Impacts of NPWT on outcomes such as infection and re-operation should also be considered, as should patients’ view of the treatment. The type of patient group recruited and the outcomes of interest will all influence the duration of follow-up of any planned study.

In terms of how NPWT is evaluated, investigators must carefully consider the level of pragmatism that will be employed in any future trial.[84](#_ENREF_84) There is a range of NPWT machines available for use including: those that use gauze dressings; foam dressings; single use machine and repeat use devices. There is no good evidence of any differences in the clinical or cost-effectiveness of different machines, thus the trial design choice of whether to mandate use of a specific machine or allow sites to use their current NPWT provision will be down to the investigator. Whilst use of a single device will reduce the ‘noise’ in an evaluation, it is likely to limit the appeal of involvement to potential sites as well as the potential generalisability of data. Thus a pragmatic approach will arguably reflect effectiveness findings as they might be seen in the NHS and also make a large study more feasible. The same is true in terms of a NPWT usage protocols (e.g. levels of pressure and cycle length) as well as how NPWT is used as part of the treatment pathway. The more prescriptive a future study, the less pragmatic and feasible it may become but the more ‘noise’ there will be in the findings.

Similar intervention issues also need to be considered in terms of the comparator in any future study. We know that SWHSI patients receive multiple dressings and there is no high quality evidence that one dressing type is better than another for SWHSI or any other complex wound type.[85](#_ENREF_85) Use of a specific dressing type such as hydrofibre could be explored in a trial but large deviations from use of a single dressing over the duration of a patient’s SWHSI would be expected.

Blinded outcome assessment is crucial for studies with subjective outcomes such as healing and infection.[86](#_ENREF_86) We have demonstrated here that blinded outcome assessment in a NPWT trial in people with SWHSI is possible but protocols and equipment that ensure high quality images are required. We also note the importance of taking photographs beyond the point at which the unblinded investigator considers a wound healed so that a later healing date can be recorded by a blinded assessor should they disagree with the unblinded assessment.

Careful consideration should be given to use of data collection via text message in future trials investigating treatments for SWHSI. Whilst this method has been identified as a simple, inexpensive, valid and acceptable method of data collection method in previous studies,[87](#_ENREF_87),[88](#_ENREF_88), [89](#_ENREF_89) our pilot, feasibility RCT suggested that data collection via text messaging was more successful in younger patients; respondents were, on average, almost 10 years younger than non-respondents. Other studies, which have successfully used text messaging for data collection, have also included younger populations ranging from 22.0 years (SD 1.47) [89](#_ENREF_89) to 44.0 years (SD 13.4).[87](#_ENREF_87) Future trials of SWHSI treatments should therefore consider the demographics of the target patient population prior to inclusion of such methods to ensure that if utilised, data collection is likely to be successful and so provide sufficient data for analysis.

## Questions for future research:

We consider key research questions raised by this programme of research to be:

* Which treatments are clinically and cost-effective for SWHSI for all patients or for particular patient sub-groups?
* Can particular prognostic factors predict time to healing of SWHSI?
* Do psychosocial interventions have the potential to improve quality of life in people with hard-to-heal SWHSI?
* What are the current care pathways for people with SWHSI, how do they vary nationally, and can they be optimised to improve efficiencies and outcomes?
* Is the development of evidence based practice guidelines for the management of SWHSI patients possible to benefit and inform patients, clinicians and NHS commissioning?

# Acknowledgements

This research would not have been possible without the participating patients, their relatives, and clinical staff. We are grateful to all of the patients and relatives who took part in this research programme and to the nurses and clinicians in Leeds, Hull, Humber and the East Riding of Yorkshire for their help in recruiting patients to the various components of this research programme.

We are particularly grateful to all of the patient and public involvement representatives involved in this research programme, but specifically; Stephen Dixon, Barbara Piggot and Pauline Stabler, who have provided indispensable input across the programme of work.

The contribution of Claire Acey to the coordination of all elements of this programme is also gratefully acknowledged.

Finally we would like to thank the members of the Data Monitoring and Ethics Committee for Workstream 4: Professor Peter Vowden, Professor Robert Hinchliffe, Dr Sarah Brown and Christine Gratus.

**Data Sharing**

All data requests should be submitted to the corresponding author for consideration. Access to anonymised data may be granted following review

# Contributions of Authors

**Professor Ian Chetter** (Professor, Vascular Surgery) was the chief investigator and led the research programme and chaired the Programme Management Group. Professor Chetter led Workstreams 1 and 4.

**Catherine Arundel** (Research Fellow, Health Research and Trials) contributed to the design, conduct, analysis, interpretation and reporting of Workstream 4.

**Dr Kerry Bell** (Statistician, Health Research and Trials) undertook the statistical analysis and interpretation for Workstream 1.

**Hannah Buckley** (Statistician, Health Research and Trials) undertook the statistical analysis and interpretation and advised on conduct for Workstream 1 and advised on the design, conduct and statistical analysis for Workstream 4.

**Professor Karl Claxton** (Professor, Economics) oversaw all aspects of Workstream 2 (design, conduct, analysis, interpretation and reporting).

**Belen Corbacho Martin** (Health Economist, Health Research and Trials) undertook the economic analysis and interpretation for Workstream 4.

**Professor Dame Nicky Cullum** (Professor, Nursing) contributed to the conception, design, conduct, analysis and reporting of all Workstreams and input to the programme management and strategy.

**Dr Jo Dumville** (Senior Lecturer, Health Sciences) contributed to the design, conduct, analysis and reporting of all Workstreams.

**Caroline Fairhurst** (Statistician, Health Research and Trials) undertook the statistical analysis for Workstream 4.

**Dr Pedro Saramago Goncalves** (Research Fellow, Health Economics) undertook the analyses in Workstream 2, and contributed to the design, conduct, interpretation and reporting of Workstream 2.

**Eileen Henderson** (Assistant to Medical Director, NHS Needs) ensured all Workstreams met NHS needs and were relevant to NHS decision uncertainty.

**Karen Lamb** (Research Coordinator, Wound Research) contributed to the design and conduct of Workstream 1 and the design, conduct, analysis and reporting of Workstream 4.

**Judith Long** (Project Manager, Vascular Surgery Research) led and undertook qualitative data collection and analysis and reporting for Workstream 4.

**Dorothy McCaughan** (Research Fellow, Health Research) led and undertook qualitative data collection and analysis and reporting for Workstream 3.

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**Angela Oswald** (Tissue Viability Matron, Wound Care and Research) provided clinical leadership and expertise in relation to negative pressure wound therapy.

**Laura Sheard** (Senior Research Fellow, Health Research) undertook qualitative data collection and analysis for Workstream 3.

**Marta O Soares** (Senior Research Fellow, Health Economics) supervised all aspects of Workstream 2 (design, conduct, analysis, interpretation and reporting). She also contributed to the design, conduct, analysis and reporting of Workstreams 1 and 4.

**Nikki Stubbs** (Clinical Pathway Lead, Wound Research) contributed to the design, conduct, analysis and reporting of Workstreams 1 and 4.

**Professor David Torgerson** (Professor, Health Research and Trials) contributed to the management of the programme of work and the design, conduct, analysis, interpretation and reporting of Workstreams 1 and 4.

**Professor Nicky Welton** (Reader, Statistics and Health Economic Modelling) oversaw the design, interpretation and reporting of the analyses in Workstream 2.

# Publications

**Publications - Published**

Workstream 1

Chetter I, Oswald A, Fletcher M, Dumville J, Cullum N. A survey of patients with surgical wounds healing by secondary intention; an assessment of prevalence, aetiology, duration and management. *Journal of Tissue Viability* (2017), <http://dx.doi.org/10.1016/j.jtv.2016.12.004>

Chetter, I., Oswald, AV., McGinnis, E., Stubbs, N., Arundel, C., Buckley, H., Bell, K.,  Dumville JC., Cullum, NA., Soares, MO., and Saramago, P. Patients with surgical wounds healing by secondary intention: A prospective, cohort study. International Journal of Nursing Studies. Available from:  <https://doi.org/10.1016/j.ijnurstu.2018.09.011>)

Workstream 3

McCaughan D, Sheard L, Dumville J, Cullum N, Chetter I. Patient’s perspectives and experiences of living with a surgical wound healing by secondary intention: an in-depth qualitative study. International Journal of Nursing Studies (2018), <https://dx.doi.org/10.1016/j.jtv.2016.12.004>

Workstream 4

Arundel C, Buckley H, Clarke E, Cullum N, Dixon S, Dumville J *et al*. Negative pressure wound therapy versus Usual Care for Surgical Wounds Healing by Secondary Intention (SWHSI trial): study protocol for a randomised controlled pilot trial. *Trials,* 2016, 17:535 DOI: 10.1186/s13063-016-1661-1.

Arundel C, Fairhurst C, Corbacho-Martin B, Buckley H, Clarke E, Cullum N et al. Pilot, feasibility randomized clinical trial of negative pressure wound therapy versus usual care in patients with surgical wounds healing by secondary intention. BJS Open, 2018, 2: 99-111.

**Publications – Accepted for Publication**

**Publications –Submitted for Publication**

Workstream 2

Saramago P, Claxton K, Welton NJ, Soares M. Bayesian econometric modelling of observational data for cost-effectiveness analysis: Establishing the value of negative pressure wound therapy in the healing of open surgical wounds.

Workstream 3

McCaughan D, Sheard L, Dumville J, Cullum N. Nurses’ and surgeons’ views and experiences of surgical wounds healing by secondary intention: a qualitative study.

Workstream 4

Long J, Meethan K, Arundel C, Clarke E, Firth A, Sylvester M, Chetter I.Exploring experiences of nurse participation in conducting a randomised controlled trial of wound care treatments.

# Disclaimers

This report presents independent research funded by the National Institute for Health Research (NIHR) (RP-PG- 0609-10171). The views and opinions expressed by authors in this publication are those of the authors and do not necessarily reflect those of the NHS, the NIHR, CCF, NETSCC, PGfAR or the Department of Health. If there are verbatim quotations included in this publication the views and opinions expressed by the interviewees are those of the interviewees and do not necessarily reflect those of the authors, those of the NHS, the NIHR, NETSCC, the PGfAR programme or the Department of Health.

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# Appendices

## Appendix 1 – Cross Sectional Survey Publication

Chetter, I., Oswald, AV., Dumville JC., and Cullum, NA. A survey of patients with surgical wounds healing by secondary intention; an assessment of prevalence, aetiology, duration and management. Journal of Tissue Viability. 2016 Dec 21. Available from: <https://dx.doi.org/10.1016/j.jtv.2016.12.004>

## Appendix 2 – Cohort Study Publication

Chetter, I., Oswald, AV., McGinnis, E., Stubbs, N., Arundel, C., Buckley, H., Bell, K.,  Dumville JC., Cullum, NA., Soares, MO., and Saramago, P. Patients with surgical wounds healing by secondary intention: A prospective, cohort study. International Journal of Nursing Studies. 2019; 89: 62-71. Available from:  <https://doi.org/10.1016/j.ijnurstu.2018.09.011>)

## Appendix 3 – Cross-Sectional Survey Data Collection Instrument

**A survey of Surgical Wounds Healing by Secondary Intention (SWHSI) and their care: Data capture form**

Date of completion

|  | **DD** |  | **MM** |  | **YYYY** |  |
| --- | --- | --- | --- | --- | --- | --- |
|  |  | / |  | / |  |  |

**Section 1: Details of healthcare worker completing this form**

1. Your Job title

Community nursePractice nurseSpecialist nurse (Community)Podiatrist

Hospital-based nurse (ward) Hospital-based nurse (outpatient)

Other:\_\_\_\_\_\_\_\_\_\_­­­\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_

Section 2: Patient details

Patient’s age years Patient’s gender: Male Female

**Ethnicity:**

White British White Irish White Other Black African Black Caribbean Black Other

Asian Indian Asian Pakistani Asian Bangladeshi Asian Other White and black Caribbean

White and black African White and Asian Other mixed background Chinese Other

**2. Where is this patient currently being treated? (Tick one box or all that apply)**

**CASTLEHILL:**  Hospital outpatient Hospital ward

If selected, give name and number of ward: \_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_

**HULL ROYAL INFIRMARY:** Hospital outpatient Hospital ward

If selected, give name and number of ward: \_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_

**COMMUNITY:** Podiatry clinic Nursing/care home GP practice

Own/another’s home Other Community clinic

Other\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_

**Section 3: Wound details**

**3. How many surgical wounds healing by secondary intention (SWHSI) does this patient have?**

1 2 3 4 5 6

**IF THE PATIENT HAS MORE THAN ONE SWHSI PLEASE ANSWER THE FOLLOWING QUESTIONS FOR THE WOUND THAT YOU THINK IS THE LARGEST**

**4. How long has the patient had this SWHSI?**

weeks OR days

**5. What type of surgery lead to this SWHSI?**

Orthopaedic Colorectal Breast Neurosurgery

Trauma Plastics Cardiothoracic Oral and maxillofacial surgery

Vascular Urology Upper GI Obs/gynaecological

Other (please give details)\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_ Don’t know

**6. Please also record the name of the specific type of surgery if possible**

(e.g. hernia repair, c-section, pilonidal sinus) \_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_

**7. If possible please record the date of original surgery that lead to the SWHSI: / Day Month Year**

**8.Was this surgery:** Emergency?Elective?Don’t know?

**9. Was the SWHSI a result of:**

A planned healing by secondary intention

A surgically closed wound — **fully** broken open (**dehisced**) due to (for e.g.) infection or poor healing

A surgically closed wound – **partially** broken open (**partially dehisced)**

A surgically closed wound which was then **surgically opened** to become a surgical wound healing by secondary intention

Other (please give details): \_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_ Don’t know

**10. In your opinion, did infection significantly contribute to the development of the SWHSI?**

Yes No Don’t Know

**11. Is this patient receiving antibiotic therapy in relation to their SWHSI?**

Yes No Don’t Know

**12. If this wound was surgically closed and broke open (is a dehisced wound), please record how long after surgery the wound dehisced and where the patient was located when this occurred?**

Days

In hospitalIn the communityDon’t know

**13. What treatments is this patient’s SWHSI currently receiving?**

Dressings

If selected, please indicate frequency of dressing changes = per day / week

Negative pressure wound therapy

If selected, please indicate frequency of application = applications per day / week

Other If other, please state which.

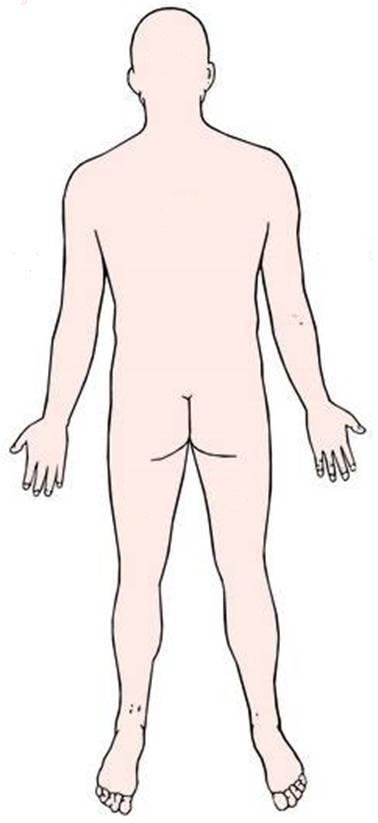
If selected, please indicate frequency of application = per day / week

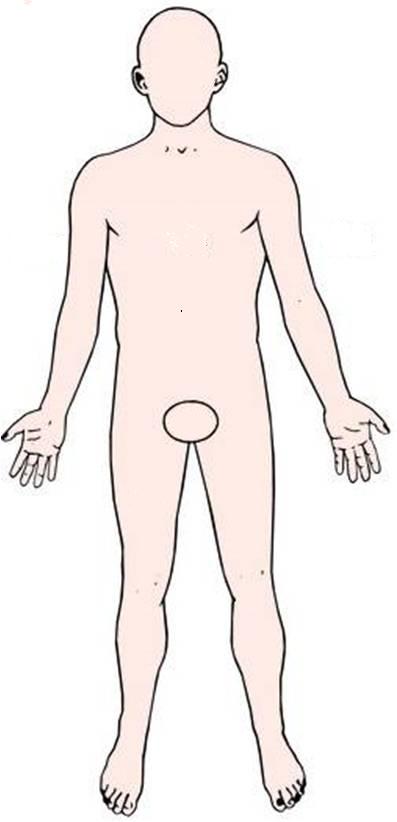
**14. Is this patient receiving treatment for their SWHSI elsewhere?**

Yes No Don’t Know

If yes, please state where:\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_

**15. On the picture below, please draw and label clearly the location of all current SWHSI for this patient.**





Please add any comments you may have regarding data collection in this patient population

## Appendix 4 – Cohort Results – Adjusted Cox Proportional Hazards model results for time to wound healing

|  |  |  |
| --- | --- | --- |
|  | Hazard ratio (95% CI) | p-value |
| Diabetes present (vs not) | 0.81 (0.61, 1.08) | 0.16 |
| Female (vs male) | 0.97 (0.77, 1.22) | 0.80 |
| CVD present (vs not) | 1.03 (0.81, 1.22) | 0.79 |
| Infection at any point (vs not) | 0.65 (0.51, 0.84) | <0.01 |
| Baseline area above median (vs below) | 0.46 (0.36, 0.59) | <0.01 |
| Reason for SWHSI\* |  |  |
| Planned due to infection | 1.35 (0.96, 1.89) | 0.29 |
| Planned for other reason | 0.43 (0.10, 1.76) |
| Dehisced | 1.16 (0.68, 1.97) |
| Partially dehisced | 1.24 (0.89, 1.75) |
| Surgically opened | 0.86 (0.46, 1.61) |
| Contamination level of surgery† |  |  |
| Clean-contaminated | 0.75 (0.46, 1.25) | 0.04 |
| Contaminated | 0.52 (0.32, 0.86) |
| Dirty | 0.56 (0.36, 0.89) |

\* Reference category = planned due to being unable to approximate wound edges

† Reference category = clean

## Appendix 5 – Cost Effectiveness Study: Bayesian econometric modelling of observational data for cost-effectiveness analysis - Establishing the value of Negative Pressure Wound Therapy in the healing of open surgical wounds

**Introduction**

System level decisions regarding the use of health care technologies often rely on an assessment of clinical and cost effectiveness, a process known as health technology assessment (HTA). Assessment of clinical effectiveness relies on causal evidence that a technology improves health outcomes. The randomised controlled trial (RCT) is an experimental study design which randomises participants to receive alternative interventions. The randomisation ensures that any differences in outcomes can be attributed to treatment allocation and causality is established.

Observational studies (i.e. non-randomised) are, however, an increasingly important source of evidence in supporting decisions about use of health care technologies. Recent policy changes such as, for example, the ‘new’ Cancer Drugs Fund (CDF) in the UK determine that cancer drugs for which significant clinical uncertainties remain can be funded conditional on evidence being collected to inform a review of the decision 3 years on [1]. It explicitly considers the possibility of such evidence being of observational nature, collected as the treatment becomes in use in the NHS via an existing registry [2]. An equivalent framework in cancer has also been recently proposed for comparative effectiveness in the US with use of the large administrative databases such as Surveillance, Epidemiology and End Results (SEER) – Medicare linked data [3].

Also, HTA processes are increasingly being widened to technologies such as medical devices or diagnostic tests [4-6] that face no regulatory requirement to demonstrate effectiveness, and thus often present with limited clinical evidence [7-9]. Despite, these technologies are widely used within health systems. One such example is Negative Pressure Wound Therapy (NPWT), a medical device claimed to accelerate the healing of wounds such as pressure ulcers or surgical wounds left open to heal. NPWT was evaluated by NICE guidelines in the UK in 2008 for the healing of open surgical wounds as part of a wider appraisal on the prevention and management of surgical site infection [10, 11]. When faced with inconclusive effectiveness evidence, NICE refrained from making a negative recommendation on the use of NPWT but recommended further research. Since, there have been two subsequent revisions of the guidance, in 2011 [12] and 2013 [13], the latter updating the original guidance. In what concerns NPWT for open surgical wounds, no significant evidence emerged after the original guidance was issued. In all this time, the NHS has funded, and it still funds, NPWT but has no insight into its value for money in relation to dressings which are much cheaper alternatives. In cases such as this, observational data may provide crucial intelligence in support of adoption and research decisions.

But non-randomised, observational evidence means that there is no control over treatment assignment. In this situation patients receiving the treatments may differ in aspects that are also related to the outcome (prognostic variables), generating potential for confounding. Analyses may attempt to adjust for potential imbalances where information on relevant prognostic variables has been collected within the non-randomised study and there is a good understanding of the process of selection into treatment. For this, a plethora of methods is available including regression adjustment, propensity score adjustment and matching methods [14]. However, causality cannot be established by the use of adjustment as these methods do not rule out the possibility of confounding on prognostic factors that have not been observed – unobserved confounding. There are alternative adjustment methods that aim to control for unobserved confounding, namely Instrumental Variable (IV) approaches [15-17]. These approaches use a variable – an instrument – that is associated with treatment assignment but that does not directly affect the health outcome (only through treatment assignment). This allows the identification of ‘pure’ changes in treatment assignment (not related to confounders), and in this way estimate causal effects. In practice, the IV method is not yet well established in the health care literature, with only few applications having been published to date [18-22].

There is some guidance in the literature for the analysis of observational data for HTA, mostly descriptive of available methods (such as DSU Faria et al [14]), or in the form of generic checklists/questionnaires [23] [24] [25]. Despite this growing literature, there are yet few examples of the application of these methods in HTA, particularly those involving instrumental variable regression. This paper thus explores an applied example relating to the clinical and cost-effectiveness of NPWT in the healing of surgical wounds left open to heal using data from an observational cohort study. This study aims to identify the challenges of the analyses of observational data, which included both adjustment for observables and instrumental variable regression, to establish clinical and cost-effectiveness. The paper starts with a description of the application, which includes a summary of the observational data used to make inferences on clinical effectiveness (section 2). The methods of analyses are then described which include the development of a generic framework of analyses (section 3). The following section (section 4) describes the results of analyses. The paper finishes with a discussion of the challenges encountered (section 5) that can be generalised to the use of IVs in other HTA contexts.

**Description of the application and observational data available**

The application concerns the use of negative pressure wound therapy (NPWT) as an alternative to dressings (e.g. foam, hydrocolloid or alginate) for the healing of surgical wounds healing by secondary intention (SWHSI). SWHSIs are surgical wounds that have either broken down after closure at surgery (e.g., due to infection) or were intentionally left open at surgery and they heal from the bottom up. NPWT is a medical device that is applied to the wound surface and creates a suction force (or vacuum) removing tissue fluid away from the treated wound area into a canister [26]. It has been claimed that NPWT speeds-up wound healing by removing excess fluid, increasing tissue perfusion and removing bacteria [27]. However, despite a recent Cochrane systematic review having identified two randomised controlled trials investigating the relative effectiveness of NPWT on SWHSI [28], it could not draw any conclusions as the outcome data reported on both studies was very limited.

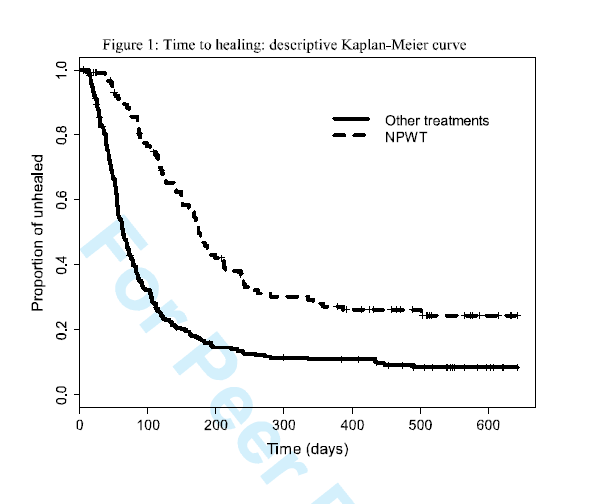
NPWT is, however an expensive treatment, that is widely used in the UK and elsewhere. Our analyses thus uses evidence from a recent observational cohort study undertaken in the UK [29] that recruited patients at inception of their SWHSI. This is the largest and most comprehensive study to date in this population. The data was used to explore the effectiveness of NPWT on time to wound healing, which is the clinical outcome of wound treatments most valued by patients [30]. Given the observational nature of the study, to ascertain causality analyses aimed to both adjust estimates for confounding on observed factors and to perform IV estimation. Treatment effectiveness estimates obtained in this way were subsequently used to inform the cost-effectiveness (CE) analysis by considering the impact of differences in time to wound healing on Health-Related-Quality-of-Life (HRQoL) and on costs. The ultimate aim of analyses was to inform decision making in the UK and explore whether further research to reduce any decision uncertainty is worthwhile.

**Summary description of the data**

The pivotal study [29] used was a longitudinal cohort study conducted over a 21 month period (18.02.13 to 30.11.14) in primary, secondary and community settings at eight study sites across Yorkshire, UK. Participants were recruited with incident SWHSIs requiring treatment, of 3 weeks’ duration or less. The study’s inclusion and exclusion criteria can be found elsewhere [31]. The data collected within the study was comprehensive, and included details on the use of treatments over the ‘life’ of the wound, time to healing and other wound-related events (e.g. infection), health resource use and HRQoL data, amongst other data. The minimum follow up period of participants was 12 months.

The study recruited 393 participants. At baseline, 56.5% (n=222) patients were male, the mean age was 54.1 years (SD= 18.1). Baseline data indicate that 40.0% had dehisced after surgery and the remainder were intentionally left open at surgery. The most common location of the SWHSI was the abdomen (33.6%). Colorectal surgery was the most common type of surgery originating the SWHSI (39.7%), and of the surgeries leading to the SWHSI, 60.1% were classed as emergencies. There was a high proportion (23.4%) of wounds greater than 25cm2 in area (mean area: 32.0cm2; median area: 6cm2) and 60% of wounds were recorded as full thickness. Patients were followed up by, on average, 499 days (SD: 127.4), ranging from 13 days to 651 days. Out of the total 393 participants, 22 participants died (5.6%) and 320 (81%) healed within the study. The mean time to healing of those that healed was 99 days (25% healed within the first 44 days and 75% healed within 122 days). A full list of summary characteristics can be found in Appendix 1, Table A1.1 in Supplementary material.

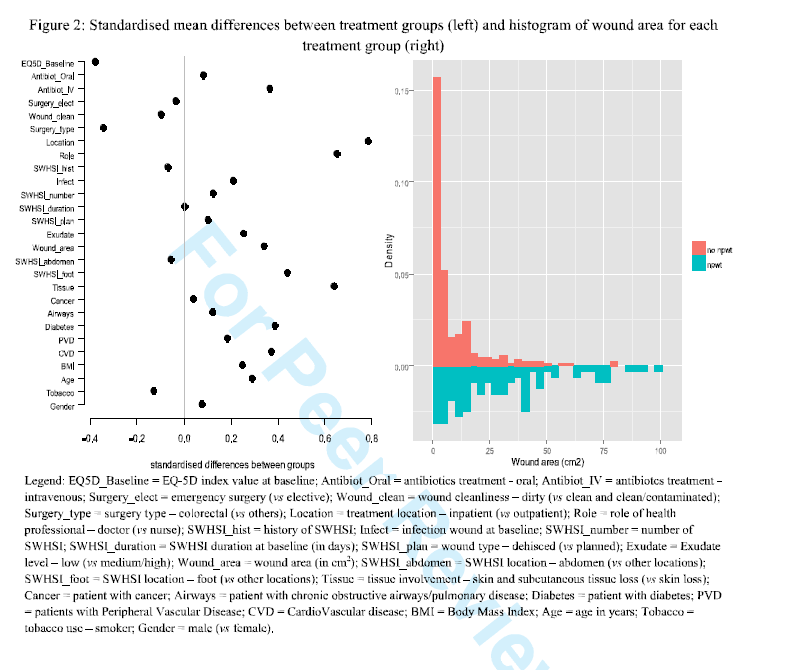
115 participants (29%) were treated with NPWT at some point during follow-up (89 at baseline and 26 during follow up). Given the small number of participants receiving NPWT during follow-up it was decided to consider all NPWT users together. These 115 participants spent, on average, 37 days on NPWT (SD 64.6 days, median 21 days, inter-quartile range (8 days to 37.5 days). Of those receiving NPWT, only 69% (79 participants) healed within the study compared with 87% of people who never received NPWT. The data also suggest that patients who received NPWT took longer to heal than those who did not receive NPWT (median time to healing of 175 days vs. 63 days, respectively) – see Figure 1.



**Imbalances and overlap between the groups**

Patients who received NPWT had more serious wounds than those who did not. People who received NPWT had larger wounds (the majority of NPWT patients had a large (>25 cm2) wound compared with only 12% of non-NPWT patients) and were more likely to have experienced skin and subcutaneous tissue loss whilst patients who did not receive NPWT had wounds involving skin only. NPWT patients were more likely to be treated as hospital inpatients whilst most non-NPWT patients were outpatients. Most treatment decisions for NPWT patients were made by a doctor whilst in non-NPWT patients this responsibility was fairly split between doctors and nurses. These differences demonstrate that there is the potential for selection bias in the cohort data.

The plot on the left of Figure 2 shows the mean differences between groups (NPWT minus non-NPWT) standardised (by dividing the differences by the standard deviation of the whole sample) for a set of baseline covariates. It demonstrates that while there may be differences between the groups across a multitude of factors, none of the analysed covariates shows a difference bigger than 1 standard deviation across groups. Also, for each individual covariate we analysed the overlap between groups, that is, we compared the distribution of values assumed for each covariate across groups to assess if there were regions of non-overlap (example plot on the right of Figure 2 for wound area). We verified that there was always some overlap. These findings indicate that the mechanism of selection of patients into the treatment groups may not be clearly determined.



**Censoring and hard-to-heal**

Due to the limited follow-up duration in the cohort study and due to loss to follow-up, there were 73 patients who did not heal within the study, introducing censoring in the data. These 73 patients were followed-up on average for 416 days, suggesting they may be somehow a ‘hard to heal’ subgroup (average time to healing in those that healed was 99 days). Also, the ‘hard-to-heal’ patients differed in their baseline characteristics from the patients who healed, with 23% more diabetics, 24% more patients with larger wounds, 26% more foot and 27% less abdominal wounds, 22% less dehisced wounds, 30% more inpatients, 20% more patients seen by a doctor, 25% less colorectal surgery and finally 23% more subcutaneous tissue loss. A full list of summary characteristics by healing status can be found in Appendix 1, Table A1.2 in Supplementary material.

**Methods**

**Framework of analysis**

We aimed to evaluate whether causal effects of NPWT on healing of SWHSI patients may make this technology effective and cost-effective when compared with standard dressings. By establishing time to healing as the only parameter directly affected by treatment, HRQoL weights and costs associated with resource use are assumed only dependent on whether the patient is healed or not. Note that NPWT may have further direct effects on HRQoL (independent of healing), for example, in assisting with management of the wound; these are, however, likely to be less significant in magnitude and in duration as NPWT is typically used for only a short duration of time. The analyses use cost per Quality Adjusted Life Years (QALY) gained as the cost-effectiveness outcome [32]. A one year time horizon was considered and an NHS perspective adopted. Formally, we aim to quantify the impact of NPWT in expected time to healing, . The difference in QALY between the interventions, , can then be expressed as:

|  |  |
| --- | --- |
| where, and represent the HRQoL weights of patients healed and unhealed, respectively, and is thus the increment in HRQoL weight associated with healing. The difference in costs,, would be calculated in an analogous way considering disease related costs, , but would also need to consider the costs of the treatments themselves, . | Equation 1 |
|  | Equation 2 |
|  | Equation 3 |
| Non-NPWT group  NPWT group | Equation 4 |

Incremental disease costs are calculated in an analogous way to incremental QALYs, with representing the costs of unhealed patients and the costs of patients that healed (Equation 3). Treatment related costs consider that patients receive some form of treatment up to healing. The daily costs associated with the ‘Non-NPWT group’ is based on average cost of dressings in participants who have received other treatments, , and is simply calculated by multiplying this cost by the difference in time to healing . For patients receiving NPWT, an average daily cost of NPWT () is applied to the mean time on NPWT treatment on the cohort study, , and in the remaining time patients are assumed to use dressings [with a daily cost equal to patients in the ‘Non-NPWT’ arm (Equation 4)]. The description above identifies the evidence requirements for this assessment.

**Implementation and software**

A Bayesian approach was taken throughout. Within a Bayesian approach the uncertainty over predicting treatment allocation is fully considered, and thus correctly reflected in decision uncertainty. The separate statistical/econometric models were implemented in WinBugs [33]. Results of the individual analysis were reported with 95% credible intervals (CrIs). Model selection was based on the deviance information criterion (DIC) [34-36], which reflects a trade-off between model fit and model complexity. DIC differences of 5 were considered meaningful [34, 37]. Econometric tests on the relevance and validity of instruments are not developed in the Bayesian context, and frequentist methods were thus used [38]. The WinBugs simulations were used within the software package R [39] to determine cost-effectiveness. Decision uncertainty was reported using the probability of each intervention being cost-effective.

**Modelling of HRQoL weights and costs**

The HRQoL weights were derived from the EQ-5D questionnaire [40] applied to patients in the cohort study at baseline and every 3 months thereafter (up to 18 months). A panel data approach (a mixed model with random intercept) was used (Equation 5). A time-dependent indicator of whether the patient had healed or not was the only included covariate, assuming that utility values differ between healed and unhealed states, not depending on treatment status. The outcome variable was change in the index score from baseline (*t*=0), , for each observation point within each patient , to capture both within and across patient variation. Exchangeability across time within individuals is assumed.

|  |  |
| --- | --- |
| Modelling of HRQoL weights |  |
| for i=1,…,n and t ϵ (3,6,9,12,15,18); where *Xit* indicates whether patient *i* is healed on time interval *t*. Where is the mean change in EQ-5D from baseline; is the effect of healing, corresponding to in Equation 1; is the within patient variation (i.e. across time) in change scores; and is the across patient variation in change scores. | Equation 5 |
| Modelling of costs  Proportion of individuals with non-zero costs |  |
| for i=1,…,n and t ϵ (3,6,9,12,15,18); where *Xit* indicates whether patient *i* is healed on time interval *t*. Where is the effect of healing on the probability of consuming health resources; is the mean odds of a non-zero cost while unhealed; and is the within patient variation across time intervals.  *Mean costs given non-zero cost* | Equation 6 |
| ,  for i=1,…,ncost>0 and t ϵ (3,6,9,12,15,18); where *Xit* indicates whether patient i is healed on time interval *t*. Where is the effect of healing on costs (log), corresponding to in Equation 3; are the costs while unhealed (log); is the within patient variation in the costs (log) (i.e. across time); is the shape parameter of the Gamma distribution. | Equation 7 |

Vague priors were used throughout (not shown here). Flat uniform priors were used for variance parameters. The estimate of directly informed the term in Equation 1, in the cost-effectiveness analysis.

As with EQ-5D, resource use was collected within the cohort study at baseline and at 3 monthly intervals, and included GP visits, nurse visits, outpatient visits and hospital admissions. Disease specific costs per patient were obtained by multiplying resource use by relevant unit costs (2014 prices). Unit costs were obtained from Personal Social Services Research Unit (PSSRU) 2014 [41] and NHS reference costs 2013-2014 [42]. Treatment costs were obtained from the British National Formulary [43] as well as specific costing information from the two centres (Hull and Leeds) on NPWT. A detailed listing of the specific values of unit costs is shown in Appendix 2, Table A2.1 in the Supplementary material.

Many observations over the different time points were expected to have zero costs. A Bayesian two-part mixed model was developed: the first-part (Equation 6) captures the probability of zero costs and the second-part (Equation 7) describes the average costs of those with non-zero values. A mixed Gamma model with *log* link was used due to data skewness. Note that costs for patients healed are not necessarily expected to be zero as time to healing collected within the cohort study refers to an index wound and the patient may have other wounds.

**Modelling of time to healing**

In cost-effectiveness, where expected values are of interest, time to event outcomes are traditionally analysed using parametric survival analysis which account for censoring. However, in this study, parametric analyses would struggle to provide a good fit due to the asymptote observed in Figure 1. More complex, and therefore flexible, functions (such as splines) would need to be used; however, these are not readily available in software packages used for Bayesian analyses (such as WinBugs [33, 36]). Also, tests to the validity of instruments have not, to our knowledge, been developed in this context, which would hamper the process of selection of appropriate instrumental variables. For this reason, we take a different approach. We first generate a complete dataset which allows for an initial exploration of the IVs analysis using linear regression, statistical tools in which IV methods are well established. However, we acknowledge that linear regression assumes that times to event (conditional on the explanatory variables) are Normally distributed, which is unlikely due to the right skewness of these data. We therefore extend the analyses to more explicitly consider the hard to heal patients, which accounts for some degree of skewness.

Using a complete dataset

To generate a complete dataset, censored times to healing were imputed by assuming that patients healed the day after they were censored. This will closely reflect the data but will systematically underestimate healing times in censored individuals as it is unlikely that they have all healed so close to censoring. The regression approach to time to healing adopted here aims to evaluate the treatment effect of NPWT, *t*, conditional on a set of relevant adjustment factors that have been observed, *A*. This regression approach may be seen as comparable to propensity score matching. The model implemented is described in Equation 8.

|  |  |
| --- | --- |
|  | Equation 8 |
|  |
| for i=1,…,n, *A* is the design matrix. |

When IVs are considered, a two-stage regression is needed. The first stage predicts treatment allocation conditional on the instrument, *z*, and a set of relevant predictors, *B*. The predicted values for treatment allocation, here probabilities, , are then used in a second stage regression of time to healing that, again, conditions on the same set of covariates, *B*. The model used was:

|  |  |  |
| --- | --- | --- |
| (stage 1) |  | Equation 9 |
|  |
| (stage 2) |  |
|  |
| for i=1,…,N, *z* the instrument(s) and *B* the design matrix. | |

We also explored treatment effect interactions. An interaction term will be endogenous (i.e. subject to confounding) in describing health outcome, even if the covariate is not itself endogenous. This means that we need to define two first stage regressions (stage 1A and 1B) and, therefore two valid instruments, one for each endogenous term, the treatment variable and the treatment interaction variable. However, if *z* is a valid instrument for the treatment variable and if the interaction *w* is exogenous then *z.w* is a valid instrument for the interaction term [44-46]. The set of associated regressions when evaluating the treatment effect then becomes:

|  |  |  |
| --- | --- | --- |
| (stage 1A) |  | Equation 10 |
|  |
| (stage 1B) |  |
|  |
| (stage 2) |  |
|  |
| for i=1,…,N, *z* the instrument(s), *w* the interaction and *C* the design matrix. | |

Standard non-informative Normal priors were used (not shown).

**Selection of variables for adjustment**

By definition, relevant adjustment covariates are those that are associated with outcomes and are imbalanced across treatment groups, i.e. the intersection of covariates that are associated with outcomes and treatment allocation. While identification of covariates associated with treatment allocation canbe based on our sample, there is a concern that relevant predictors of healing cannot. This is because, due to the potential imbalances in treatment assignment, the relationship of other predictors and outcome may also be confounded. There is also an absence of good epidemiological information in this area and thus a lack of crucial intelligence on the clinical trajectory, outcomes and determinants of outcomes for people with SWHSI. For this reason, instead of using the intersection of the covariates that are associated with outcomes and treatment allocation, we used their union to define the adjustment set. This means we may lose precision in the estimates by including potentially irrelevant covariates, but we may gain in accuracy on the point estimate by not missing important confounding factors.

To identify factors associated with treatment assignment we used a logistic regression with treatment received as the dependent variable. A thorough model selection process was devised. It started by regressing all available baseline covariates individually to identify an initial set of potentially relevant covariates. Selection was based on differences of 5 units in the DIC [36] in relation to the null model. Models using combinations of these covariates were then evaluated (2 by 2, 3 by 3, etc), and the covariate set in the model with the best DIC was selected to be further used for adjustment in the linear regression model for time to healing. Note that statistical significance on the effects of the individual covariates was not used here purposefully. Instead, we considered the effects of adding covariates on reducing the DIC, i.e. on improving the overall model fit considering its parsimony.

To identify determinants of healing (and potential treatment effect modifiers, i.e. whether NPWT is more effective in a subgroup of patients), we looked at the relationship of available covariates with healing on those participants that used NPWT, and separately, on those that did not use NPWT to avoid potential confounding. Thus, we have fitted two separate regressions in *(i)* the subset of NPWT patients and in *(ii)* the subset of non-NPWT patients. A covariate selection process was conducted using the same principles as those described above for both models to identify a set of covariates that have been determined important in either or both subsets. To accommodate potential treatment effect modifiers we have fitted treatment by covariate models to the full dataset using all adjustment covariates identified.

**Identification of Instrumental Variables, z**

A critical step in adjusting for unobservables using IV regression is the identification of instrument(s). An instrument, *z*, is something that (i) is associated with treatment assignment but (ii) is not directly affecting the health outcome (except through its effect on treatment assignment). The project team defined *a priori* a set of potential instruments which related to clinicians’ practice patterns and stated preferences on the use of NPWT. This decision was supported by previous applications in HTA which used this instrument [20]. The expectation is that any individual patient will be more likely to be treated with NPWT if the clinician has an observed or revealed preference for it. However, for this instrument to be valid, clinicians that prefer NPWT cannot have any influence over time to healing (the outcome) except through the choice of this particular treatment.

To characterise practice patterns we assessed whether the same health professional had prescribed NPWT to their previous patient. It was assumed that previous treatment used by the treating health professional was not confounded by the heath professional’s patient’s case mix. We also surveyed health professionals who recruited patients into the cohort study regarding their stated preferences for NPWT and relevant proxies. We collected beliefs about whether NPWT was better at managing the specific wounds being considered, whether health professionals believed the treatment to be expensive, and whether they believed it to represent good value for money. We have assumed that health professionals who thought NPWT was better/less expensive or better value would be more likely to use NPWT in a particular patient than those that expressed opposite beliefs. Further details on the survey can be found in Appendix 3 – Supplementary material.

A series of analyses and formal tests were conducted to assess the performance of each instrument – Appendix 4 – Supplementary material. Tests undertaken considered if there was evidence of endogeneity (using the Durbin-Wu-Hausman test [47]); if there was evidence of the instrument set not being valid (using the Hansen-Sargan test [48, 49]); if there was evidence of a weak instrument set (using the Stock and Yogo procedure [50]); and finally if there was evidence of model misspecification (using the Pesaran-Taylor reset test [51]). These tests were conducted in a frequentist setting as, to our knowledge, these have not yet been developed in the Bayesian framework. The instrument(s) selected were then used in inferences undertaken in a Bayesian framework.

**Extended modelling approach to more explicitly consider the ‘hard to heal’ subpopulation**

In this section we broadened the analyses to ignore the imputation and instead model the cohort data in two parts: the first part describing the probability of healing within follow-up and the second describing the expected time to healing for those that healed. This allows a more detailed characterisation of the ‘hard-to-heal’ population (patients that did not heal within follow-up, i.e. censored). Also, the use of linear regression can be considered more appropriate the data on time to healing for those that healed shows less pronounced skewness.

A two-step procedure was implemented where (1) a logistic regression was used to evaluate the expected probability of healing within the follow-up, , and (2) a linear regression estimated the expected time to healing for the population that healed within follow-up, – omitting from this second step of the analyses those patients that have been censored. The main advantage of this strategy is that it allows the determinants of the probability of healing to differ from determinants of time to healing (conditional on having healed in the short term). We have implemented adjustment on observables first (analogous to that described earlier), and an adjustment on unobservables using IV regression. The implementation of the IV regression is more complex as a treatment effect is included in each equation and thus IVs are required for both. Also, to our knowledge, tests for instruments have not been developed within two-part models and thus we used the exploratory analyses with the complete dataset to select the instrument(s) to be used throughout.

Within the IV regression the predicted values for treatment allocation, , here probabilities, are used in the two regressions identified above. The following equation algebraically describes the implemented model:

|  |  |  |
| --- | --- | --- |
| (stage 1) |  | Equation 11 |
|  |
| (stage 2A) |  |
|  |
| (stage 2B) |  |
|  |
| for i=1,…,N, *z* the instrument(s) and *x* and *v* constitute the design matrix. | |

Previously, we directly obtained a time to healing estimate for each treatment to inform the cost-effectiveness analysis. Within the current modelling approach, time to healing estimates for each treatment, k, were obtained through:

|  |  |
| --- | --- |
| where is the predicted probability of healing within follow-up (from the logistic regression in the first step model), is a the expected time to healing for censored observations, and the conditional time to healing in the subpopulation that healed within follow-up (from the linear regression in stage 2B). | Equation 12 |

The difference in time to healing evaluated for each treatment, i.e. NPWT and no NPWT, was used as input to Equation 1. The costs were analogously calculated and used as inputs to Equation 2-4.

Expert opinion on the expected time to healing for censored observations, the ‘hard to heal’ subpopulation, was sought for and used to evaluate cost-effectiveness. The beliefs of the three health professionals involved in the project were elicited on the additional time to 50% and 90% of patients healed (50th and 90% percentile) -- the wording of the questions are reproduced in Appendix 5 – Supplementary material. We derived the parameters of a Gamma distribution (*a* and *b*) from the elicited quantities from each expert and formally pooled the natural logarithm of the Gamma parameter values using a standard multivariate Normal formulation, described below:

|  |  |
| --- | --- |
| for i=1,…,3. is a 2x1 vector and each element was assigned a Normal uninformative prior; *a* and *b* are, respectively, the shape and scale parameters of the Gamma distribution. is the 2x2 covariance matrix to which a Wishart prior was assigned with the degrees of freedom as small as possible (i.e. 2, the rank of *V*) and a scale matrix reflecting some assessment of the order of magnitude of the covariance matrix. | Equation 13 |

**Results**

**Modelling of HRQoL weights and costs**

There were 1484 observations of the EQ-5D index score over all time points and 1166 observations of disease related costs over time (614 of which had a zero value of costs, 53.7%). A descriptive summary of results is shown in Appendix 2, Table A2.2, Supplementary material. The formal modelling of the EQ5D index score (Table 1) show the effect of healing is small (an increase of 0.055 in the index score for those who healed compared with those who did not) but statistically significant (credible interval does not include zero). The modelling of costs evaluated the effect of healing on the probability of patients incurring a non-zero cost and on the mean costs incurred (Table 1). Results show that, overall, expected costs for unhealed and healed patients were, respectively, £1124.4 and £258.9 per quarter – a difference of £865 being in this way attributed to healing (the standard error over the difference was £111.9). Further details can be found in Appendix 2, Tables A2.3 and A2.4, Supplementary material.

Table 1: EQ5D index score and disease-related costs (regression analysis)

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
| Model |  | Mean , £ | 95% CrI | |
| Expected EQ5D unhealed | | 0.091 | 0.036 | 0.146 |
| Expected EQ5D healed | | 0.091+0.055  = 0.146 | 0.098 | 0.193 |
| Difference in EQ5D attributed to healing | | 0.055 | 0.015 | 0.094 |
| Expected costs unhealed | | 1124.45 | 916.9 | 1359.1 |
| Expected costs healed | | 258.91 | 208.1 | 317.7 |
| Difference in costs attributed to healing | | 865 | 674.2 | 1126.5 |

The estimated patient-time on NPWT at any stage was 36.9 days on average (SE = 6.0). The average per patient cost of NPWT treatment is thus evaluated at £1,180.0 (SE = £189.2).

**Effectiveness**

**Using the complete dataset**

Concerning the identification of the determinants of treatment allocation in the cohort, results showed that wounds were more likely to be treated with NPWT if the wound was larger, if there was more tissue involvement and if the patient was an inpatient (results not shown here). Concerning the determinants of healing, the following were associated with healing within at least one treatment group: wound history (‘Yes’ *vs*. ‘No’ to having had a SWHSI before) and treatment location (inpatient vs. outpatient). Of these, when included as an interaction term with NPWT in the full dataset, the only treatment effect modifier identified was wound history.

Table 2 summarises effectiveness results of modelling complete time to healing data after imputation: model 0 is unadjusted (presented for completeness), model 1 adjusts for observables but excludes the interaction term, and model 2 also includes the interaction term as a treatment-effect modifier (“wound history”). The results show that, after adjustment, patients using NPWT are still expected to take longer to heal than those that do not use NPWT – on average 73.2 days longer (model 1). This result is statistically significant as the credible interval does not include the value of zero. The addition of the interaction term between treatment and history (model 2) shows that NPWT is expected to increase time to healing compared with the use of dressings alone. However the magnitude of this effect differs: patients with a history of SWHSI were estimated to take 181 days longer to heal with NPWT than with dressings, whereas patients without a history of SWHSI healed in an additional 42 days with NPWT.

Regarding the instrumental variable approach, previous treatment used by the treating health professional was the variable that performed best as an instrument according to the statistical frequentist tests (results not shown here, Appendix 4 – Supplementary material). Modelling results on time to healing using this instrument showed that the expected time to healing of patients using NPWT was still higher than non-NPWT patients – Table 2, model 3 and 4. Results obtained were thus broadly consistent with those for models 1 and 2.

Table 2: Effectiveness results. Complete dataset.

|  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- |
| Model ID | model 0 | model 1 | model 2 | model 3 | model 4 |
| Instrument used, *z*: | none | none | none | previous treatment | previous treatment with interaction |
| Equation: | TTH | TTH | TTH | (stage 2)  TTH | (stage 2)  TTH |
| Adjustment covariates: | none | observables | observables + interaction | observables | observables + interaction |
| Area (>25cm2), *x1* |  | 18.0 | 21.1 | 23.8 | 36.2 |
|  | [-23.1, 58.0] | [-20.3, 62.1] | [29.8, 43.7] | [-23.7, 56.3] |
| Treatment location, *x2* |  | 45.3 | 43.8 | 48.9 | 55.3 |
|  | [11.3, 79.2] | [9.9, 76.8] | [3.0, 63.8] | [10.8, 70.8] |
| Tissue involvement, *x3* |  | 31.9 | 26.6 | 33.8 | 37.2 |
|  | [-1.5, 65.0] | [-5.3, 58.7] | [-8.0, 73.1 | [-2.0, 50.6] |
| History, *w* |  | 7.5 | -29.3 | 7.2 | -10.3 |
|  | [-28.4, 42.9] | [-71.5, 12.1] | [-29.5, 44.6] | [-61.4, 7.4] |
| NPWT, *t* | 108.0 | 73.2 | 41.9 | 56.9 | 9.1 |
| [73.6, 142.2] | [33.8, 112.8] | [-1.1, 84.1] | [-71.7, 192.8] | [-120.2, 55.9] |
| NPWT x History, *w.t* | -- | -- | 138.7 | -- | 69.4 |
| -- | -- | [56.9, 221.8] | -- | [-67.5, 118.0] |
| Constant | 116.8 | 81.4 | 92.7 | 81.1 | 86.7 |
| [97.9, 135.2] | [53.3, 110.0] | [64.5, 120.8] | [52.3, 109.1] | [56.7, 97.0] |
| Observations | 393 | 372 | 372 | 372 | 372 |

Imputation using minimum date of healing ; TTH = Time to healing

+ Tissue involvement, skin and subcutaneous tissue loss (*vs* skin loss)

++ Treatment location: inpatient (*vs* outpatient)

**Extended analysis**

The determinants of the probability of healing (stage 2A, Equation 11) identified were BMI and wound location. For time to wound healing, determinants identified were surgery type (colorectal *vs*. other surgeries), wound duration and diabetic foot wounds (stage 2B, Equation 11). No evidence of relevant interaction terms was found.

The extended model predicted NPWT was associated with poorer healing outcomes (46 expected additional days to wound healing compared to the non-NPWT patients, among healed patients), using previous treatment used by the health professional as the instrument, Table 3 model b1.

Table 3: Time to healing. Extended modelling approach.

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
| Model ID | model b0 | | model b1 | |
| Equation | (stage 2A)  P[heal] (OR) | (stage 2B)  TTH | (stage 2A)  P[heal] (OR) | (stage 2B) TTH |
| Type of regression model | Logit | OLS | IV, Logit | IV, OLS |
| Adjustment | none | none | adjustment set | adjustment set |
| Area (>25cm2), *x1* | -- | -- | 0.52 | 27.7 |
| -- | -- | [0.24, 0.99] | [0.6, 54.5] |
| Treatment location+, *x2* | -- | -- | 0.52 | 30.9 |
| -- | -- | [0.22, 1.04] | [9.2, 52.3] |
| Tissue involvement++, *x3* | -- | -- | 0.50 | 11.4 |
| -- | -- | [0.25, 0.91] | [-8.1, 30.9] |
| BMI, *v1* | -- | -- | 1.04 | -- |
| -- | -- | [1.00, 1.09] | -- |
| Location – foot, *v2* | -- | -- | 0.34 | 30.1 |
| -- | -- | [0.16, 0.64] | [9.2, 52.3] |
| Surgery type, *v3* | -- | -- | -- | 13.1 |
| -- | -- | -- | [-6.1, 32.4] |
| SWHSI duration, *v4* | -- | -- | -- | 2.3 |
| -- | -- | -- | [0.6, 4.0] |
| Diabetic feet, *v5* |  |  |  | 42.8 |
|  |  |  | [9.1, 76.3] |
| NPWT, *t* | 0.35 | 69.0 | 0.59 | 46.0 |
| [0.20, 0.57] | [48.2, 89.1] | [0.28, 1.12] | [19.6, 72.5] |
| Constant, γ*1* | 6.56 | 82.0 | 6.98 | 36.9 |
| [4.70, 9.37] | [71.9, 92.1] | [1.62, 29.55] | [12.4, 61. 3] |
| Observations | 393 | | 354 | |

OR = Odds ratio; TTH = time to healing;

+ Treatment location: inpatient (vs outpatient);

++ Tissue involvement, skin and subcutaneous tissue loss (vs skin loss)

**Cost effectiveness**

The results on healing, utilities and costs were combined to generate cost-effectiveness estimates for NPWT. For the extended analysis, evidence relating to the additional days until healing after censoring for unhealed patients within the follow-up period was elicited from three experts. The results are shown in Table 4. The responses highlight that experts believe that up to 10% of these ‘hard to heal’ patients may be unhealed two to ten years after having exiting the cohort study. When formally pooling the three experts’ judgements, the parameter values for the Gamma distribution implied a mean additional time to healing of 1038.5 days (based on the median of the simulations). Such a formal pooling approach reflects (between expert) uncertainty over the mean, which, due to the limited sample, is very significant here. Given mortality has not been considered in the modelling, and to reflect the fact that patients may die before healing, we replaced time to healing by life expectancy in patients predicted to heal after their life expectancy. Considering the gender split in our sample (56.4% were male), the life expectancy for the sample is 83.9 years of age [52].

Table 4: Elicited evidence on additional time to healing from follow-up for censored patients

|  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- |
|  | Elicited | | Fitted values for parameters of a Gamma distribution | | | | |
|  | 50th percentile, days | 90th percentile, days | Shape,  1st and 3rd quartiles | Scale,  1st and 3rd quartiles | Mean, days  1st and 3rd quartiles | 50th percentile, days  1st and 3rd quartiles | 90th percentile, days  1st and 3rd quartiles |
| Expert 1 | 1044 | 3234 | 1.12 | 1290 | 1445 | 1031 | 3322 |
| Expert 2 | 496 | 679 | 15.3 | 33.1 | 506 | 495 | 683 |
| Expert 3 | 180 | 3650 | 0.23 | 5222 | 1201 | 176 | 3176 |
| Pooled using formal synthesis (95% CrI) |  |  | 1.79  (0.03, 54.5) | 615  (241, 1615) | 1038  (29, 39065) | 559  (0, 28011) | 1820  (15, 37161) |

Cost effectiveness results for the complete dataset analysis (Table 5) suggest, with little uncertainty that NPWT is not clinically or cost effective for the healing of open surgical wounds.

Table 5: Cost effectiveness results.

|  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- |
|  | Complete dataset | | | | | | Extended analysis |
|  | model 1 | model 2 | | model 3 | model 4 | | model b2 |
|  |  | w history | w/o history |  | w history | w/o history |  |
| Inc. QALYs | -0.012 [0.005] | -0.029 [0.012] | -0.007 [0.004] | -0.008 [0.011] | -0.013 [0.017] | -0.001 [0.011] | -0.027 [0.017] |
| Inc. costs | 1,979  [316] | 3,573  [534] | 1,592  [330] | 1,749.4 [809.8] | 2,144.8 [1,210.8] | 1,187.0 [844.9] | 3,116.1 [1025.9] |
| ICER | Dominated | Dominated | Dominated | Dominated | Dominated | Dominated | Dominated |
| Prob. CE[£20k]\* | 0 | 0 | 0 | 0.026 | 0.053 | 0123 | 0.002 |
| Prob. CE[£30k]\* | 0 | 0 | 0 | 0.032 | 0.060 | 0.144 | 0.003 |

\* Probability that NPWT is cost-effective at £20,000/QALY and £30,000/QALY, respectively;

Standard errors in brackets.

The extended analyses indicated that for average patient characteristics (BMI = 29, diabetes = 26%, cardiovascular or peripheral disease = 43%, smoker = 29%, wound area bigger than 25cm2 = 24%, emergency surgery = 64%, location other than abdomen = 66%, open wound planned = 41%, history of SWHSI = 25%) treatment with NPWT would require an average of 251 days to heal, while without NPWT 137 days, on average, would be required (Equation 12). Cost-effectiveness results, based on analysis of observational data, suggest that, with little uncertainty that NPWT does not compare favourably with wound dressings. (Table 5 - model b2).

**Discussion**

Recent policy developments, in the UK and elsewhere, are increasingly establishing the use of observational data to support decisions about the use of health care technologies, particularly where significant clinical uncertainties remain. This paper uses an applied example relating to the clinical and cost-effectiveness of NPWT in the healing of SWHSI using data from an observational cohort study. In exploring different ways of adjusting for confounding in observational studies, we implemented adjustment for observables (using regression) and unobservables (using instrumental variable regression). The different modelling approaches produced similar results, all suggesting that NPWT is neither an effective or cost-effective technology compared to standard dressings. The IV approach reduced the mean additional days to heal for NPWT patients compared with other treatments from 112 [95%CI, (94,141)] (unadjusted estimate) to 57 days with a wide credibility interval [95%CrI, (-72,193)], potentially better reflecting the existing uncertainty surrounding the effectiveness of NPWT. Any remaining existing confounding should be considered a source of decision uncertainty.

Our application identified many challenges to the analysis of observational data that have not been hitherto considered in guidance. A first challenge for analyses relates to core definitions, such as of outcomes affected by treatment or the definition of treatments themselves. In terms of outcomes, our analyses focused on time to wound healing, the outcome that is considered clinically most relevant [28]. However, treatment may also affect other outcomes: it may reduce the rate of wound infection or facilitate wound management. In this sense, it is important to acknowledge that failing to identify the outcomes of treatment can misinform recommendations. In what concerns the definition of the treatments, given the limited sample size our study pooled patients that received NPWT at baseline and patients that received NPWT at a later stage. It may be argued, however, that patients receiving NPWT at inception can differ (and have a different prognosis) from those that received NPWT during follow-up. There may also be a potential bias from the presence of time-dependent confounding, as patients who start NPWT after baseline are likely to have been switched to NPWT as a result of previous treatment failure. In addition, we have merged the different dressings used within the cohort into a single comparator (the ‘non-NPWT’ group). This intervention ‘lumping’ may be a source of further heterogeneity. All analyses of observational data are likely to have to make similar decisions on practical grounds. Within observational datasets, heterogeneity is expected to be more pronounced than in RCTs that define clear inclusion and exclusion criteria, determine the intervention and how it is applied and often determine follow-up and follow on care. In our application, heterogeneity in the patients recruited was extensive for example, in what concerns the location of the wound, the surgery that led to the wound, its size at baseline, and the setting of care. However, the small sample size (n=393) was insufficient to explore the consequences of existing heterogeneity, i.e. explore the implications of treatment within potentially relevant subgroups of the population (such as open abdominal wounds vs. diabetic foot and leg wounds).

A second aspect relates to the potential for the dataset to show a lack of overlap, where regions of the covariate space with relatively few treated or control units. If there is selection into treatment, lack of overlap (to a bigger or lesser extent) is expected. Inferences made for such regions rely on extrapolation [53], with results being more dependent on model specification and less on direct support from the data [54]. This is relevant for any form of adjustment, whether just on observed characteristics and/or on unobserved through IV regression. While some overlap is required to allow meaningful analyses [14], there is no clear guidance on how to establish when overlap is a significant problem. Further research is needed to understand how alternative methods (e.g. regression adjustment, matching or inverse probability weighting) could capitalise on the underlying overlap issue [54]. Our application highlighted that, in practice, it may even be difficult to identify the sources of lack of overlap, especially when no single covariate arises as meaningful.

A third aspect relates to the adjustment on observables. The fact that health outcomes and its determinants were not known *a priori* in our study, and that the mechanism for selection was also not known, meant that it was difficult to identify the appropriate adjustment set. We opted for a thorough and protocol driven variable selection process that we developed within this study and that can be generalised and used in any other application. In terms of methods, we adopted a regression adjustment approach to facilitate the further application of the instrumental variable method to address unobserved confounding. Whilst there is a range of alternative methods, such as matching approaches, their relative performance is as yet unclear [14, 24], particularly with small sample sizes and poor overlap.

Another set of challenges relates to the application of instrumental variable techniques to control for unobserved confounding. Such methods depend on finding good and reliable, but difficult to validate, sources of exogenous variation (instruments) [14]. More research is needed in defining instruments relevant in the context of HTA, and on extending analyses to outcomes such as time to event data.

Also, in our study we used a Bayesian context for inferences, which we believe has clear advantages. It allows for flexibility in specifying the model according to what is believed to be plausible without being limited to linearity or normality assumptions. Although in this work we used linearity and normality to describe time to healing, an important extension to future work is to use time to event distributions and explore potential non-linearity. Another important advantage is where the sample is small or the instruments weakly related to treatment assignment, in which case Bayesian methods are thought to return more accurate estimates of causal effects [55]. This is crucial, as in this area of research it is likely that sample size is limited. However, Bayesian research on IV models is limited and recent, relative to the broad literature from the classical (i.e. frequentist) statistical perspective.

Our study data suggest, with little uncertainty that NPWT is not clinically or cost effective for the healing of open surgical wounds.  However, because this conclusion is based solely on observational research, where there is still the potential for unresolved confounding to affect the results, even following extensive adjustment, confidence in the conclusion may not be strong. This lack of confidence may lead decision makers and funders to justify calls for definitive evidence from an RCT.

This is increasingly relevant as analyses based on observational data are used more widely to inform system level decisions, such as those required within the CDF [57]. Future methodological research is also needed to help guide the many practical challenges faced and improve confidence in the results of such analyses.

**List of abbreviations**

|  |  |
| --- | --- |
| Abbreviation | Description |
| BMI | Body Mass Index |
| CDF | Cancer Drugs Fund |
| CE | Cost-Effectiveness |
| CrI | Credible Interval |
| DIC | Deviance Information Criterion |
| DSU | Decision Support Unit |
| EQ-5D | EuroQol 5-Dimensions |
| GP | General Practitioner |
| HRQoL | Health-Related-Quality-of-Life |
| HTA | Health Technology Assessment |
| IV | Instrumental Variables |
| MCMC | Monte Carlo Markov Chain |
| NHS | National Health System |
| NICE | National Institute for Health and Care Excellence |
| NIHR | National Institute for Health Research |
| NPWT | Negative Pressure Wound Therapy |
| OLS | Ordinary Least Squares |
| OR | Odds Ratio |
| PSSRU | Personal Social Services Research Unit |
| QALY | Quality Adjusted Life Years |
| RCT | Randomised Controlled Trial |
| SD | Standard Deviation |
| SEER | Surveillance, Epidemiology and End Results |
| SWHSI | Surgical Wounds Healing by Secondary Intention |
| TTH | Time To Healing |
| UK | United Kingdom |

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**Supplementary Data**

Appendix 1 Table A1.1: Summary characteristics of patients using NPWT

|  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- |
|  | All  (N= 393) | Received NPWT  (N= 115) | | Did not receive NPWT  (N=278) | |
|  | value | N | value | N | value |
| Patient characteristics at baseline |  |  |  |  |  |
| Age – years - mean (SD) | 54.1 (18.1) | 115 | 57.8 (16.4) | 278 | 52.53 (18.6) |
| Body Mass Index– mean (SD) | 28.9 (6.6) | 115 | 30.0 (6.3) | 278 | 28.4 (7.1) |
| Gender – male – n (%) | 222 (56.4%) | 115 | 68 (59.1%) | 278 | 154 (55.4%) |
| Tobacco use – smoker - n (%) | 112 (28.5%) | 115 | 28 (24.3%) | 278 | 84 (30.2%) |
| Characteristics of the surgery |  |  |  |  |  |
| Type – colorectal (*vs* others) - n (%) | 156 (39.7%) | 115 | 32 (27.8%) | 278 | 124 (44.6%) |
| Emergency (*vs* elective) - n (%) | 236 (60.1%) | 112 | 70 (62.5%) | 259 | 166 (64.1%) |
| Cleanliness – dirty (*vs* clean and clean/contaminated) - n (%) | 247 (62.8%) | 113 | 68 (60.2%) | 276 | 179 (64.4%) |
| Characteristics of the wound |  |  |  |  |  |
| Number – mean (SD) | 1.13 (0.5) | 115 | 1.2 (0.6) | 278 | 1.1 (0.4) |
| History – n (%) | 93 (23.4%) | 106 | 24 (22.6%) | 270 | 69 (25.6%) |
| Area – >25cm2 – n (%) | 93 (23.4%) | 115 | 61 (53.0%) | 276 | 32 (11.6%) |
| Type – dehisced (*vs* planned) - n (%) | 157 (40.0%) | 115 | 50 (43.5%) | 278 | 107 (38.5%) |
| Tissue involvement – skin and subcutaneous tissue loss (*vs* skin loss) - n (%) | 162 (41.2%) | 115 | 73 (63.5%) | 278 | 89 (32.0%) |
| Location – foot (*vs* other locations) - n (%) | 59 (15.0%) | 103 | 29 (28.2%) | 255 | 30 (11.8%) |
| Location – abdomen (*vs* other locations) - n (%) | 132 (33.6%) | 103 | 36 (35.0%) | 255 | 96 (37.6%) |
| Duration at baseline – days - mean (SD) | 7.9 (5.9) | 115 | 7.9 (5.7) | 278 | 7.9 (6.0) |
| Infection at baseline – n (%) | 79 (20.1%) | 115 | 30 (26.1%) | 278 | 49 (17.6%) |
| Exudate level – low (*vs* medium/high) - n (%) | 217 (55.2%) | 112 | 74 (66.1%) | 267 | 143 (53.6%) |
| Health carer and provision of care |  |  |  |  |  |
| Treatment location – inpatient (*vs* outpatient - n (%) | 226 (57.5%) | 115 | 98 (85.2%) | 278 | 128 (46.0%) |
| Role of health professional – doctor (*vs* nurse) - n (%) | 253 (64.4%) | 115 | 100 (87.0%) | 274 | 153 (55.8%) |
| Other treatments (used by at least 10% of participants at any point) |  |  |  |  |  |
| Hydrofibre - n (%) | 258 (65.6%) | 115 | 66 (57%) | 278 | 192 (69%) |
| Basic wound contact dressing - n (%) | 214 (54.4%) | 115 | 60 (52%) | 278 | 154 (55%) |
| Foam - n (%) | 111 (28.2%) | 115 | 39 (34%) | 278 | 72 (26%) |
| Alginate dressing - n (%) | 49 (12.5%) | 115 | 19 (16.5%) | 278 | 30 (11%) |
| EQ-5D at baseline - mean (SD) | 0.425 (0.45) | 114 | 0.304 (0.49) | 269 | 0.476 (0.427) |

Table A1.2: Summary characteristics of patients according to patients healing status

|  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- |
|  | All  (N= 393) | Healed patient  (N= 320) | | Unhealed patient  (N=73) | |
|  | value | N | value | N | value |
| Patient characteristics at baseline |  |  |  |  |  |
| Age – years - mean (SD) | 54.1 (18.1) | 320 | 54.0 (18.0) | 73 | 54.4 (18.7) |
| Body Mass Index– mean (SD) | 28.9 (6.6) | 320 | 29.1 (6.5) | 73 | 28.0 (7.1) |
| Gender – male – n (%) | 222 (56.4%) | 320 | 177 (55.3%) | 73 | 45 (61.6%) |
| Tobacco use – smoker - n (%) | 112 (28.5%) | 320 | 88 (27.5%) | 73 | 24 (32.9%) |
| Diabetes - n (%) | 103 (26.2%) | 320 | 70 (21.9%) | 73 | 33 (45.2%) |
| Characteristics of the surgery |  |  |  |  |  |
| Type – colorectal (*vs* others) - n (%) | 156 (39.7%) | 320 | 142 (44.4%) | 73 | 14 (19.2%) |
| Emergency (*vs* elective) - n (%) | 236 (60.1%) | 300 | 191 (63.7%) | 71 | 45 (63.4%) |
| Cleanliness – dirty (*vs* clean and clean/contaminated) - n (%) | 247 (62.8%) | 318 | 197 (61.9%) | 71 | 50 (70.4%) |
| Characteristics of the wound |  |  |  |  |  |
| Number – mean (SD) | 1.13 (0.5) | 320 | 1.1 (0.5) | 73 | 1.2 (0.6) |
| History – n (%) | 93 (23.4%) | 307 | 78 (25.4%) | 69 | 15 (21.7%) |
| Area – >25cm2 – n (%) | 93 (23.4%) | 319 | 62 (19.4%) | 72 | 31 (43.1%) |
| Type – dehisced (*vs* planned) - n (%) | 157 (40.0%) | 320 | 141 (44.1%) | 73 | 16 (21.9%) |
| Tissue involvement – skin and subcutaneous tissue loss (*vs* skin loss) - n (%) | 162 (41.2%) | 320 | 118 (36.9%) | 73 | 44 (60.3%) |
| Location – foot (*vs* other locations) - n (%) | 59 (15.0%) | 291 | 34 (11.7%) | 67 | 25 (37.3%) |
| Location – abdomen (*vs* other locations) - n (%) | 132 (33.6%) | 291 | 122 (41.9%) | 67 | 10 (14.9%) |
| Duration at baseline – days - mean (SD) | 7.9 (5.9) | 320 | 8.1 (5.8) | 73 | 6.8 (6.2) |
| Infection at baseline – n (%) | 79 (20.1%) | 320 | 60 (19.7%) | 73 | 19 (26.8%) |
| Exudate level – low (*vs* medium/high) - n (%) | 217 (55.2%) | 309 | 175 (56.6%) | 70 | 42 (60.0%) |
| Health carer and provision of care |  |  |  |  |  |
| Treatment location – inpatient (*vs* outpatient - n (%) | 226 (57.5%) | 320 | 166 (52.2%) | 73 | 60 (82.2%) |
| Role of health professional – doctor (*vs* nurse) - n (%) | 253 (64.4%) | 319 | 196 (61.4%) | 70 | 57 (81.4%) |
| Other treatments (used by at least 10% of participants at any point) |  |  |  |  |  |
| Hydrofibre - n (%) | 258 (65.6%) | 320 | 217 (67.8%) | 73 | 41 (56.2%) |
| Basic wound contact dressing - n (%) | 214 (54.4%) | 320 | 174 (54.4%) | 73 | 40 (54.8%) |
| Foam - n (%) | 111 (28.2%) | 320 | 94 (29.4%) | 73 | 17 (23.3%) |
| Alginate dressing - n (%) | 49 (12.5%) | 320 | 35 (11.9%) | 73 | 14 (19.2%) |
| EQ-5D at baseline - mean (SD) | 0.425 (0.45) | 311 | 0.446 (0.44) | 72 | 0.335 (0.51) |

Appendix 2. Unit costs considered and results of the modelling of HRQoL weights and costs

Table A2.1: Unit costs for health service consultations

|  |  |  |
| --- | --- | --- |
| Parameter description | Value | Source |
| *Health service consultations* |  |  |
| GP visit |  |  |
| GP appointment at doctor's surgery | £42.0 | PSSRU 2014 (86) (assumed 11.7min per appointment) |
| GP appointment at home | £62.0 | as above (assumed 17.2min per appointment) |
| Nurse visit |  |  |
| Nurse appointment at doctor's surgery (practice nurse appointment) | £11.4 | PSSRU 2014 (86) (assumed 15.5min per appointment) |
| Nurse appointment at home (district nurse visit) | £19.0 | as above (assumed 20 minutes per appointment) |
| Outpatient visit |  |  |
| Doctor appointment in a hospital outpatient clinic | £111.0 | NHS Reference Costs 2013-14 (87). Figures seem to be average outpatient visit. The corresponding cost from PSSRU 2014 is £109 |
| Nurse appointment in a hospital outpatient clinic | £111.0 | As above |
| Hospital admission (daily costs) |  |  |
| Without overnight stay (day case) | £698 | NHS Reference Costs 2013-14 (87) |
| With overnight stay | £362.7 | NHS Trust Leicester 2011-12 (88) private patient tariff (updated to 2014 prices) |
| *Daily unit costs for treatments* |  |  |
| NPWT average daily cost | £31.78  (SE=0.55) | KCI £15/daily + 3 Medium KCI Granufoam + 1 Activac 300ml Canister |
| Average daily cost for dressings | £2.39  (SE=0.11) | based on the breakdown of dressings used in the cohort study and the average price of advanced dressings |

Table A2.2: EQ-5D index score and disease-related costs (descriptive analysis)

|  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- |
|  | EQ-5D index score | | | | Disease-related costs | | | |
| Months | N | Mean (SD) |  | prop < 0 \* | N | Mean (SD), £ |  | prop =0 \*\* |
| 0 | 383 | 0.425 (0.455) |  | 0.19 | 391 | 722 (1746) |  | 0.22 |
| 3 | 258 | 0.554 (0.427) |  | 0.15 | 274 | 1344 (3240) |  | 0.13 |
| 6 | 219 | 0.591 (0.425) |  | 0.16 | 234 | 525 (1111) |  | 0.51 |
| 9 | 208 | 0.594 (0.426) |  | 0.15 | 225 | 380 (1023) |  | 0.62 |
| 12 | 185 | 0.606 (0.413) |  | 0.12 | 194 | 200 (531) |  | 0.72 |
| 15 | 149 | 0.633 (0.416) |  | 0.14 | 154 | 157 (518) |  | 0.74 |
| 18 | 78 | 0.589 (0.443) |  | 0.15 | 80 | 645 (4831) |  | 0.79 |

\* Proportion of patients with an EQ-5D index score lower than 0 (health states worse than death); \*\* Proportion of patients zero costs

Table 2.3: EQ-5D index score (regression analysis)

|  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- |
| Model | Description | Parameter, description | | Mean  (SE) | 95% CrI | |
| change in EQ-5D from baseline \*\* | Mixed model with random intercept |  | Mean change from baseline | 0.091  (0.028) | 0.036 | 0.146 |
|  | Effect of healing | 0.055  (0.020) | 0.015 | 0.094 |
|  | Within patient variation in change scores | 0.401  (0.017) | 0.368 | 0.436 |
|  | Between patient variation in change scores | 0.174  (0.004) | 0.165 | 0.183 |

\*\* number of individuals 311, number of total observations 1097; 1 chains, each with 100,000 iterations (first 50,000 discarded); n.sims = 50,000 iterations saved; pD = 291.1 and DIC = -438.7

Table 2.4: Disease-related costs (regression analysis)

|  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- |
| Model | Description | Parameter, description | | Mean , £ | 95% CrI | |
| Part 1  Probability of non-zero costs \* | Mixed model with random intercept , Logistic regression |  | Effect of healing, odds ratio | -2.297 | -2.785 | -1.854 |
|  | Odds while unhealed | 1.719 | 1.316 | 2.166 |
|  | Within patient variation in odds of a non-zero cost | 1.221 | 0.950 | 1.521 |
| Part 2  Non-zero costs \*\* | Mixed model with random intercept, Gamma with log link |  | Effect of healing (log) | -0.615 | -0.837 | -0.388 |
|  | Costs while unhealed (log) | 7.190 | 7.006 | 7.367 |
|  | Within patient variation in the costs (log) | 0.656 | 0.530 | 0.791 |
| *alpha* | Shape parameter of the Gamma distribution | 0.985 | 0.866 | 1.108 |
| Estimates from two part model | |  |  |  |  |  |
| Probability of non-zero costs (unhealed) | | *p* |  | 0.846 | 0.789 | 0.897 |
| Probability of non-zero costs (healed) | | *p.heal* |  | 0.360 | 0.310 | 0.411 |
| Expected costs unhealed | |  |  | 1124.45 | 916.9 | 1359.1 |
| Expected costs healed | |  |  | 258.91 | 208.1 | 317.7 |
| Difference attributed to healing | |  |  | 865 | 674.2 | 1126.5 |

\* number of individuals 315, number of total observations 1166, DIC 1356, 2 chains, each with 150,000 iterations (first 100,000 discarded), n.thin = 10; n.sims = 5,000 iterations saved.

\*\* number of individuals 268, number of total observations 552, DIC 8763, 2 chains, each with 150,000 iterations (first 100,000 discarded), n.thin = 10; n.sims = 5,000 iterations saved.

Appendix 3. Details on the survey to health professionals

The survey was designed to obtain instruments from the health professionals who recruited into the cohort study. It was piloted with 4 health professionals belonging to the SWHSI project research team.

Survey:

*We are contacting you because you are listed has having delivered care to a participant in our open surgical wounds study (http://www.york.ac.uk/healthsciences/swhsi/wk1/). The study has progressed well, recruiting nearly 400 people with surgical wounds healing by secondary intention. All study data has been collected and analyses are underway.*

*To complement the cohort data we would like to ask you a few questions about your experience and use (or non-use) of negative pressure wound therapy as a treatment for surgical wounds healing by secondary intention (SWHSI). We don’t expect this survey to take more than 10 minutes to complete.*

*Information is not being collected to reflect on individual practices – rather we want to explore the possible effectiveness of negative pressure wound therapy using the cohort data. We are undertaking very cautious analysis as we have observational rather than randomised data: your responses will help us explore statistical approaches that aim to reduce the risk of making biased estimates from non-randomised data*

*The questions below are by necessity broad. When you complete them please try and think of a future patient in your clinical practice with a surgical wound healing by secondary intention (SWHSI).*

*The definition of a SWHSI we want you to consider is: a wound resulting from surgery which is healing by secondary intention i.e. an open surgical wound healing from the bottom up via the formation of granulation tissue and where the open wound requires treatment.*

*This definition includes: (1) wounds that have been left open following surgery (i.e. due to contamination, swelling or infection or because there is an empty space below the wound); (2) wounds that may have been originally closed by sutures, clips etc. following surgery but are now partially or completely split open/have broken down/are dehisced; (3) open wounds resulting from surgical or sharp debridement even if, prior to surgery, these were nonsurgical in origin i.e. surgical debridement of a grade III/IV pressure ulcer, sharp debridement of a foot wound.*

*We understand that not all SWHSI you see will be eligible for treatment with negative pressure wound therapy; however, we would like you to think about those wounds where the treatment might clinically be an option.*

*1. Before you start answering the survey, please record your professional role*

*a) Foundation Year 1 & 2 hospital-based doctor*

*b) Hospital-based surgeon*

*c) Hospital-based physician*

*d) GP*

*e) Ward Nurse*

*f) TVN*

*g) Practice Nurse*

*h) District Nurse*

*i) Other (please specify)*

*2. In general, I believe negative pressure wound therapy is a better treatment for managing eligible surgical wounds healing by secondary intention than other wound dressings.*

*a) Strongly agree*

*b) Agree*

*c) Neither agree or disagree*

*d) Disagree*

*e) Strongly disagree*

*f) Other (please specify)*

*3. Imagine you consult with a new patient who has a surgical wound healing by secondary intention:*

*How likely is it that you use negative pressure wound therapy at some point in the management of their wound?*

*i) Assuming CURRENT practices and procedures in your organisation around availability of negative pressure wound therapy*

*a) Extremely likely*

*b) Likely*

*c) As likely as using other wound dressings*

*d) Unlikely*

*e) Extremely unlikely*

*ii) Imagining you have unlimited access to negative pressure wound therapy*

*a) Extremely likely*

*b) Likely*

*c) As likely as using other wound dressings*

*d) Unlikely*

*e) Extremely unlikely*

*4. Please describe the types of surgical wounds healing by secondary intention that you would use negative pressure wound therapy on.*

*5. Are you responsible for deciding on the use of negative pressure wound therapy...*

*i) ...on a newly formed surgical wound healing by secondary intention?*

*a) Always*

*b) Often*

*c) Sometimes*

*d) Rarely*

*e) Never*

*ii) ...on a longstanding surgical wound healing by secondary intention*

*a) Always*

*b) Often*

*c) Sometimes*

*d) Rarely*

*e) Never*

*6. Would you like to use negative pressure wound therapy in patients with surgical wounds healing by secondary intention more than you do – but are unable to?*

*a) Yes*

*b) No*

*c) If yes, what factors may prevent negative pressure wound therapy use?*

*7. In your mind, how expensive is it to use negative pressure wound therapy to treat surgical wounds healing by secondary intention (in terms of cost per patient treated)?*

*a) Very expensive*

*b) Expensive*

*c) As expensive as other treatments, such as dressings*

*d) Cheap*

*e) Very cheap*

*8. In general, I believe that the use of negative pressure wound therapy represents good value for money for surgical wounds healing by secondary intention.*

*a) Strongly agree*

*b) Agree*

*c) Neither agree or disagree*

*d) Disagree*

*e) Strongly disagree*

*f) Don't know*

*9. In the last 12 months, approximately how many times have you met with a company representative to discuss the use of negative pressure wound therapy?*

Survey results:

Of the 393 patients in the cohort, 361 had been identified with a health professional that had been primarily responsible for treatment decisions regarding his/her SWHSI at baseline. There were 180 unique health professionals identified in this way.

*Response rate to survey*

* Of the 180 clinicians listed in the dataset, we obtained an email address for 121 (64%).
* In total, 51 responded (42% of the 121, 28% of the 180)

1. Before you start answering the survey, please record your professional role

|  |  |
| --- | --- |
| Foundation Year 1 & 2 hospital-based doctor | 0 |
| Hospital-based physician | 1 |
| Hospital-based surgeon | 35 |
| GP | 0 |
| Ward nurse | 0 |
| Practice Nurse | 1 |
| District Nurse | 10 |
| TVN | 4 |
| Other | 0 |
| Total | 51 |

2. In general, I believe negative pressure wound therapy is a better treatment for managing eligible surgical wounds healing by secondary intention than other wound dressings.

|  |  |
| --- | --- |
| Strongly disagree | 0 |
| Disagree\* | 1 |
| Neither agree or disagree | 10 |
| Agree | 30 |
| Strongly agree | 10 |
| Total | 51 |

\*Health professional adds the following: “Depends on every individual wound”

3. Imagine you consult with a new patient who has a surgical wound healing by secondary intention: how likely is it that you use negative pressure wound therapy at some point in the management of their wound?

a. Assuming CURRENT practices and procedures in your organisation around availability of negative pressure wound therapy

|  |  |
| --- | --- |
| Extremely unlikely | 1 |
| Unlikely | 8 |
| As likely as using other wound dressings | 18 |
| Likely | 16 |
| Extremely likely | 8 |
| Total | 51 |

b. Imagining you have unlimited access to negative pressure wound therapy

|  |  |
| --- | --- |
| Extremely unlikely | 1 |
| Unlikely | 4 |
| As likely as using other wound dressings | 14 |
| Likely | 16 |
| Extremely likely | 10 |
| Total | 44 |

4. Please describe the types of surgical wounds healing by secondary intention that you would use negative pressure wound therapy on.

|  |  |
| --- | --- |
| 1 | 1.Primary deep spine infection requiring surgical intervention without instrumentation; 2. secondary deep spine infection following spinal instrumentation |
| 2 | abdominal cavities, |
| 3 | Abdominal wounds |
| 4 | abdominal wounds and amputation of limbs |
| 5 | Any large wounds would benefit or any slow to heal wounds |
| 6 | Any wound with associated cavity and evidence of granulation. Typically diabetic foot, fasciotomy and groin wounds in my practice |
| 7 | As a rhinologist and anterior skull base surgeon it is difficult to apply dressings within the nasl cavity so I allow them to heal by secondary intention |
| 8 | Chest wounds and leg wounds |
| 9 | Clean granulating wounds with significant tissue loss especiacially if excessive exudate e.g. necessitating several usual dressing changes per day |
| 10 | de hissed wounds / surgical wounds |
| 11 | Deep cavities & laparostomies |
| 12 | Deep wounds healing by secondary intention particularly if infected |
| 13 | dehisced abdo and other surgical wounds diabetic and non diabeteic foot uclers post amputation pressure ulcers |
| 14 | Dehisced abdominal surgical wound Deabetic foot ulcers |
| 15 | Dehisced wound following major surgery - usually dehisces as a result of post op or pre op radiotherapy. |
| 16 | dehissed wounds extensive debridment large open wounds with excessive exudate |
| 17 | diabetic foot infection after surgical debridement where the wound is large and clean with good blood supply |
| 18 | diabetic foot wounds, dehist surgical wounds |
| 19 | dirty infective necrotic wounds and laparostomies |
| 20 | Fasciotomy wounds. Diabetic feet after surgery eg amputation of forefoot. Laparostomy after trauma |
| 21 | fasciotomy, Laparostomy, diabetic foot sepsis |
| 22 | Fasciotomy, ligation of femoral vessels after IV drug use induced mycotic aneurysm (on top of sartorius flap), open abdomen (laparostomy), traumatic wounds / tissue defects. |
| 23 | Generally contaminated wounds e.g. A superficial / occ full thickness laparotomy dehiscence for faecal peritonitis |
| 24 | I tend to use it for larger wounds. I have also used it as an interim measure for wound management after removal or infected hip prostheses |
| 25 | infected deep wounds |
| 26 | infection which can't be closed instead of old packing of wounds wounds with skin loss |
| 27 | laparotomy |
| 28 | large abdominal cavity wound, diabetic foot amputation or toe amputation,pressure ulcers |
| 29 | Large cavity wounds with flat surronding tissue to enable good dressing contact eg, chest wound, abdomen |
| 30 | LARGE CAVITY WOUNDS WITH HIGH EXUDATE LEVELS |
| 31 | large midline superficial dehiscence with substantial subcutaneous fat layer, open abdomen with good layer of granulation tissue over viscera |
| 32 | Large wounds where NPWT likely to sig reduce healing time. Wounds with significant exudate. |
| 33 | Large wounds; wounds with potential circulatory issues; significant leakage wounds; wounds associated with poor patient mobility |
| 34 | larger areas and wounds with excessive discharge |
| 35 | larger, undermined wounds, cavities with no fascial dehiscence, large exudative wounds, infected wounds, predominantly midline laparotomies, would consider in laparostomies where mesh has been placed |
| 36 | leg wounds, breast wounds |
| 37 | Midline laparotomy wounds Perineal wounds post APER |
| 38 | Moist, sloughy/purulent wounds. Those with surrounding oedema. |
| 39 | non infected wounds cavity wounds |
| 40 | Open Abdomens, Fasciotomy wounds, Transmetatarsal Amputations & toe amputations, Hip disarticulations, dehisced abdominal wounds, infected groin wounds and I&D groin wounds, fenestrations wounds post Pneumonectomy, lobectomy or chronic empyema. Also necrotising Fasciitis wounds, toe amputation, calcanectomy and diabetic foot ulcers debrided, gastroschisis and exomphalous on neonates, cat 3 and 4 pressure sores, incision and drainage wounds and removal of infected metalwork to spines, other bones in body and feet, arms & legs. Girdlestone and infected hip replacements. Also APER wounds where rectum and surrounding tissues excised, leaving large cavity. Bursitis, infected knee sinus / tract, infected mesh repairs where large seroma, mediastinitis and infected sternal wound dehiscences. Infected and dehisced I&D of Saphenous Vein Graft wounds. Breast wounds, where flap TRAM/VRAM flap dehiscence and debrided, seroma of breast after WLE and radiotherapy. |
| 41 | Open fracture Superficial wound infection with wound breakdown |
| 42 | post-operative, pressure ulcers, post debridement for infection |
| 43 | Pressure sores, non-graftable beds in need of preparation for SSG or dead space filling. |
| 44 | Pretibial wounds, some lower limb trauma wounds, abscess cavity wounds post drainage |
| 45 | Primarily Exudation |
| 46 | superficial wound dehsicence following abdominal surgery - usually for peritonitis |
| 47 | Tends to be wounds vreated in the acute setting / trauma + laparostomy |
| 48 | TNP dressing a good for large wounds that are highly exudative, wounds that need stimulating to granulate in preparation for grafting or reconstruction, temporary protective covering of structures (tendon nerves bowel etc) or implants such as metal work. In general it should be used as part of a reconstructive strategy rather than in lieu of one. |
| 49 | wound absces/sepsis with dehiscence, loss of tissue |
| 50 | wounds that are difficult to nurse |
| 51 | Wounds with a significant cavity or high exudate |

5. Are you responsible for deciding on the use of negative pressure wound therapy…?

|  |  |  |
| --- | --- | --- |
|  | ...on a newly formed SWHSI? | ...on a longstanding SWHSI? |
| Never | 8 | 8 |
| Rarely | 7 | 7 |
| Sometimes | 9 | 11 |
| Often | 18 | 19 |
| Always | 9 | 8 |
| Total | 51 | 51 |

6. Would you like to use negative pressure wound therapy in patients with surgical wounds healing by secondary intention more than you do – but are unable to?

|  |  |
| --- | --- |
| No | 41 |
| Yes\* | 10 |
| Total | 51 |

\* If yes, what factors may prevent negative pressure wound therapy use?: (1) accessibility, (2) Availability of the equipment / access to this mode of intervention for the smaller wounds where this could be applied , (3) during acute laparotomy / intentional laparostomy, difficult to obtain VAC in emergency situation, (4) Finances, CCG funding and organisation of output NPT, (5) Knowledge of colleagues regarding use of TNP, (6) TVI nurses, (7) Use in community; cost

7. In your mind, how expensive is it to use negative pressure wound therapy to treat surgical wounds healing by secondary intention (in terms of cost per patient treated)?

|  |  |
| --- | --- |
| Very cheap | 0 |
| Cheap | 2 |
| As expensive as other treatments, such as dressings | 19 |
| Expensive | 28 |
| Very expensive | 2 |
| Total | 51 |

8. In general, I believe that the use of negative pressure wound therapy represents good value for money for surgical wounds healing by secondary intention.

|  |  |
| --- | --- |
| Don't know | 1 |
| Strongly disagree | 0 |
| Disagree | 2 |
| Neither agree or disagree | 14 |
| Agree | 29 |
| Strongly agree | 5 |
| Total | 51 |

9. In the last 12 months, approximately how many times have you met with a company representative to discuss the use of negative pressure wound therapy?

|  |  |
| --- | --- |
| 0 | 32 |
| 1 | 12 |
| 2 | 4 |
| 3 | 1 |
| 4 | 1 |
| 20 | 1 |
| Grand Total | 51 |

Appendix 4. Selection of instrumental variables

Instruments are variables that are good predictors of allocation to NPWT but which do not directly predict healing; the instruments impact on health outcome through their impact on treatment allocation only. We have a number of potential instruments available, mostly derived from a survey implemented. Further details on the survey can be found in Appendix 3.

Instrument validity and relevance

A series of tests are available that allow ascertaining each assumption. The test proposed by Durbin-Wu-Hausman (STATA® syntax: *estat endogenous*) allows evaluating whether the presumed endogenous variable is in fact endogenous. If the null hypothesis of exogeneity cannot be rejected, then one should revert to using OLS. On what concerns instrument validity, the Sargan–Hansen test of over-identifying restrictions can be used (only applicable when there are more instruments than the number of endogenous variables). The null hypothesis is that the instruments are valid, and that these are correctly excluded from the outcome equation of interest (STATA® syntax: *estat overid* after *ivregress gmm*). To assess relevance, the Shea’s partial-R2 measure reflects the correlation between the excluded instruments and the endogenous regressor. Even where valid and relevant, a non-zero but small correlation between the set of instruments and the endogenous regressors can lead to the problem of weak instruments, again biasing IV estimation of treatment effects. To assess whether instruments are weak, the procedures set out in Stock and Yogo can be used (STATA® syntax: *estat firststage, forcenonrobust all*). Overall, it is also of interest to ascertain whether the model is adequately specified in general. The adapted version of the Ramsey’s reset test for IVs is here used. If p-value <0.05 we reject the null that there are no neglected non-linearities.

Results to this battery of tests were presented in an intuitive way, by categorising results according to conclusions drawn on statistical significance.

• Is there evidence of endogeneity? We categorised results based on a p-value on the Durbin-Wu-Hausman test, such that the response to the previous question is:

Yes if p-value < 0.05,

Maybe if 0.05 <pvalue <0.1

No if p-value>0.1

• Is there evidence of the instrument set not being valid? The Hansen-Sargan test was used. Responses to the previous question were categorised into

Yes if p value <0.05

Maybe if 0.05 <pvalue <0.1

No if p-value>0.1

• Is there evidence of a weak instrument set? Categorisations of possible answers to this question were based on the F statistic, and confirmed using the Yoko.

No if F > 10

Maybe if 8< F <10;

Yes if F < 8

• Is there evidence of model misspecification? Categorisations of possible answers to this question were based on the Pesaran-Taylor reset statistic:

No p-value>0.1

Maybe if 0.05 <pvalue <0.1

Yes if p value <0.05

The theoretical plausibility of the health professionals’ instruments (such as their treatment preferences, or beliefs about the treatment’s value for money) relies on assuming health professionals’ to be unrelated to outcome except through their preferences, that is, if there are better health professionals in general at achieving health outcomes for their patients then this is unrelated to their preferences for NPWT. One may argue that this may not be plausible. Thus, we rely on the available statistical tests for the validity of the instruments. However, in small samples, as is the case with the cohort study, tests may have low power to reject the validity of the instruments (when this is false).

Characteristics of instruments being evaluated

|  |  |  |  |
| --- | --- | --- | --- |
| Variable name | Source | Description or survey question | Response format |
| prevtreat | Cohort data | NPWT used on the previous patient treated by the health professional | Yes(1) / No(0) |
| Tnpbetter | Survey | In general, I believe NPWT is a better treatment for managing eligible SWHSI than other wound dressings. | Strongly disagree/ Disagree/  Neither agree or disagree/ Agree/ Strongly agree |
|  | Survey | Imagine you consult with a new patient who has a SWHSI: how likely is it that you use NPWT at some point in the management of their wound? |  |
| usetnpnewptc |  | a) Assuming CURRENT practices and procedures in your organisation around availability of NPWT | Extremely unlikely/ Unlikely/ As likely as using other wound dressings/ Likely/ Extremely likely |
| usetnpnewpt |  | b) Imagining you have unlimited access to NPWT |
| usetnpmore | Survey | Would you like to use NPWT in patients with SWHSI more than you do – but are unable to? | Yes/ No |
| tnpexpensive | Survey | In your mind, how expensive is it to use NPWT to treat SWHSI (in terms of cost per patient treated)? | Very cheap/ Cheap/ As expensive as other treatments, such as dressings/ Expensive/  Very expensive |
| tnpgoodvfmoney | Survey | In general, I believe that the use of NPWT represents good value for money for SWHSI | Don't know/ Strongly disagree/ Disagree/ Neither agree or disagree/ Agree/ Strongly agree |
| ntimesrep | Survey | In the last 12 months, approximately how many times have you met with a company representative to discuss the use of negative pressure wound therapy? | Numeric |

Results of the instrument selection process

OLS model results

|  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- |
|  | | (1) | (2) | (3) | (4) | (5) |
|  | | Outcome | Outcome | Outcome | Outcome | Outcome |
|  | | OLS | OLS | OLS | OLS | OLS |
|  | | Set 1 | Set 2 | Set 2 + interaction | Set1 U set2 | Set1 U set2 + interaction |
| X: location2 | |  | 47.66\*\* | 46.18\*\* | 45.36\*\* | 43.33\* |
|  | |  | [17.02] | [16.76] | [17.22] | [16.98] |
| X: swhsi\_hist2 | |  | 10.540 | -27.94 | 7.43 | -29.25 |
|  | |  | [18.20] | [20.95] | [18.24] | [20.91] |
| X: area>25cm2 | | 24.06 |  |  | 17.81 | 21.6 |
|  | | [20.20] |  |  | [21.01] | [20.73] |
| X: tissue3 | | 34.89\* |  |  | 31.88 | 26.51 |
|  | | [16.38] |  |  | [16.69] | [16.52] |
| T: NPWT | | 88.98\*\*\* | 89.74\*\*\* | 56.83\*\* | 73.80\*\*\* | 42.1 |
|  | | [19.21] | [18.57] | [20.51] | [20.34] | [22.07] |
| T: NPWT x hist | |  |  | 142.97\*\*\* |  | 138.92\*\*\* |
|  | |  |  | [40.34] |  | [40.44] |
| Constant | | 100.82\*\*\* | 91.84\*\*\* | 102.37\*\*\* | 81.20\*\*\* | 92.84\*\*\* |
|  | | [10.63] | [13.25] | [13.38] | [14.12] | [14.33] |
| Observations | | 372 | 372 | 372 | 372 | 372 |
| R-squared | | 0.108 | 0.113 | 0.142 | 0.125 | 0.152 |
| AIC | | 4794.4 | 4792.3 | 4781.8 | 4791.4 | 4781.5 |
|  | Standard errors in brackets | | | |  |  |
|  | \*\*\* p<0.01, \*\* p<0.05, \* p<0.1, + p<0.2 | | | |  |  |

Bayesian IV model without interaction

Selection of individual instruments based on relevance

|  |  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
|  | | Summary statistics | | | | Regression analysis | | | |
| Variable | | Obs | Mean | Std. Dev. | Correlation with tnp2 | N | AIC\* | R2 | Strength of association\*\* |
| S1 | Prevtreat | 393 | 0.226 | 0.419 | 0.279 | 372 | 394.4 | 0.188 | Very strong |
| S2 | Tnpbetter | 393 | 0.969 | 0.597 | -0.108 | 372 | 365.6 | 0.248 | Very strong |
| S3 | usetnpnewpt | 393 | 1.405 | 0.927 | -0.135 | 372 | 421.9 | 0.128 | None |
| S4 | usetnpmore | 393 | 0.178 | 0.383 | -0.034 | 372 | 417.1 | 0.137 | Weak |
| S5 | tnpexpensive | 393 | 1.359 | 0.615 | -0.002 | 372 | 421.8 | 0.128 | None |
| S6 | tnpgoodvfmoney | 393 | 1.232 | 0.655 | -0.101 | 372 | 421.6 | 0.129 | None |
| S7 | ntimesrep | 393 | 0.975 | 3.171 | 0.029 | 372 | 415.9 | 0.140 | Strong |
|  | 2x2 (best models) |  |  |  |  |  |  |  |  |
| S8 | S1 + S3 | -- |  |  |  | 372 | 394.9 | 0.191 | <0.001, <0.1 |
| S9 | S1 + S6 | -- |  |  |  | 372 | 394.6 | 0.191 | <0.001, <0.1 |
|  | 3x3(best models) |  |  |  |  |  |  |  |  |
| S10 | S1 + S2 + S6 | -- |  |  |  | 372 | 395.1 | 0.184 | <0.001, No, No |

\*\* the null model shows an AIC of 418.7 and an R2 of 0.129

\* categorisation based on p-value on coefficients in the first stage regression: Very strong < 0.001, strong p <0.05, weak p <0.1, None p>0.1

For some of these the correlations are low, which may lead to efficiency losses when using IV compared to OLS

|  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- |
|  | (1) | (2) | (3) | (4) | (5) |
|  | (stage 2)  Outcome | (stage 2)  Outcome | (stage 2)  Outcome | (stage 2)  Outcome | (stage 2)  Outcome |
|  | IV 1 | IV 2 | IV 3 | IV 6 | IV 9 |
| tnp2 | 33.498 | 69.392 | -106.528 | 105.978 | 42.6 |
|  | [76.374] | [170.019] | [186.311] | [176.533] | [69.01] |
| location2 | 63.403\* | 51.691 | 109.092 | 39.753 | 60.42\*\* |
|  | [30.135] | [56.710] | [63.188] | [58.789] | [27.61] |
| swhsi\_hist2 | 9.295 | 9.334 | 9.147 | 9.372 | 9.31 |
|  | [17.926] | [17.312] | [21.599] | [16.868] | [18.32] |
| Constant | 99.717\*\*\* | 96.298\*\*\* | 113.053\*\*\* | 92.814\*\*\* | 98.84\*\*\* |
|  | [13.924] | [19.836] | [23.502] | [20.124] | [17.72] |
| Observations | 374 | 374 | 374 | 374 | 374 |
| R-squared | 0.087 | 0.106 | 0.045 | 0.107 | 0.093 |
| Is treatment endogenous? | No | No | No | No | No |
| Are instruments valid? | -- | -- | -- | -- | Yes |
| Are instruments weak? | No | Yes | Yes | Yes | No |
| Is the model adequately specified? | Yes | Yes | Yes | Yes | Yes |

Bayesian IV model without interaction: empirical IVs

|  |  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
|  |  | Summary statistics | | | | Regression analysis | | | |
|  | Variable | Obs | Mean | Std. Dev. | Correlation with tnp2 | N | AIC\* | R2 | Strength of association |
|  |  |  |  |  |  |  |  |  |  |
| E1 | tissue3 | 393 | 0.412 | 0.493 | 0.293 | 372 | 394.4 | 0.188 | Very strong |
| E2 | area\_fil\_c~2 | 391 | 0.238 | 0.426 | 0.444 | 372 | 365.6 | 0.248 | Very strong |
|  |  |  |  |  |  |  |  |  |  |
|  | E1+E2 |  |  |  |  | 372 | 352.3 | 0.279 | <0.001, <0.001 |
|  |  |  |  |  |  |  |  |  |  |
|  | Multiple instruments  (only best models shown) |  |  |  |  |  |  |  |  |
|  | E2+S1 |  |  |  |  | 372 | 350.7 | 0.282 | <0.001, <0.001 |
|  | E1+E2+S1 |  |  |  |  | 372 | 336.8 | 0.312 | <0.001, <0.001, <0.001 |
|  | E1+E2+S1+S2 |  |  |  |  | 372 | 332.1 | 0.324 | <0.001, <0.001, <0.001, <0.05 |
|  | E1+E2+S1+S2+S6 |  |  |  |  | 372 | 331.4 | 0.329 | <0.001, <0.001, <0.001, <0.05, No |

\* the null model shows an AIC of 418.7 and an R2 of 0.129

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
|  | (1) | (2) | (3) | (4) |
|  | (stage 2)  Outcome | (stage 2)  Outcome | (stage 2)  Outcome | (stage 2)  Outcome |
|  | E1 | E2 | E2+S1 | E1+E2+S1+S2 |
|  | empirical | empirical | empirical IVs | All IVs |
| tnp2 | 140.726\*\* | 222.764\*\* | 166.27\*\*\* | 133.1\*\* |
|  | [51.947] | [76.125] | [45.5] | [38.8] |
| location2 | 30.967 | 1.648 | 22.60 | 33.46 |
|  | [22.906] | [27.366] | [22.00] | [20.37] |
| swhsi\_hist2 | 10.685 | 9.496 | 10.76 | 10.66 |
|  | [16.615] | [16.734] | [18.51] | [18.23] |
| Constant | 86.925\*\*\* | 81.691\*\*\* | 84.46\*\*\* | 87.66\*\*\* |
|  | [12.957] | [14.785] | [14.06] | [13.67] |
| Observations | 372 | 374 | 372 | 372 |
| R-squared | 0.095 | 0.093 | 0.072 | 0.100 |
| Is treatment endogenous? | No | Yes | Maybe | No |
| Are instruments valid? | -- | -- | Yes | Yes |
| Are instruments weak? | No | No | No | No |
| Is the model adequately specified? | Yes | Yes | Yes | Yes |

Bayesian IV model with interaction

Having two endogenous variables, just as if having another endogenous variable X4 and you did not realize that X4=X2\*X3. But if Z is a valid instrument, and X3 is truly exogenous, then Z\*X3 is a valid instrument, too.

|  |  |  |
| --- | --- | --- |
|  | tnp2 | histtnp |
| prevtreat | 0.310 | 0.170 |
| tnpbetter | 0.101 | -0.030 |
| usetnpnewpt | 0.129 | 0.047 |
| usetnpmore | -0.020 | 0.018 |
| tnpexpensive | 0.007 | 0.027 |
| tnpgoodvfm~y | 0.105 | 0.059 |
| ntimesrep | 0.034 | -0.034 |
| prevtreath~t | 0.156 | 0.505 |
| tnpbetterh~t | -0.042 | 0.413 |
| usetnpnew~st | -0.013 | 0.458 |
| usetnpmore~t | 0.005 | 0.205 |
| tnpexpensi~t | -0.020 | 0.427 |
| tnpgoodvfm~t | -0.024 | 0.462 |
| ntimesreph~t | -0.052 | 0.043 |

For some of these the correlations are low, which may lead to efficiency losses when using IV compared to OLS

|  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- |
|  |  | regression on t, treatment | | | regression on tw, interaction with history | | |
|  | Instrument, z | R2 | AIC | Strength of association of z on t | R2 | AIC | Strength of association of z.w on t.w |
| 0 | null model | 0.279 | 352.3 | -- | 0.275 | -98.4 | -- |
| 1 | prevtreat | 0.313 | 338.4 | Very strong | 0.382 | -153.8 | Very strong |
| 2 | tnpbetter | 0.296 | 347.2 | Very strong | 0.277 | -95.5 | None |
| 3 | usetnpnewpt | 0.285 | 353.1 | None | 0.281 | -97.6 | Weak |
| 4 | usetnpmore | 0.279 | 356.0 | None | 0.276 | -94.8 | None |
| 5 | tnpexpensive | 0.279 | 356.2 | None | 0.276 | -94.7 | None |
| 6 | tnpgoodvfm~y | 0.289 | 351.0 | Strong | 0.281 | -97.5 | None |
| 7 | ntimesrep | 0.280 | 355.5 | None | 0.283 | -98.5 | None |

Categorisation based on p-value on coefficients in the first stage regression: Very strong < 0.001, strong p <0.05, weak p <0.1, None p>0.1

Only relevant instrument when used in isolation is prevtreat.

Multiple

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
|  | regression on t | | regression on tw | |
| Instrument set, z | AIC | R2 | AIC | R2 |
| Null model | 352.3 | 0.279 | -98.35 | 0.275 |
| prevtreat | 338.4 | 0.313 | -153.8 | 0.382 |
| prevtreat tnpbetter | 333.5 | 0.329 | -154.4 | 0.390 |
| prevtreat tnpgoodvfmoney | 336.8 | 0.323 | -154.5 | 0.390 |
| prevtreat usetnpnewpt | 340.1 | 0.317 | -150.9 | 0.384 |
| prevtreat ntimesrep | 341.8 | 0.314 | -152.0 | 0.386 |
| prevtreat tnpexpensive | 341.9 | 0.314 | -150.2 | 0.383 |
| prevtreat usetnpmore | 342.2 | 0.313 | -150.1 | 0.383 |
| tnpbetter tnpgoodvfmoney | 348.5 | 0.301 | -96.1 | 0.286 |
| tnpbetter ntimesrep | 350.5 | 0.298 | -95.9 | 0.286 |
| tnpbetter tnpexpensive | 350.5 | 0.298 | -91.6 | 0.277 |
| tnpbetter usetnpnewpt | 350.7 | 0.297 | -96.7 | 0.287 |
| tnpbetter usetnpmore | 350.8 | 0.297 | -92.1 | 0.278 |
| tnpgoodvfmoney ntimesrep | 352.0 | 0.295 | -101.5 | 0.296 |
| usetnpnewpt tnpgoodvfmoney | 354.1 | 0.291 | -95.0 | 0.284 |
| usetnpmore tnpgoodvfmoney | 354.6 | 0.290 | -93.9 | 0.282 |
| tnpexpensive tnpgoodvfmoney | 354.9 | 0.281 | -98.9 | 0.284 |
| usetnpnewpt ntimesrep | 355.6 | 0.288 | -99.9 | 0.293 |
| usetnpnewpt usetnpmore | 356.7 | 0.286 | -95.4 | 0.285 |
| usetnpnewpt tnpexpensive | 357.0 | 0.285 | -93.9 | 0.282 |
| tnpexpensive ntimesrep | 359.3 | 0.281 | -94.5 | 0.283 |
| usetnpmore ntimesrep | 359.3 | 0.281 | -94.8 | 0.284 |
| usetnpmore tnpexpensive | 359.9 | 0.280 | -91.2 | 0.277 |

IV model with interaction: empirical instruments

|  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- |
|  | regression on t, treatment | | | regression on tw, interaction with history | | |
| Instrument, z | R2 | AIC | Strength of association of z on t | R2 | AIC | Strength of association of z.w on t.w |
| null model | 0.129 | 418.7 | -- | 0.240 | -98.5 | -- |
| tissue | 0.191 | 394.9 | Very strong | 0.364 | -147.2 | Very strong |
| area | 0.249 | 367.5 | Very strong | 0.346 | -138.7 | Very strong |

Multiple

|  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- |
|  |  | regression on t | | regression on tw | |
|  | Instrument set, z | AIC | R2 | AIC | R2 |
| 1 | area + prevtreat | 352.4 | 0.282 | -143.9 | 0.362 |
| 2 | area + tnpbetter | 362.0 | 0.264 | -136.8 | 0.350 |
| 3 | area + usetnpnewpt | 365.2 | 0.257 | -137.2 | 0.350 |
| 4 | area + usetnpmore | 369.5 | 0.249 | -136.8 | 0.350 |
| 5 | area + tnpexpensive | 369.5 | 0.249 | -136.8 | 0.350 |
| 6 | area + tnpgoodvfmoney | 364.8 | 0.258 | -137.3 | 0.351 |
| 7 | area + ntimesrep | 369.3 | 0.249 | -137.9 | 0.352 |
| 8 | tissue + prevtreat | 373.3 | 0.241 | -153.1 | 0.378 |
| 9 | tissue + tnpbetter | 392.2 | 0.201 | -145.2 | 0.364 |
| 10 | tissue + usetnpnewpt | 393.6 | 0.198 | -145.3 | 0.364 |
| 11 | tissue + usetnpmore | 396.6 | 0.192 | -145.2 | 0.364 |
| 12 | tissue + tnpexpensive | 396.8 | 0.192 | -145.2 | 0.364 |
| 13 | tissue + tnpgoodvfmoney | 392.5 | 0.201 | -145.6 | 0.365 |
| 14 | tissue + ntimesrep | 396.8 | 0.191 | -146.5 | 0.367 |
| 15 | area + tissue | 353.6 | 0.284 | -184.7 | 0.431 |
| 16 | area + tissue + prevtreat | 338.5 | 0.316 | -189.0 | 0.441 |
| 17 | area + tissue + tnpbetter | 347.0 | 0.300 | -182.8 | 0.431 |
| 18 | area + tissue + usetnpnewpt | 352.5 | 0.290 | -182.9 | 0.432 |
| 19 | area + tissue + usetnpmore | 355.5 | 0.284 | -182.8 | 0.431 |
| 20 | area + tissue + tnpexpensive | 355.5 | 0.284 | -182.8 | 0.431 |
| 21 | area + tissue + tnpgoodvfmoney | 350.2 | 0.294 | -183.5 | 0.433 |
| 22 | area + tissue + ntimesrep | 355.1 | 0.285 | -183.9 | 0.433 |
| 23 | area + tissue + prevtreat + tnpbetter | 334.8 | 0.330 | -217.1 | 0.487 |
| 24 | area + tissue + prevtreat + usetnpnewpt | 339.8 | 0.321 | -217.0 | 0.487 |
| 25 | area + tissue + prevtreat + usetnpmore | 341.9 | 0.317 | -217.0 | 0.487 |
| 26 | area + tissue + prevtreat + tnpexpensive | 341.6 | 0.318 | -217.4 | 0.488 |
| 27 | area + tissue + prevtreat + tnpgoodvfmoney | 336.5 | 0.327 | -218.1 | 0.488 |
| 28 | area + tissue + prevtreat + ntimesrep | 341.5 | 0.318 | -217.6 | 0.488 |

Appendix 5. Elicitation of the additional time to heal

Questions to the Clinical experts:

*Our cohort study included 393 patients. Of these, 320 healed within the study – mean time to healing was 99 days (25% healed within the first 44 days and 75% healed within 122 days. The remaining 73 patients (representing 18.7% of the total) didn’t heal (50 reached the end of follow-up, and the remaining exited the study for reasons unrelated to their SWHSI). These 73 patients were followed-up on average for 416 days, and obviously didn’t heal within this time frame – these may be ‘hard to heal’. Now, in our analyses, we need to make some assumption about how much longer these patients would have taken to heal. We hope you can help with this.*

*I’ll first describe this ‘hard to heal’ subgroup of patients:*

*- 34% were diabetic AND had a foot wound (compared to 9.6% in those that healed).*

*- More wounds were larger than 25cm2 at baseline (43%, compared to 19% in those that healed)*

*- there were less abdominal wounds (15%, compared to 42% in those that healed)*

*- only 22% of the wounds were originally dehisced (compared to 44% in those that healed)*

*- more patients were inpatients at baseline and more patients were treated by a doctor at baseline*

*- less wounds were from colorectal surgery (19%, compared to 44% in those that healed) most other characteristics for which we collected information did not appear as different in both groups.*

*These patients were followed up for an average of 416 days and their wounds haven’t healed.*

*What is your best guess to how much longer, on average, would their wounds take to heal? \_\_\_\_\_days*

*What is your best guess to how much longer it would take to see the majority (90%) of these patient healed? \_\_\_\_\_days*

## Appendix 6 – Search Strategies for identification of external evidence to supplement cohort data

1. Search Strategy - Dressings

We searched the following electronic databases:

The Cochrane Wounds Group Specialised Register (searched 10 Jan 2012);

The Cochrane Central Register of Controlled Trials (CENTRAL; *The Cochrane Library* 2012, Issue 1);

Ovid MEDLINE (1946 to 10 Jan 2012);

Ovid EMBASE (1974 to 10 Jan 2012);

EBSCO CINAHL (1982 to 10 Jan 2012).

**Ovid MEDLINE search**

1 MeSH descriptor: [Bandages] explode all trees

2 MeSH descriptor: [Hydrogels] explode all trees

3 MeSH descriptor: [Alginates] explode all trees

4 (dressing\* or hydrocolloid\* or alginate\* or hydrogel\* or foam or bead or film or films or tulle or gauze or non-adherent or non adherent):ti,ab,kw (Word variations have been searched)

5 or/1-4

6 exp Surgical Wound Infection/  
7 exp Surgical Wound Dehiscence/  
8 (surg\* adj5 infect\*).tw.  
9 (surg\* adj5 wound\*).tw.  
10 (surg\* adj5 site\*).tw.  
11 (surg\* adj5 incision\*).tw.  
12 (surg\* adj5 dehisc\*).tw.  
13 (wound\* adj5 dehisc\*).tw.  
14 (wound\* adj5 infect\*).tw.  
15 (wound adj5 disrupt\*).tw.  
16 wound complication\*.tw.  
17 or/6-16  
18 (intent\* or second\* or heal\* or complic\*).tw.  
19 ((open\* or clos\*) adj5 wound\*).tw.  
27 25 or 26  
28 24 and 27  
29 12 and 28  
30 randomised controlled trial.pt.  
31 controlled clinical trial.pt.  
32 randomi?ed.ab.  
33 placebo.ab.  
34 clinical trials as topic.sh.

35 randomly.ab.

36 trial.ti.  
37 exp animals/ not humans.sh.  
38 29 and 37

1. Search Strategy - Cohort studies

We searched the following electronic databases:

Ovid MEDLINE (1946 to 31 Dec 2013);

Ovid EMBASE (1974 to 31 Dec 2013);

EBSCO CINAHL (1982 to 31 Dec 2013).

**Ovid MEDLINE search**

1. exp Surgical Wound/

2. exp Surgical Wound Dehiscence/

3. (surg\* adj5 wound\*).ti,ab.

4. (surg\* adj5 site\*).ti,ab.

5. (surg\* adj5 incision\*).ti,ab.

6. (surg\* adj5 dehisc\*).ti,ab.

7. 1 or 2 or 3 or 4 or 5 or 6

8. (intent\* or second\*).ti,ab.

9. ((open\* or clos\*) adj5 wound\*).ti,ab.

10. 8 or 9

11. 7 and 10

12. SWHSI.ti,ab.

13. 11 or 12

14. epidemiologic studies/

15. exp Case-Control Studies/

16. exp Cohort Studies/

17. case control.ti,ab.

18. (cohort adj (study or studies)).ti,ab.

19. Cohort analy$.ti,ab.

20. (Follow up adj (study or studies)).ti,ab.

21. (observational adj (study or studies)).ti,ab.

22. Longitudinal.ti,ab.

23. Retrospective.ti,ab.

24. Cross sectional.ti,ab.

25. Cross-sectional studies/

26. 14 or 15 or 16 or 17 or 18 or 19 or 20 or 21 or 22 or 23 or 24 or 25

27. 13 and 26

28. exp Wound Healing/

29. (wound\* adj3 heal\*).ti,ab.

30. 28 or 29

31. 27 and 30

32. limit 27 to ed=19460101-20131231

33. limit 31 to ed=19460101-20131231

1. Search Strategy - Economic and health utility studies

We searched the following electronic databases:

Ovid MEDLINE (1946 to 31 Dec 2013);

Ovid EMBASE (1974 to 31 Dec 2013);

EBSCO CINAHL (1982 to 31 Dec 2013);

NHS Economic Evaluation Database (2013, Issue 12).

**Ovid MEDLINE search**

1. exp Surgical Wound/

2. exp Surgical Wound Dehiscence/

3. (surg\* adj5 wound\*).ti,ab.

4. (surg\* adj5 site\*).ti,ab.

5. (surg\* adj5 incision\*).ti,ab.

6. (surg\* adj5 dehisc\*).ti,ab.

7. 1 or 2 or 3 or 4 or 5 or 6

8. (intent\* or second\*).ti,ab.

9. ((open\* or clos\*) adj5 wound\*).ti,ab.

10. 8 or 9

11. 7 and 10

12. SWHSI.ti,ab.

13. 11 or 12

14. ECONOMICS/

15. "Costs and Cost Analysis"/

16. "Cost Allocation"/

17. Cost-Benefit Analysis/

18. "Cost Control"/

19. "Cost Savings"/

20. "Cost of Illness"/

21. "Cost Sharing"/

22. "Deductibles and Coinsurance"/

23. Medical Savings Accounts/

24. Health Care Costs/

25. Direct Service Costs/

26. Drug Costs/

27. Employer Health Costs/

28. Hospital Costs/

29. Health Expenditures/

30. Capital Expenditures/

31. "Value of Life"/

32. exp ECONOMICS, HOSPITAL/

33. exp Economics, Medical/

34. Economics, Nursing/

35. Economics, Pharmaceutical/

36. exp "Fees and Charges"/

37. exp BUDGETS/

38. (low adj cost).mp.

39. (high adj cost).mp.

40. (health?care adj cost$).mp.

41. (fiscal or funding or financial or finance).tw.

42. (cost adj estimate$).mp.

43. (cost adj variable).mp.

44. (unit adj cost$).mp.

45. (economic$ or pharmacoeconomic$ or price$ or pricing).tw.

46. 14 or 15 or 16 or 17 or 18 or 19 or 20 or 21 or 22 or 23 or 24 or 25 or 26 or 27 or 28 or 29 or 30 or 31 or 32 or 33 or 34 or 35 or 36 or 37 or 38 or 39 or 40 or 41 or 42 or 43 or 44 or 4

47. 13 and 46

## Appendix 7 – Patient Interviews Paper

McCaughan D, Sheard L, Cullum N, Dumville J, and Chetter I. Patient’s perceptions and experiences of living with a surgical wound healing by secondary intention: A qualitative study. International Journal of Nursing Studies. 2018, 77, p29-38. Available at: <https://doi.org/10.1016/j.ijnurstu.2017.09.015>

## Appendix 8 - Nurses’ and surgeons’ views and experiences of surgical wounds healing by secondary intention: a qualitative study.

**INTRODUCTION**

Every year, more than 10 million surgical operations are performed in the NHS in the United Kingdom ([www.nhsconfed.org/resources/key-statistics-on-the-nhs](http://www.nhsconfed.org/resources/key-statistics-on-the-nhs)). Most surgical wounds heal by primary intention, that is to say, the edges of the surgical incision are closed together, using stitches or clips, until the cut edges unite. Healing of an open surgical wound that takes place from the base of the wound upwards, through the formation of new tissue, is called ‘healing by secondary intention’.

Surgical wounds heal by secondary intention for a variety of reasons. It may have been planned at surgery to leave the wound open to heal by secondary intention, or a wound that was closed after surgery can break down (dehisce) due to infection. The types of wounds that are sometimes left open to heal include those resulting from excision of infected soft tissue such as pilonidal sinuses (Al-Khamis et al., 2010) and breast abscesses (Lewis et al, 2001). Concurrent infection is a recognised risk factor for dehiscence of closed abdominal wounds (Graham et al., 1998; Sandy-Hodgetts et al., 2013; Spiliotis et al., 2009) where the edges of the surgically closed wound split apart, leaving the wound open. Wounds resulting from colorectal surgery are particularly prone to dehiscence due to infection (McLaws et al., 2000; Tanner et al., 2009), resulting in full or partial separation of the wound edges, which may then be left to heal through secondary intention, or closed surgically after partial healing (NICE, 2013).

Until very recently, data concerning the epidemiology of surgical wounds healing by secondary intention (hereafter referred to as open surgical wounds) have largely been absent both for the UK and globally. Two published audit studies originating in the North of England, UK, one in Bradford (Vowden and Vowden, 2009) and one in Hull (Srinivasaiah et al., 2007) estimated that open surgical wounds made up approximately 28% of all prevalent acute (mainly surgical/traumatic) wounds receiving care. More recently, Hall et al. (2014) reported a point prevalence of dehisced surgical wounds of 0.07 per 1000 population in a UK city with a population of 751,485. A further study (Chetter et al., 2017) measured the prevalence of open surgical wounds over a two week period in primary, community and secondary care settings, and found a prevalence of 0.41 per 1000 population (total population 590,585), with almost half of the wounds planned to heal by secondary intention. These findings suggest that open surgical wounds are relatively common.

Open surgical wounds can be challenging to manage, as they are often large, deep, prone to infection and produce copious amounts of exudate (Dumville et al., 2015), yet a strong evidence base to guide the management of these wounds is currently lacking (Dumville et al., 2015; National Institute for Health and Clinical Excellence (NICE), 2008). Open surgical wounds are often managed with a variety of dressings, requiring patients to undergo frequent dressing changes, and, sometimes, painful packing of the wound. There is no evidence to suggest that any one dressing is better than another (Vermeulen, 2004); additionally, results from a recent systematic review (Norman et al., 2016) indicate that there is no robust evidence on the relative effectiveness of any antiseptic/antibiotic/anti-bacterial preparation evaluated to date for use on open surgical wounds. Open surgical wounds may also be treated by further surgical intervention, such as debridement and skin grafting, which may require patients to be hospitalised, with implications for quality of life (Sandy-Hodgetts et al., 2013; Smith et al., 2013). Given the potential complexity, size and slow nature of healing of open surgical wounds, interest in alternative treatment options is high. An intervention that is increasingly used in wound care generally is negative pressure wound therapy (NPWT), a system that comprises a non-adherent, porous wound dressing (such as gauze or foam), with a transparent film to seal the wound, and a drainage tube that is connected to a vacuum source to exert negative pressure. Negative pressure has been claimed to promote wound healing by removing exudate and reducing infection, although there is a lack of robust evidence to support these claims (Dumville et al., 2015).

Open surgical wounds have been under-researched to date. Evidence concerning their epidemiology, impact on patients’ health related quality of life and the effectiveness and cost-effectiveness of treatments is limited. The study reported here sits within a wider programme of work that addresses these knowledge gaps. This study aimed to explore the views and experiences of surgeons and nurses who routinely manage open surgical wounds in relation to treatment and healing, and the findings complement those relating to patients’ experiences of living with an open surgical wound (McCaughan et al., 2018).

**METHODS**

An exploratory qualitative approach was adopted to gain new insights into a phenomenon about which little is known (Pope and Mays, 2006). Semi-structured interviews were used to allow for flexibility in data collection, permitting the researcher to explore how the participants make sense of the topic under investigation(Flick, 2014).

Setting and sample

The study sample was drawn from two centres in the north of England, and included clinicians working in hospital and community care settings. Potential participants were contacted via clinical networks, email and telephone, and sent an information leaflet about the study, with a request to contact the researcher if they were interested in taking part. The total study sample included five surgeons and seven nurses, purposively sampled from amongst health professionals with responsibility for caring for patients with open surgical wounds (see Table 1 Details of study sample).

Data collection

Interviews took place from January-August 2012 and were facilitated by a short, semi-structured topic guide (see Appendix 1) based on the research questions and the experiences of the research team. Data collection continued until no new information was forthcoming (Baker and Edwards, 2012). DM and LS conducted interviews at participants’ place of work. Surgeons’ interviews ranged from 30 to 45 minutes, and nurses’ from 60 to 75 minutes. All interviews were audio-recorded and fully transcribed.

Data analysis

Data were analysed for thematic content using ‘Framework’ approach, regarded as particularly well-suited to generating clinical practice-oriented findings (Gale et al., 2013). We followed the recommended sequential steps of familiarisation with the data, thematic analysis to develop a coding scheme, indexing, and charting of data, which involved re-arranging data according to thematic content. DM and LS met frequently to discuss expansion and modification of the coding frame. Data handling was facilitated by the use of electronic spreadsheets to summarise and chart data, and allow for comparison within and between cases. Analysis was both systematic and iterative; we looked for similarities and differences across the data set, making connections and identifying salient themes. Our aim was to remain close to participants’ accounts while moving towards a coherent interpretation of the complete data set. Active seeking of ‘negative’ cases, that is to say, elements in the data that seem to contradict the emerging explanations, helped to refine the analysis (Mays and Pope, 2000). Use of reflective notes and memo-writing throughout the analytic process also enhanced rigour of the study (Barbour, 2001).

Researcher characteristics

DM is a registered nurse and LS a sociologist; both are experienced in applied health services research using qualitative methods. The different backgrounds of the researchers did not result in significant differences in data collection or interpretation.

Data reporting

Findings are reported according to SRQR reporting guidelines (O'Brien et al., 2014).

Patient and public involvement

Patient advisors were instrumental in shaping the design of the overall programme of work in which this study sits.

**Ethics**

The study received research ethics (NRES Committee Yorkshire and The Humber – Leeds Central, REC reference 11/YH/0313) and governance approval. All study participants were given verbal and written information relating to the study aims and their involvement. Written consent was obtained and participants were given assurances concerning the confidentiality and anonymity of their responses. It was made clear to participants that they could withdraw from the study at any time without giving a reason.

**RESULTS**

**Surgeons’ perceptions**

*Factors thought to influence the development of open surgical wounds*

Surgeons described the types of wounds associated with the various operations they perform. The main types of open surgical wounds identified were extensive abdominal cavity wounds (for example, laparostomy wounds and/or dehisced surgical wounds); cavity wounds after pilonidal sinus surgery; large, open wounds on the feet of patients with diabetes; axilla and groin wounds, associated with removal of lymph nodes for cancer. These wounds were generally perceived as slow to heal, particularly the open surgical wounds that result from colorectal surgery that are prone to infection.

*‘this sort of intrinsic diabetic poor healing often takes months to heal and there are a number of patients…with wounds failing to heal for 18 months or longer.’* (VS1)

*‘it’s* [slow to heal wounds] *not an uncommon situation, particularly with acute surgery and particularly with post-operative complications…obviously with colorectal surgery our surgical site infections are quite high because it tends to be dirty surgery, so superficial dehiscence is unfortunately quite common as well…’* (GS2)

Surgeons broadly agreed on a range of factors that contribute to slow/lack of healing, including emergency surgery, infection, obesity, and other risk factors such as patients’ nutritional and smoking status, age, diabetes, cancer, arterial and/or vascular disease, restricted mobility, impaired immune system and medication.

*‘often the unhealed ones [wounds] are the emergency operations…whereas the elective patients are people that are planned to come in, infection and breakdown occurs, but it is less common.’* (GS1)

*‘in terms of that sort of superficial dehiscence with big subcutaneous fat layer, big deep cavity, you only really see that in these super obese [patients] with the big abdominal fat aprons’* (GS2)

*‘malnutrition, being elderly, poor blood supply and vascular diseases, smokers, diabetics…people with poor mobility... are traditionally seen as things which slow the whole process right down… people on drugs, steroids and the like…I think these factors do play a role’* (GS1)

*Devolving wound care to community nurses and ‘looking after our own’*

General surgeons commented that the level of their involvement with wound management in the immediate post-operative period is closely linked to the nature of the surgery that has been carried out, the patient’s general condition and condition of their surgical wound. In most cases, nurses would assume responsibility for patients’ wound care after their discharge from hospital, with more intensive follow up by surgeons of patients whose wounds were not healing as well as expected. Contrastingly, patients with diabetes and foot wounds, and those undergoing plastic surgery, were described as having routine intensive follow up by surgeons and nurses working in these specialities. For example, vascular surgeons reported routinely measuring and documenting wound status during patients’ follow up visits. The plastic surgeon (PS) interviewed for the study described intensive follow up of patients through specialist plastics clinics for post-operative patients, where patients would be seen frequently by a consultant and/or specialist nurses until their wound(s) healed, an approach he summarised in the phrase *‘we look after our own’.*

*‘plastic dressing clinic is basically my post-operative patients, so they’ll come on a weekly basis until they’re healed…they’re under the care of a consultant…and they’ll stay with us until they are healed. We don’t discharge anybody to the community. We don’t discharge anybody to the tissue viability nurses. We look after our own.’* (PS)

*Assessment is multifaceted and complex*

During interview, surgeons provided detailed accounts of typical assessments of an open surgical wound that they might carry out to determine healing processes. Indicative factors related to: the size of the wound; whether the wound is infected; presence of slough in the wound; whether the wound appears to have healed superficially, but remains unhealed at a deeper level; presence or absence of granulation tissue; level of exudate; the condition of the wound edges; the patient’s general condition, including nutritional state and ability to mobilise; signs of over-granulation; whether the wound seems ‘static’ and/or appears to be colonised; blood supply at the wound site. Figure 1 provides detailed description of a wound assessment drawn from the interview with GS1, which is illustrative of reports from all of the surgeons.

*Surgeons favoured NPWT for certain types of open surgical wounds*

Surgeons described using a variety of approaches for the management of open surgical wounds, though one option, NPWT, was favoured above others. Use of NPWT (or *‘VAC*’ or *‘VAC pac’* as it was often referred to) was said to be increasing, and surgeons described complex, cavity wounds which were likely to be slow to heal (for example, extensive abdominal wounds associated with laparostomy or large, deep wounds to the feet of patients with diabetes), as *‘ideal candidates’* for NPWT.

*‘we do use negative pressure wound increasingly…the plastic surgeons for a long period of time have used negative pressure wound therapy… and colorectal surgeons use negative pressure systems a lot for the laparotomy type situation’* (VS2)

*‘my personal preference is to use vacuum assisted pressure dressing, the abdominal VAC dressings…I’m a big fan of VAC dressing’* (GS2)

*‘for deep soft tissue wounds…you know, a thing called necrotising fasciitis where people lose a vast amount of skin…it’s [NPWT] brilliant, absolutely brilliant…it’s a Godsend, it really is…’* (GS1)

Preference for NPWT was linked to personal experience of positive outcomes of treatment, patient perspectives, and implications for healthcare resources. Surgeons commented that NPWT controlled wound exudate, sealed the wound (thereby potentially lowering risk of infection), supported the growth of granulation tissue, and generally hastened wound healing. They also thought that its use enhanced patients’ quality of life, through increased convenience (due to a reduced need for dressing changes) and promotion of patient mobility. Additionally, surgeons associated NPWT with shorter in-hospital patient stays and reduced community nurse workload. Overall, surgeons viewed NPWT as a cost-effective and revolutionary approach to the treatment of hard to heal, open surgical wounds.

*‘often in the perineum, the groin area, difficult areas to get dressings to stick, to stay in, put the VAC in - it’s marvellous…they* [patients] *can go home, they can ambulate, some can even go back to work.’* (PS)

*‘my own personal preference is to use VAC – it controls exudates, keeps the wound tidy, good at controlling sepsis, and in the long term is supposed to encourage granulation…’*  (GS2)

*‘VAC has revolutionised the management of the large wound… it increases healing, it’s got all sorts of proven roles in improving the healing process. It physically shrinks the wound down… encourages granulation tissue….a VAC-able wound might close in 1 month whereas by secondary intention with open packing it will be 3 to 6 months.’* (PS)

*it’s* [NPWT] *got to be cheaper than £400 per day in hospital’* (VS2)

A major drawback of NPWT highlighted by general surgeons was a perceived risk of intestinal fistulation in patients with large abdominal cavity wounds, such as those associated with deep dehiscence or laparostomy. General surgeon 1 referred to a recent report of an audit of clinical practice that suggested it was safe to use NPWT on this type of wound, though he harboured reservations.

*‘the risk of course with intestines is that the negative VAC pressure will cause the intestines to fistulate, so that’s the big worry… I’m not so sure that it is entirely safe…though there is some data presented last week at the Association of Surgeons [conference] that would suggest the risk is no greater than not using it’* (GS1)

Other perceived disadvantages to use of NPWT were its lack of suitability for patients who are frail or have cognitive impairment, while service-related disadvantages included limited availability of the necessary equipment in the community and its high cost.

*Inferred cost-effectiveness*

Three of the five surgeons highlighted the lack of research evidence to support NPWT, yet they felt that their own and colleagues’ experience supported its use, a perception reinforced by its increasingly widespread and seemingly safe use in clinical practice. Surgeons considered NPWT cost-effective due to earlier discharge of patients with complex wounds from hospital, reduced need for dressing changes at home, thereby reducing community nurses’ workload, and its potential for expediting patients’ return to paid employment.

*‘it’s very anecdotal…I mean if you look for the evidence of VAC there isn’t a lot of evidence for it…but in my experience I think it does speed up granulation of tissue formation and sort of artificially stimulate cicatrisation and smallerisation [sic] of the wound’* (GS2)

*‘these complex wounds end up needing to have prolonged hospital stays and being in a hospital bed is expensive… there is a big drive… to get them home’* (VS1)

*‘VAC is just great…it speeds things up and encourages the wound to heal quicker...it reduces the workload right down’* (GS1)

*‘the [patient] has had about 3-4 weeks off [work] in total as opposed to months and months to heal’* (PS)

The plastic surgeon interviewed for the study commented that sufficient evidence is already currently available to unequivocally support the use of NPWT. He referred to a number of studies apparently demonstrating its effectiveness and contrasted increasing use of NPWT in the plastics specialist out-patient clinics and elsewhere in the hospital, with *‘old fashioned packing’* of wounds, which, he said, was becoming increasingly rare. This surgeon, the strongest advocate of NPWT amongst those interviewed, stated that the advent of NPWT had *‘changed practice considerably’.*

*‘Louis Argenta…Argenta’s paper from America… he has got numerous papers on VAC…you’d have to read the Louis Argenta paper for the advantages of VAC’* (PS)

[Louis Argenta is a surgeon who was involved in the commercial development of systems designed to deliver NPWT]

*‘there are numerous studies on VAC. It’s the most published thing in plastic surgery and wound care management, I promise you. There’s loads on it.’* (PS)

*‘we’re leaving a lot less wounds to old fashioned packing with dressings…now we put VAC on and the whole thing is a lot cleaner and bette…the old days of packing a wound are pretty much gone for us.’* (PS)

Three surgeons referred to receiving information from representatives from commercial companies manufacturing products used in the application of NPWT.

*‘Reps for VAC therapies…I’ve seen enough of those!’* (GS1)

*Dressing selection usually devolved to nurses*

Surgeons’ knowledge concerning dressings for open wounds was, by their own admission, limited. General surgeons 1 and 2 said they relied on nurses to make decisions about appropriate dressings because it is difficult to *‘keep up to speed’* with all the new products coming on to the market, and various dressings *‘go in and out of fashion’*. General surgeon 1 commented that he does not see commercial representatives in connection with dressings, though he thought they might be a source of information for nursing staff about new products.

*‘I’ll admit a degree of ignorance here…I would normally leave that to my nursing staff…they sort the wounds out’* (GS2)

*‘various things go in and out of fashion…as the years have gone on I’ve relied more on being told what is the dressing to be used…I am aware of the basics but I’m not quite up to speed with the detail’* (GS1)

The lack of robust evidence to support treatment choices in the care of slow to heal or non-healing open surgical wounds was highlighted by venous surgeon 2.

‘*I think chronic wounds requiring secondary intention healing is an area that has been extremely well ignored over the past 50 years…the evidence base is usually based on some sort of case studies as opposed to competitive randomised controlled trials and certainly very rarely dressing to dressing, so the evidence is based on ‘I’ve seen 10 patients on who it worked really well, thank you very much’…and then there is a bit of experience, things you have used for a long period of time and know work reasonably well’* (VS2)

**Nurses’ perceptions**

*Wound types perceived as likely to be slow to heal*

Agreement was widespread amongst nurses that wounds resulting from abdominal surgery (particularly colorectal surgery, or surgery to repair a hernia) were more likely to be slow to heal, or non-healing, than other types of open surgical wounds, and that these were also the type of wound most likely to dehisce. Other open surgical wounds cited as sometimes slow to heal were wounds resulting from Caesarean section, or those that follow treatment for a fistula, perianal abscess or pilonidal sinus.

*‘the non-healing wounds are usually associated to abdomens, hernia repairs and things that have burst open…’*  (TVN2)

*‘it’s the fistulas that don’t heal…’* (SS)

*‘they tend to be mainly the perianal abscesses* [that are slow to heal]*’* (DN1)

*‘we tend to get quite a lot of dehisced wounds post-surgery…we get a lot of hernia repairs, we get a few C-sections…’* (DN2)

*Nurses described multifaceted patient assessment, including psychosocial aspects*

Nurses reported taking a range of factors into account during assessment of a patient with an open surgical wound, including: wound size and duration, state of the wound bed and type of tissue in the wound, presence or absence of granulation tissue, levels of exudate, wound pain, wound odour, signs of infection, condition of surrounding skin; patient mobility and hygiene needs; diet and nutritional status; general levels of comfort; the patient’s feelings about their quality of life; whether family members are likely to be involved in wound care; and the patient’s potential for self-care of the wound.

Due to time constraints, hospital, district and community nurse participants’ main focus was on assessment of the condition of the patient’s wound; only one study participant (district nurse 2) mentioned using a wound-specific assessment tool (Watret, 2005; Dowsett and Newton, 2013) when carrying out first-time visits to patients. Tissue viability nurses reported having more available time for a broader, holistic approach to assessment that encompassed wider consideration of patients’ care needs: *‘all the things that matter to patients, and not just what we put on the wound’* (TVN1).

Tissue viability nurses regarded themselves as a *‘first port of call’* (TVN3) for provision of expert advice to community-based nurses caring for patients with complex, non-healing wounds. Some patients might be referred to tissue viability nurses almost immediately on discharge from hospital, due to the type of surgical procedure undertaken and the complex nature of their wound, and tissue viability nurses mentioned sometimes gathering background information about the history of the wound from the surgeon who had operated on the patient to inform their decisions on wound management. District and community nurses were also likely to refer patients for assessment by tissue viability nurses if wound healing appeared to have stalled or stopped.

*‘it’s usually the abdominal wounds, post-surgery. Complex patient, probably had some complex bowel surgery, perhaps perforated bowel, history of infection, under-nourished, lots of other things that have gone on with that type of surgery…very acutely unwell…’* (TVN1)

*‘They [community nurses] refer to us if they’ve been seeing the patient and they’re not improving they’ll refer to us for assessment.’* (TVN2)

*Factors perceived as likely to increase the risk of poor wound healing*

Nurses cited a variety of factors as potentially implicated in poor healing of open surgical wounds, which overlapped closely with those identified by surgeons: ‘complexity’ associated with comorbidities (such as Crohn’s disease), the reason for surgery (for example, people who experience perforated bowel), the nature of the surgical procedure (patients left with large, deep, cavity wounds), presence of a ‘foreign body’ (for example, retained surgical mesh), obesity, wound infection, age and general health, and lack of concordance with treatment. Figure 2 provides illustrative quotations relating to nurses’ views of factors implicated in slow healing of open surgical wounds.

*Wound healing can be unpredictable and difficult to achieve*

Nurses were asked for their views and experiences of how long open surgical wounds might take to heal. As noted above, the types of wounds said to take a long time to heal were deep cavity wounds, pilonidal sinuses and perianal abscesses, and wounds arising from hernia repairs where surgical mesh was inserted during the operation, which were said to take weeks, months or even years to heal.

*‘open cavity wounds* *can take a long, long, time…they* [patients] *are left with this hole basically… sometimes they do heal, eventually, but it’s a long haul…it could take years.’* (TVN2)

*‘colorectal fistulas are very debilitating…the bowel breaks down and the gut breaks down…they take months to heal.’* (SS)

*‘it was a hernia repair…down to the mesh…a really, really nasty wound that took a long time to heal…’* (SS)

Wound healing was described as sometimes unpredictable and erratic; a wound may progress well, stop healing for a period with no obvious reason (referred to as ‘stasis’), and then re-commence healing. Stasis was said to sometimes occur after removal of NPWT. Nurses also described instances where an open wound had almost completely healed, except for a small ‘hole’ which persisted, and partially healed wounds that continued to ‘gape’ in one area. An additional factor said to delay the final stages of wound healing was over-granulation.

*‘patients are told it [NPWT] will completely heal the wound and it only heals it part of the way, and then when we take it off, they’re anxious that it’s slowing down…’* (TVN3)

*‘one particular patient that had a hernia repair, 4 years ago now, had VAC at that point, he’s still got a wound and he’s been to plastics. I mean the area has reduced, it’s only 1 by 1* [inches] *but it’s still there and the surgeon has said that basically it’s never going to heal up.’*  (TVN3)

*‘the flesh had grown but the skin can’t close over the top, it bulges, and it’s quite pink and bleeds quite easily….it* [over-granulation] *just slows down the final stages of healing’* (DN1)

*Nurses described a precision approach to open surgical wound management that was also perceived as evidence-based*

Nurses described their wound management decisions as influenced by a wide array of factors, some wound specific, some patient-specific (including psychosocial factors and family circumstances), and some related to perceived cost-effectiveness of specific dressings. Factors considered included: the site, size and nature of the wound; the condition of the wound bed (clean or sloughy); exudates from the wound (amount and nature); presence of infection and/or odour; condition of surrounding skin; patient reporting pain; patient comfort; hygiene needs; patients’ lifestyle; patient’s potential for self-care (or involvement of family member).

Individual nurses’ choice of wound care products appeared to be based on their knowledge of local guidance, represented through formularies and protocols, whose recommendations were regarded as evidence based. Tissue viability nurses reported that their involvement in compilation and development of these resources for use by other nurses influenced their own choice of dressings. In addition, all of the nurses interviewed valued being able to draw on colleagues’ expertise to support decision-making.

*‘our protocol is 2 weeks of a silver dressing if there is any infection and then re-assess it…’* (DN2)

*‘I think doing the wound care infection guidelines had helped me with my decision making…we’ve got an algorithm now in the community…it does give the nurses a bit of an idea when they should be actioning antibiotics and when not and when to put antimicrobials on…’* (TVN2)

*‘I’ll start off with our First Choice dressing list first, because they are usually the things that work and if they’re not doing their job, I’ll ask my colleagues…*’ (TVN2)

Nurses acknowledged that one of the functions of local guidance was to contain costs but indicated that patients’ needs would be carefully considered when choosing between different treatment options, and the cheapest would not automatically be selected. Dressings not contained in the local formulary might be obtained via a doctor’s prescription.

*‘obviously there is a push for being cost-effective…however, it’s what the patient need is…Aquacel is quite a reasonably priced dressing…if we needed to use silver, that’s considerably more expensive but that wouldn’t waver us using it’* (DN1)

*‘How it works in district nursing…our initial assessment we tend to choose dressings off our formulary and we have justification products which are like your silver products, antimicrobials, that type of thing, and anything other than that usually gets prescribed via the consultant or the GP’* (DN2)

Dressings described as frequently used included Aquacel (to control exudate); Aquacel ribbon (to pack a pilonidal sinus related wound); charcoal dressing (to control odour); dressings that debride the wound; and silver dressings for wounds that are not healing and appear to be sub-clinically infected. Aquacel dressing (and Aquacel ribbon) were frequently cited as nurses’ first choice for packing cavity wounds, though some nurses linked their use with over-granulation. Nurses reported that patients whose open surgical wounds were being packed after treatment for pilonidal sinus experienced less pain when their cavity wound was packed with Aquacel ribbon rather than gauze.

*Nurses’ perceptions of Negative Pressure Wound Therapy*

Six of the seven nurses viewed NPWT as effective in the treatment and management of open surgical wounds. Patients who might otherwise have to remain in hospital for twice daily dressing changes were said to go home to the care of the district nursing service, and require less dressing changes with NPWT than with ‘traditional’ dressings. Other perceived benefits of NPWT related to management of wound exudate, and the good ‘seal’ on the wound that might be attained, preventing leakage, and promotion of the growth of granulation tissue.

*‘for a lot of patients NPWT is very effective… rapid growth* [of granulation tissue], *excellent for managing exudate…gets them out of hospital quicker, only needs doing twice or 3 times per week, whereas if they weren’t on VAC it would probably be at least twice a day and they would still be in hospital…’* (TVN1)

According to the senior ward sister (SS) in study SITE-B, acute care nurses often have limited knowledge of using NPWT, at least on the ward where she works, and they look to the hospital-based tissue viability nurse for support.

*‘there’s maybe just a small number of us who can do it…tissue viability will come and support you…’* (SS)

This senior hospital-based nurse also expressed the view that district/community nurses have wide experience of the use of NPWT, an opinion that was at odds with the views of the tissue viability nurses in study SITE-A, who commented that these nurses often need guidance in application of NPWT from tissue viability nurses and/or from patients who have become expert in its use.

*‘the district nurses know what they are doing…there’s a lot of training for them in the community and they’re very up on how to look after and care for them.’* (SS, SITE-B)

*‘some [patients] have been in hospital with it* [NPWT] *for quite a long time and manage the VAC-pac themselves and almost direct the nurses on how to do it because they’ve watched 5, 6 10 nurses on the ward and they say, ‘no, you do it this way’’* (TVN3, SITE-A)

Tissue viability nurse 1 described working alongside district and community nurses when carrying out assessments of wounds regarded as complex and/or non-healing, to improve their knowledge of managing these wounds, and to provide ‘hands-on’ instruction in application of NPWT.

*‘if I’ve got a patient on VAC…I might need to re-teach the nurses to cut the foam…all my visits, where possible are done jointly with the [patient’s] primary nurse, so that there is always a discussion, a question and answer session’* (TVN1)

Only one of the nurses (tissue viability nurse 3), expressed strong reservations about NPWT as a universally beneficial treatment for patients with (usually dehisced abdominal) open surgical wounds. This nurse’s experience of using ‘VAC’ did not concur with its promotion as *‘the answer to everything’* in the management of difficult to heal wounds, and she felt that it was sometimes *‘oversold’* to patients by hospital staff, raising unrealistic expectations for wound healing. In her experience, longer-term healing of an open surgical wound could be impeded by the use of NPWT compared to conventional dressings. Tissue viability nurse 3 suggested that the use of foam (rather than gauze) in the application of NPWT could be detrimental to healing through the formation of less *‘robust’* granulation tissue.

*‘things like topical negative pressure has become like the answer to everything, but it’s not…I’ve found that it is frustrating for patients because they’re told it will completely heal the wound and it only heals it part of the way and then when we take it off they’re quite anxious …’* (TVN3)

*‘I think surgical wounds seem to do slightly better using the gauze system… as opposed to the foam…I have noticed that the foam tends to cause the granulation tissue to not be as robust so I think that in a way tends to slow healing down…’* (TVN3)

Like the surgeons, tissue viability nurse 3 also referred to a need for caution when considering use of NPWT in patients who might be at risk of developing a fistula following bowel surgery and/or patients with active cancer.

*‘with using the topical negative pressure, you’ve got to consider, have they got an active cancer because the actual process* [of using NPWT] *is encouraging the cancer cells to grow…with perforated bowels for rectal and bowel tumours, for that type of surgery, you end up with a risk of fistula…there is evidence of an increased risk of fistula…’* (TVN3)

Disadvantages of NPWT from a patient perspective mentioned by nurses were anxiety and disruption to sleep caused by the alarm ‘bleeping’, and restrictions to mobility, even with “portable” devices, as physically frail patients could find it difficult to manage the equipment. Tissue viability nurse 1 suggested that patients’ tolerance for NPWT can be short-lived. Patients who are happy to be ‘wired up’ to the *‘VAC-pac’* in the immediate post-operative period can become frustrated by the restrictions imposed by the equipment when they wish to increase their level of activity and irritated by the various noises it makes.

*‘the pump alarms, they get disturbed sleep or they can be quite noisy…some of the pumps you can hear them sucking’*  (TVN1)

*‘there are some patients that come out of hospital very quick* *and maybe quite elderly and frail and have had minimal education about how to use the pump…they haven’t got a clue and are quite frightened of that pump, particularly when it alarms and it’s bleeping at 3 in the morning…’*  (TVN1)

*‘They’re really happy when they come home* *because the VAC is doing the job and it’s got them home, but give them 2 to 3 weeks as their mobility improves and general health, they start to do other things it becomes a bit of a nuisance…they’re always carrying this pump around…’* (TVN1)

**DISCUSSION**

The main types of open surgical wounds managed by surgeons and nurses were open abdominal cavity wounds (laparostomy and dehiscence); wounds relating to treatment for pilonidal sinus; large, open wounds on the feet of patients with diabetes; and axilla and groin wounds. The most favoured treatment option for these types of open cavity wounds was negative pressure wound therapy, due to the good dressing seal that can be obtained, and the potential for reduced likelihood of infection, resulting in perceived speedier healing of the wound. Although a lack of robust evidence to support the use of NPWT was mentioned by four of the five surgeon respondents, notably in relation to cost-effectiveness, this was not perceived as particularly problematic when weighed against personal positive experiences of NPWT, its increasing use in surgical practice, and perceived benefits for patients. Surgeons attributed perceived cost-effectiveness of NPWT to their experiences of earlier discharge of patients from hospital than can be achieved with use of conventional dressings, reduction in the need for dressing changes by community-based nurses, resulting in decreased workload and accrual of savings to the NHS, and patients being able to return to paid employment more quickly. Surgeons did not refer to the varying levels of expertise or the need for widespread training amongst community nurses in the application of NPWT that were highlighted as problematic by tissue viability nurses. A major drawback to use of NPWT (cited mainly by surgeons) was its potential to cause intestinal fistula when used in an abdominal cavity wound, for example, following laparostomy, where the gut and other intra-peritoneal organs may be exposed. Some nurse participants expressed reservations concerning use of foam rather than gauze in the application of NPWT, gauze viewed as less likely to cause pain to patients and more conducive to healing. Nurses and surgeons shared the view that NPWT is not a suitable treatment for the very frail (who could find the equipment difficult to manage) and/or for patients with cognitive impairment.

Evidence to support the widespread use of NPWT in routine clinical practice is currently lacking (Dumville et al., 2015) and there is considerable disagreement over whether it offers significant clinical benefit or is cost effective. Early research by Argenta (Argenta and Morykwas,1997) supporting the use of NPWT (mentioned by a study participant) was a case series of 300 patients with chronic and acute wounds, of which most were reported to respond positively to NPWT. This research, which was non-comparative, was contemporaneous with additional research published by Argenta and colleagues in the same year reporting data on the use of NPWT animals (swine models) (Morykwas et al.,1997).

Barker and Carlson (2011) have suggested that *‘investment in the commercial development and market application of TNP (topical negative pressure/negative pressure wound therapy) seems to have considerably outstripped investment in the understanding of the basic science which underpins its potential efficacy, or robust assessment of its effectiveness in clinical trials.’*  In our study, we were struck by clinicians’ own inferences regarding the cost-effectiveness of NPWT based on perceived shorter length of hospital stay and more rapid healing. These strong beliefs are not supported by hard research evidence; a systematic review published around the time of these interviews identified only two studies involving 69 participants in total and concluded an absence of evidence for NPWT in the treatment of open surgical wounds (Dumville et al., 2015). Dumville et al. (2015) have highlighted the need for more robust evidence to support increasing use of NPWT, based on randomised controlled trials that are adequately powered to detect treatment effects of a specified size (if they exist), and where sample size calculations have been carried out to estimate the number of people that should be recruited to a trial. Furthermore, trial follow up needs to be sufficiently long to allow important outcome events, such as complete wound healing, to occur. The two trials included in Dumville et al.’s (2015) review were small, and the follow up period of the study was uncertain, resulting in a limited evidence base, with further problems in quality caused by the reporting of limited outcomes. In summary, while there are increasing numbers of publications promoting the use of NPWT (Nie and Yue, 2016; Oreja et al., 2017; Othman, 2012), high level patient-oriented scientific evidence has lagged behind and more rigorous evaluation is needed, in the form of randomised controlled trials with economic evaluation. In the meantime, the National Institute of Health Care and Excellence (NICE, 2013) has issued interventional procedures guidance on NPWT as a management option for the open abdomen (where the gut and intraperitoneal organs are exposed), stating that current evidence concerning the use of NPWT for management of the open abdomen is sufficient to support its use, while pointing to the need for further research, specifically in relation to efficacy outcomes such as impact on wound care and healing rates and duration of hospital stay.

Surgeons interviewed for our study suggested that patient acceptability of NPWT is high, due to reduced requirement for dressing changes, and because it may allow patients to be more physically and socially active. However, nurses mentioned patients feeling constricted in their movement and activities due to being attached to the NPWT equipment; they also reported sleep disturbance amongst patients because of the ‘bleeping’ noises. Specialist tissue viability nurses in our study highlighted problems relating to the difficulty of removing the foam component of NPWT because of granulation tissue that had anchored it to the wound, noting that this could be painful for patients, a problem highlighted elsewhere (Upton and Andrews, 2015; Vuolo 2009). They also referred to a general lack of training amongst community nurses in the application of NWPT. These study findings reflect results from a review of 25 studies relating to patients’ experiences of having NPWT (Upton, 2013) that indicate that certain aspects of NPWT may impact negatively on patients’ wellbeing. The authors of the review report that the type of dressing used during treatment (foam or gauze) can have a significant effect on patients’ experiences of pain, and that patients may suffer raised anxiety, due to patient and nurses’ unfamiliarity with the equipment (Upton et al., 2013). Findings from our interview study with 20 patients (McCaughan et al, 2018) exploring patient perspectives of living with an open surgical wound, align with these results. A majority (11/20) of the patients we interviewed indicated that dressing changes were painful when sponge or foam was used, and exhibited anxiety about possible introduction of infection if district nurses seemed uncertain of how to apply NPWT. Patients in our study also reported being disinclined to mobilize outside the home with NPWT in situ, because the equipment is cumbersome, making it difficult to move around, and/or because they felt embarrassed due to its appearance, perceived associated smell, or associated noise from the alarm. Janssen et al.’s review study (2016) also identified increased patient anxiety during the early stage of treatment with NPWT, attributed to non-portability of the device.

Surgeons displayed varying levels of knowledge relating to the plethora of wound care products and dressings available on the market and suggested that different wound dressings come into and go out of ‘fashion’; selection of dressings for surgical wounds was largely devolved to nurses, considered to have greater knowledge of benefits of specific wound products. Acquacel was frequently cited as the preferred dressing for open surgical wounds as it is highly absorbent and can be left in place for up to seven days, thus requiring fewer dressing changes than some alternative products. However, there appeared to be a lack of consistency concerning selection of wound products for open surgical wounds amongst participants in our study, which is not surprising, as recent guidance from the National Institute for Health and Care Excellence (<https://www.nice.org.uk/advice/esmpb2/chapter/Key-points-from-the-evidence>) highlights the lack of evidence concerning the effects of dressings in healing of chronic wounds, and emphasises the need for further research to inform clinical practice. Little is known about how nurses and surgeons and nurses currently make decisions concerning selection of available wound products, for primary or more complex wounds (Rooshenas et al., 2016), and our study findings provide valuable insights into this under-researched area of clinical practice.

As far as we are aware, this is the first study specifically designed to investigate in parallel surgeons’ and nurses’ views about the management and treatment of open surgical wounds healing by secondary intention. Although data collection took place in 2012, we have been unable to identify any similar interview study that includes surgeons’ perspectives, and nor has there been any randomised controlled trial of NPWT in management of open surgical wounds since our data were collected. Findings from our study therefore lay the groundwork for further research into this important aspect of healthcare about which so little is known. We purposively selected clinicians working in different settings and specialities in order to investigate a range of views and approaches to the management of open surgical wounds in different patient populations. We regarded the clinicians comprising the study sample as ‘key informants’ due to their close involvement in the day-to-day, ‘hands-on’ care delivery to patients with open surgical wounds, well-positioned to identify and discuss relevant management and treatment issues. Particularity, rather than generalizability, is recognised as the hallmark of good qualitative research (Creswell, 2009), and our detailed findings provide nuanced insights into an important area of clinical practice almost wholly devoid of investigation. Nonetheless, the relatively small sample size has implications for extrapolation of findings, though we would argue that our study sensitizes readers to new ways of thinking which constitute a form of *‘conceptual generalisability’* (Green and Thorogood, 2018, p309).

**CONCLUSIONS AND IMPLICATIONS**

Clinicians in our study favoured the use of negative pressure wound therapy and viewed it as a cost-effective option for the management and treatment of open surgical wounds, except for patients for whom intestinal fistula might be a risk, and patients who might find the equipment difficult to manage, due to frailty or cognitive impairment. Study participants reported growing use of NPWT across different patient populations, with different types of open surgical wounds, based on clinicians’ own experiences and recommendations from commercial companies.

Despite its increasingly widespread use, evidence to support the cost-effectiveness of negative pressure wound therapy is currently lacking (Barker and Carlson, 2011; Dumville et al., 2015; Trujillo-Martin et al., 2011; Ubbink et al., 2008). Findings from our study highlight the urgent need for full, independent appraisal of NPWT, in hospital and community settings, in the form of large randomised controlled trials incorporating full economic evaluation. Results from rigorous studies, including systematic reviews (NICE, 2016; Chetter et al., *Surgical wounds healing by secondary intention: characterising and quantifying the problem, identifying effective treatments, and assessing the feasibility of conducting a randomised controlled trial of negative pressure wound therapy versus usual care,* *in preparation*) also indicate that there is insufficient good quality evidence to assist clinicians in making choices between different types of dressings for use in the management and treatment of open surgical wounds and further research is required.

Making an informed decision concerning selection of the ‘best’ dressing for open surgical wounds is hampered by the lack of independent, robust evidence regarding cost-effectiveness of the many wound care products on the market (Dumville et al., 2015; Norman et al., 2016; Vermeulen et al., 2004). Nurses factored in clinical experience, recommendations from local wound care formularies and protocols, patient acceptability and cost to their decision making. Until further evidence becomes available, this appears to be a reasonable strategy.

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**Appendix 1 Topic Guidefor use with surgeons and nurses**

* **Could you please tell me about your clinical role in the care of patients with surgical wounds that are difficult or slow to heal.**
* **What are your experiences of caring for patients with wounds which are difficult or slow to heal?**

*(Probe: approximately how often do you see patients with surgical wounds which are slow to heal? why do you think wounds don’t heal or heal very slowly in some patients? what are the main issues for you as a clinician? who looks after these patients after discharge from hospital?)*

* **What are the aspects of wound management that need to be considered when choosing treatment options for patients with hard to heal surgical wounds?**

*(Probe: management of pain and exudates; frequency of dressing changes; availability of clinical staff with appropriate skills and training; patient needs and convenience)*

* **What would you consider to be the desirable performance characteristics of treatment options?**

*(Probe: symptom management; wound cleaning/debridement; signs of healing and sustainability; patient acceptability; cost-effectiveness)*

* **What kinds of outcomes might be achieved for patients with surgical wounds that are difficult to heal, and how might these vary for different types of wounds and patient subgroups?**
* **From your perspective as a health care professional, what are the challenges of looking after a patient with a surgical wound that is difficult to heal?**

*(Probe: patient adherence to treatment; dealing with patients’ feelings about their wound; own feelings as a health care professional when wound is not healing)*

* **Are there any other aspects that have not already been discussed or that you would like to expand on?**

**Figure 1 Detailed description of wound assessment (General Surgeon 1)**

*‘I don’t formally measure it, so I don’t get a ruler out, I could do I suppose, but more often than not people will tell me because they’ve been keeping an eye on it, and they will know whether it’s bigger or smaller or the same size, so I don’t feel the need to measure it. What I’m particularly interested in is a number of things; is there any infection, so if there is, I need to set about draining that, that’s one of the most important things and that can occur if the skin heals over the top before it’s healed below. So if it shows signs of that, then I will open it out again and break down any healed skin, if there’s a cavity underneath it, deliberately do that to let any infection out. I’m looking for granulation tissue at the base of the wound and round the edges and I’m always pleased when I see lots of that, it’s healthy. I’m looking at the wound edges to see whether indeed they look healthy and pink and whether they’re active really, active and healing. I think those are the things I look for. Occasionally it would look as though the wound has actually healed apart from a tiny little spot and those are the ones that we’ve got to be very careful about because it’s those where it’s healed over the top first and there’s a cavity underneath, so I always give it a good prod and poke with something. Now, we used to have a thing called a sinus probe and they’re few and far between these days, so I use a thing called a microbiology swab which has got like a very long Q-tip and it’s used for taking swabs and then sending off to the lab and I use that to open out holes and make them bigger, it works beautifully, seeing as we’ve got rid of sinus probes. I think that’s all I look for really. I look at the patient, of course, to see whether they look better than the last time I saw them and make sure, to see if they look nourished, see if they look fitter, all of those things which would indicate, of course, that they’ve got the resource to heal their wound. If they’re looking dreadful then they’re not going to heal their wound no matter how small it is…over-granulation, that is something to look out for in wounds, it’s usually not too much of a problem but it does slow down healing…’* (General Surgeon 1)

**Figure 2 Nurses’ views of factors implicated in slow healing of open surgical wounds**

*‘complex patient, probably had some complex bowel surgery, perhaps perforated bowel, history of infection, undernourished, lots of other things that have gone on with that type of surgery…been very unwell, very acutely unwell, unplanned, and for whatever reason, has gone on not to heal.’* (TVN1)

*‘if they’ve got poor prognosis from the cancer point of view…or if they’ve had multiple operations…’* (TVN3)

‘*colorectal fistulas are very debilitating….the bowel breaks down and the gut breaks down and they have to have TPN [total parenteral nutrition]…they take months to heal.’* (SS)

‘*you do tend to see the diabetic patients and you know that they are going to be slower to heal…if their sugar levels are up you know that the healing is not going to be quite as brilliant.’* (DN1)

*‘a lot of it is due to patients with co-morbidities or who’ve had previous surgery…’* (DN2)

*‘we’ve had one patient and the wound does heal up and then it sort of pops again…it’s healing but it’s not healing underneath, so there is something underlying…’* (CN)

*‘I think people that are overweight, are going to run into problems…it’s those wounds that don’t heal very well.’* (DN1)

*‘you find with the abdos, if they’ve had a dehisced hernia repair and they’ve taken the mesh out because it’s been infected, they don’t seem to have a base of granulation tissue…it’s just body cavity that you see…it’s not going to knit together…so they are left with this hole basically…sometimes they do eventually heal, but it’s a long haul…’* (TVN2)

*‘We have had quite a few wounds with infection, infected surgical wounds, whereby obviously the healing process is hindered because of the infection, so it takes longer to heal…’* (DN2)

*[non-compliance] ‘there was a gentleman… he insisted on taking dressings off, fiddling about with dressings in between visits and for all the goodwill in the world, we can say to people, don’t touch it until the nurse comes but then sometimes you get there and they’ve taken it off…’*  (DN2)

**Table 1 Details of sample of surgeons and nurses**

**Surgeons**

|  |  |  |  |
| --- | --- | --- | --- |
| **ID** | **Gender** | **Study site** | **Type of surgery** |
| General Surgeon 1 (GS1) | Male | SITE-A | General surgery |
| General Surgeon 2 (GS2) | Male | SITE-B | General surgery, specialises colorectal surgery |
| Vascular Surgeon 1 (VS1) | Male | SITE-A | Vascular surgery |
| Vascular Surgeon 2 (VS2) | Male | SITE-B | Vascular surgery |
| Plastic Surgeon (PS) | Male | SITE-A | Plastic surgery |

**Nurses** (TVN: tissue viability nurse; SS: senior sister; DN: district nurse; CN: community nurse)

|  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- |
| **ID** | **Study**  **Site** | **Gender** | **Qualifications** | **Role** | **Specialist training** |
| TVN1 | SITE-A | Female | RN; BA (Hons); specialist practitioner – district nursing; nurse prescriber | Tissue Viability Nurse Specialist  *(assessment; care planning; evaluation; prescribing; liaison with surgeons; supporting nurses and patients)* | Diploma in wound care and ulcer management |
| TVN2 | SITE-A | Female | RN; BSc (Hons); diploma in nursing; nurse prescriber. | Clinical/Tissue Viability Nurse Specialist  *(education; training; support for colleagues)* | None |
| TVN3 | SITE-A | Female | RN; BSc (Hons); district nurse; nurse prescriber | Tissue Viability Nurse Specialist  *(assessment of complex surgical wounds; instigation and monitoring of negative pressure wound therapy)* | None |
| SS | SITE-B | Female | RN | Senior Sister, acute general surgery ward with patients with abscess/fistulas /wound dehiscence | Training from ‘VAC’ therapist employed by the hospital trust and from commercial representatives |
| DN1 | SITE-B | Female | RN; district nurse | Treatment Room Nurse | Study days; experience; leg ulcer management course |
| DN2 | SITE-B | Female | RN; district nurse | District Nurse;  Link Nurse for tissue viability | Study sessions related to Link Nurse role |
| CN | SITE-B | Female | RN | Community staff nurse (case load includes wound care) | Course on wound management |

## Appendix 9 - Patient Topic Guide for Qualitative Interviews

* Ask for brief details about age, occupation, ethnicity, partner, children, etcetera, to frame the interview
* Can you tell me a little bit about yourself and how you came to have this wound? *(explore important aspects further)*
* How has this wound impacted on your daily life?
* *(from answer to above question)* What factors have affected you most and why? *(explore important aspects further)*
* What effect has the wound had on your relationship with your immediate family/ partner/ friends?
* How do you feel about the treatment you have received in connection with your wound? How could this have been improved?
* How do you feel about the interactions you have had with health care professionals? How could this have been improved?
* Any other aspects that have not already been discussed or you would like to expand upon?

## Appendix 10 – Health Care Professionals Topic Guide for Qualitative Interviews

**Topic Guide**

* **Could you please tell me about your clinical role in the care of patients with surgical wounds that are difficult or slow to heal.**
* **What are your experiences of caring for patients with wounds which are difficult or slow to heal?**

*(Probe: approximately how often do you see patients with surgical wounds which are slow to heal? why do you think wounds don’t heal or heal very slowly in some patients? what are the main issues for you as a clinician? who looks after these patients after discharge from hospital?)*

* **What are the aspects of wound management that need to be considered when choosing treatment options for patients with hard to heal surgical wounds?**

*(Probe: management of pain and exudates; frequency of dressing changes; availability of clinical staff with appropriate skills and training; patient needs and convenience)*

* **What would you consider to be the desirable performance characteristics of treatment options?**

*(Probe: symptom management; wound cleaning/debridement; signs of healing and sustainability; patient acceptability; cost-effectiveness)*

* **What kinds of outcomes might be achieved for patients with surgical wounds that are difficult to heal, and how might these vary for different types of wounds and patient subgroups?**
* **From your perspective as a health care professional, what are the challenges of looking after a patient with a surgical wound that is difficult to heal?**

*(Probe: patient adherence to treatment; dealing with patients’ feelings about their wound; own feelings as a health care professional when wound is not healing).*

* **Are there any other aspects that have not already been discussed or that you would like to expand on?**

## Appendix 11 – Analysis of Data using Framework Approach

**Familiarization with data**

From reading and re-reading transcripts

**Identifying codes and themes**

Comparison of individual accounts, searching for themes that were common or recurring in the data set. Identification of similarities and differences between individual narratives. Coding scheme developed based on from list of key themes. Coding list generated and modified where appropriate (combining codes, new codes added)

**Coding the data**

Coding scheme applied to all transcripts in the dataset, with further modification where necessary, to accommodate full range of perspectives and experiences

**Charting**

Use of ‘Excel’ spreadsheet to re-arrange segments of data within themes (arranged horizontally), and to allow for comparison between individual cases (arranged vertically), so that cross-comparison of individual accounts could be easily carried out

**Mapping and Interpretation**

Exploration of relationships between codes and themes in the data and interpretation of significance of their meaning. Identification of emerging conceptual categories. Refinement of emerging conceptual categories, in conjunction with literature

**Illustration of thematic analysis of the data set**

**Recurrent themes identified to constitute framework for analysis,** including:

Initial reactions to the open surgical wound healing by secondary intention

Perceptions of wound healing

Expressions of hope for healing

Impact of wound symptoms on daily life

Psychosocial impacts of open surgical wound and mental health

Driving and transport

Employment, finances, state benefits

Impact of open surgical wound on relationships with others and social activities

Views of different treatments for open surgical wounds

Views of NHS service provision related to care of the open surgical wound, including shortfalls in care delivery

**Systematic application of coding framework to transcriptions, and identification of ‘negative’ cases**

**Development of ‘higher level’ themes**, for example: patients’ perceptions of changing family roles; shifting sense of self/ modified self-image; coping/not coping with feelings of social isolation

**Interpretation of higher level themes,** linked to theoretical perspectives in the literature, for example: concepts of ‘biographical disruption’ (Bury, 1982) and ‘loss of self’ (Charmaz, 1983)

## Appendix 12 – Pilot, feasibility randomised controlled trial protocol paper

Arundel C., Buckley H., Clarke E., Cullum N., Dixon S., Dumville J., et al. Negative pressure wound therapy versus usual care for Surgical Wounds Healing by Secondary Intention (SWHSI Trial): study protocol for a randomised controlled pilot trial. Trials. 2016, 17:535. Available at: <https://trialsjournal.biomedcentral.com/articles/10.1186/s13063-016-1661-1>

## Appendix 13 – Pilot, feasibility randomised controlled trial: results paper

Arundel C., Fairhurst C., Corbacho-Martin B., Buckley H., Clarke E., Cullum N., et al. Pilot feasibility randomized clinical trial of negative pressure wound therapy versus usual care in patients with surgical wounds healing by secondary intention. BJS Open. 2018. Available at: https://onlinelibrary.wiley.com/doi/abs/10.1002/bjs5.49

## Appendix 14 - Exploring experiences of nurse participation in conducting a randomised controlled trial of wound care treatments

**Introduction**

Randomised controlled trials (RCTs), the ‘gold standard’ research method for evaluation of the effectiveness of interventions [1], are frequently conducted in busy clinical settings and often involve a substantial recruitment and follow up durations [2]. The concerted involvement of both participants and healthcare professionals throughout the lifetime of a trial is therefore critical to their successful conduct and completion [3].

Given the substantial involvement required for a RCT, dedicated research nurses may be involved in trial conduct, but are often seen to facilitate only participant recruitment and data collection [4]. Their involvement however, goes far beyond this. By virtue of participation in study activities, research nurses can become actively involved in the research process [5] however, this involvement is often overlooked and the experiences of research nurses in RCT conduct and examples of best practice are rarely shared for the benefit of others [6] [7]. There is however support for the sharing of experiences to improve research conduct, for example peer review of researcher – patient discussions regarding trials has been identified as being beneficial in improving both communication about trials and recruitment activity [8].

Literature regarding RCT participation, from the perspective of healthcare professionals (e.g. consultants, nurses), has frequently focused specifically upon experiences in relation to barriers and facilitators for recruitment [3][9][10][11] and therefore does not encompass experiences of trial conduct as a whole. Equally, input of clinicians, nurses and other healthcare professionals, have often been combined into a single group (‘clinicians’) [3][9] making it difficult to identify the individual perspectives of these distinct groups. Some limited data is available from nurses involved in research in secondary care settings [12] [13], however the majority of data available in relation to nurse experiences of participation in RCTs, has been derived primarily from community or primary care RCT settings [5], [14] [15], where use of research nurses in clinical trials is less prevalent compared to trials conducted in acute care settings. Irrespective, the findings of Newall et al (2009) and Potter et al (2009) undoubtedly translate across research settings [5] [14]. Newall et al (2009) identified that inclusion of nurses in planning RCTs, including development of the data collection methods and study processes, is important to improve RCT conduct, as was fostering inclusiveness of all research staff by the wider trial management team [5]. Increasing understanding of research and associated methodologies, amongst the wider nursing community, is also important to enhance both participation in research studies, and the evidence base for best practice in the conduct of RCTs [5]. Despite these translatable findings from the perspective of research nurses, experiences of research participation may not yet have been fully identified within these studies, given that there is limited available data derived from research or clinical nurses conducting RCTs in busy secondary care settings or in multi-centre RCTs conducting research across a variety of site settings (e.g. community, primary and acute care settings).

**Methods**

Aims

Given the paucity of literature of experiences of research participation from the perspective of research nurses, we sought to evaluate the research nurse experiences (both in community and secondary care settings) of participation in the National Institute for Health Research Programme Grant funded pilot, feasibility trial; Surgical Wounds Healing by Secondary Intention (SWHSI). The main objectives were to better understand issues highlighted throughout study implementation, to identify improvements required to enable nurses to support a larger RCT in this area and subsequently to extend the evidence base for effective involvement and best practice in research trials.

In Context

Increasingly negative pressure wound therapy (NPWT) is used as a treatment for surgical wounds healing by secondary intention (SWHSI). There is, however, little research evidence to support the clinical and cost effectiveness of this device. The Surgical Wounds Healing by Secondary Intention (SWHSI) trial, was a two-arm pilot, feasibility randomised controlled trial (RCT) which aimed to assess the methods for and feasibility of conducting a larger, definitive study of NPWT for SWHSI. Patients at three NHS trusts, with a SWHSI suitable for treatment with NPWT or wound dressings were randomised to receive NPWT or usual care (no NPWT) [16].

Data Collection

Research nurses were asked to complete a Likert scale questionnaire (Appendix 1) at the end of the SWHSI pilot, feasibility trial, to assess their experiences of involvement in the study. The results from this questionnaire demonstrated the need for more in- depth interviews as participants’ answers were widely varied for the same question topic, ranging from strongly agree to strongly disagree

In-depth interviews were therefore conducted using a semi-structured topic guide (Appendix 2), developed with input from the SWHSI programme team. This was to ensure that any salient topics highlighted throughout previous team meeting minutes (through which research nurses gave informal feedback), and in the questionnaire responses were covered. The in-depth interviews also provided an opportunity for the nurses to discuss any other aspects of the study and their involvement, not previously considered. Where nurses highlighted a particular issue, they were invited to make suggested improvements. Interviews averaged one hour in duration and each was audio-taped.

Ethical approval

The SWHSI study received research ethics (REC reference: 11/YH/0313) and governance approval. Oral consent was obtained prior to the interviews and the research nurses given assurances that their responses would be anonymised.

Analysis

Questionnaire data was summarised using descriptive statistics to identify the spread of responses provided by research nurses, and to identify key areas to explore during the qualitative interviews.

Interviews were fully transcribed and analysed for thematic content [17]. Data were reviewed for significant remarks pertaining to themes originally identified. Any new information gathered during individual discussions was subsequently included as additional or sub-themes. Text was independently coded to identify specific feedback that corresponded to the themes. Individual participants and their responses were pseudonymised to account for variation between the types of intervention site. Pseudonymisation was used, rather than complete anonymisation, as it was important that the study sites (community or acute) were reflected in the analysis to identify appropriate improvements for inclusion in future studies of this type. A separate document was created to record specific suggestions in relation to the content of trial documentation and formatting.

**Results**

Eight nurses responded to the Likert scale questionnaire, of which six were from acute and two were from community NHS Trust settings across the two intervention sites (Leeds and Hull).

Overall, most of the nurses (i.e. greater than 50% of respondents) found the eligibility criteria to be clear, the frequency and completion of assessments and questionnaires to be manageable and straight forward, the study processes to be clear, that the questions and forms included relevant questions and answers and that support for the study was sufficient. Despite the overall positive response, the results, as presented in Table 1, however identified that there was a range of opinions amongst the research nurses with regards key elements of the study design and conduct.

Table 1: Research Nurse Responses to Likert Questionnaire

|  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- |
|  | **Strongly agree** | **Agree** | **Neither disagree or agree** | **Disagree** | **Strongly disagree** |
| **Based on the information given before commencing the study, taking part has been what I expected** | N=0  (0.0%) | N=3  (37.5%) | N=2  (25.0%) | N=3  (37.5%) | N=0  (0.0%) |
| **I found the level of training for the study to be appropriate** | N=0  (0.0%) | N=3  (37.5%) | N=5  (62.5%) | N=0  (0.0%) | N=0  (0.0%) |
| **I found the eligibility criteria to be clear** | N=0  (0.0%) | N=5  (62.5%) | N=0  (0.0%) | N=2  (25.0%) | N=1  (12.5%) |
| **I found it easy to identify potential participants for this study** | N=1  (12.5%) | N=2  (25.0%) | N=2  (25.0%) | N=0  (0.0%) | N=3  (37.5%) |
| **I found the Pre Trial Screening form easy to complete** | N=2  (25.0%) | N=4  (50.0%) | N=0  (0.0%) | N=2  (25.0%) | N=0  (0.0%) |
| **I found the trial processes clear and easy to understand** | N=1  (12.5%) | N=3  (37.5%) | N=2  (25.0%) | N=2  (25.0%) | N=0  (0.0%) |
| **I found the randomisation process to be straight forward** | N=3  (37.5%) | N=1  (12.5%) | N=3  (37.5%) | N=1  (12.5%) | N=0  (0.0%) |
| **I found the frequency of clinical**  **assessments to be manageable** | N=1  (12.5%) | N=5  (62.5%) | N=1  (12.5%) | N=0  (0.0%) | N=1  (12.5%) |
| **I found completing the clinical assessments in this study to be straight forward** | N=1  (12.5%) | N=4  (50.0%) | N=0  (0.0%) | N=3  (37.5%) | N=0  (0.0%) |
| **I found the number of questionnaires and forms in this study to be manageable** | N=1  (12.5%) | N=5  (62.5%) | N=2  (25.0%) | N=0  (0.0%) | N=0  (0.0%) |
| **I found completing the questionnaires and forms in this study to be straight-forward** | N=1  (12.5%) | N=3  (37.5%) | N=2  (25.0%) | N=2  (25.0%) | N=0  (0.0%) |
| **The questionnaires and forms asked all relevant questions** | N=0  (0.0%) | N=4  (50.0%) | N=4  (50.0%) | N=0  (0.0%) | N=0  (0.0%) |
| **The questionnaires and forms included all relevant answers** | N=0  (0.0%) | N=5  (62.5%) | N=3  (37.5%) | N=0  (0.0%) | N=0  (0.0%) |
| **I found the level of support for this study to be appropriate** | N=3  (37.5%) | N=2  (25.0%) | N=2  (25.0%) | N=1  (12.5%) | N=0  (0.0%) |

All eight nurses were then interviewed to further explore their responses, and comments provided as part of the questionnaire. Interviews were completed face to face (n=5) or by telephone (n=3). Five key themes emerged through these interviews: 1) trial documentation; 2) screening and recruitment; 3) visit management; 4) communication and engagement; 5) safety and training

**1) Trial Documentation**

Overall trial documentation was well received well by the nurses and was found to be straightforward to complete, with similarities to other studies and previous research experiences that the nurses had. The documentation however received conflicting opinions with regards length; some nurses described the documentation as “too lengthy” whilst others considered it “about the right amount”. The time spent to obtain all required information was an issue, especially for the nurses based in the community, as certain information was only available within the acute Trusts notes, which meant that the nurses spent a lot of time chasing up this information.

One of the biggest issues perceived by the nurses was the terminology used in study documentation. The patient information leaflet was queried for potential bias, despite prior patient review.

“…*when I was reading that first time round I thought it was horrendously VAC centric and it made it sound like please don’t be disappointed if you’re not chosen to have VAC*”.

In addition, there was confusion over the inclusion/exclusion criteria and this lead to some nurses believing that the original protocol was altered which lead to them feeling undermined.

**2) Screening and recruitment**

The process of identifying potential participants varied across the sites. The most successful identification, screening and recruitment approach was consultant led recommendations.

*“I guess if it was consultant surgeon led it would be far easier to then actually recruit people because those are the guys actually doing the surgery whereas we’re just going in at the end”.*

Arrangements at one study site meant nurses were more able to screen potential participants at the pre-op stage and so were more successful in recruiting, possibly because of the direct involvement of the Principal Investigator (PI) and surgical colleagues introducing the study to patients.

Across both sites, it was found that some surgical teams and consultants were reluctant to allow recruitment of their patients to the study as there was a chance the patient would be randomised onto the conventional dressing arm rather than topical negative pressure.

*“….the surgeons like colorectal they were just not happy for the patients to go in, they would be like I'm not happy for you to randomise this patient and not get negative pressure”.*

Some nurses found that the consultant had a preferred management plan for the wound and that if the patient was randomised onto the trial then this may contradict the plan.

Few potential participants were recommended by the community Trust staff, and across all settings the research nurses spent a large proportion of their time trying to raise the profile of the trial by phoning and emailing Trust staff as well as visiting clinical areas which surprised the experienced research nurses.

*“…I remember one main issue was a lot of the consultants in the hospital…they had specific plans in place for their patients and a lot of them didn't want us to recruit those patients because they wanted a specific dressing to be in place”.*

*“….the screening is a lot more intensive then I initially anticipated…I thought it would be quite easy to find some suitable and I really struggled to be honest”.*

Surprisingly, the screening process was also affected by the time it took to accommodate and carry out the follow up visits, especially as the trial progressed and more participants were recruited, resulting in there being less time available for screening.

The research nurses found the randomisation process to be straightforward and the only issue raised was that there wasn't weekend availability.

*“…the process was fantastic, really straightforward, really easy, you'd ring up straight away get through no problem”.*

**3) Management of visits**

Research nurses across both sites found that coordinating the follow up visits to coincide with the participants regular clinic appointments was most efficient due to the ease of having a set time and reassurance that the participants would be likely to attend. By carrying out the follow up visits in clinic, the nurses were able to make the most of their time.

*“…it was easier for us to see them [patients] in the acute setting here when they came for the podiatry clinic or any other clinics here rather than going to visit them in their home”.*

*“…I did actually do a couple of joint visits at the GP surgery, I agreed to meet them at their appointment time with the practice nurse so that wasn't a problem they were fine”.*

Although this approach worked well, it wasn't always possible and in these instances the research nurses had to arrange joint home visits with the community nurses. Community nurses were willing to include the research nurses in their visits, however coordinating these visits often proved difficult.

*“…a lot of our time was wasted trying to arrange follow up visits. Sometimes you'd be a week trying to arrange an appointment to go and see a patient in the community with the district nurse. You'd get there and they'd already been or they wouldn't turn up. You would leave messages and they'd never ring you back”.*

To overcome this obstacle, the potential for the community nurses to measure and photograph the wound, on behalf of the study team, was considered but due to the inconsistency of the nurses attending the visits and the subsequent training required, it was deemed impractical to implement. The research nurses sometimes offered to undertake the whole home visit to prevent research nurse time being wasted waiting for the community nurse. Whilst this approach worked very well, it did mean that the research nurses were carrying out none research related tasks alongside data collection which they felt would not be sustainable in a larger trial; on average visits for participants randomised onto the conventional dressing arm was 15-20 minutes and 30 minutes for the topical negative pressure arm.

Time management was often an issue for the research nurses and many reported a significant amount of their time was spent coordinating and travelling to follow up visits. Due to the geographical area covered by the participating Trusts, the nurses were often spending a considerable amount of time travelling to and from visits; one nurse stated that they could be travelling up to 35 miles one way for a follow up visit.

*“…that took me an hour and a half there and then an hour and a half back, so three hours just getting there and back”.*

“*sometimes I'd be an hour just to go to a patient’s house just to take a picture and a wound grid”.*

It was suggested boundaries could be defined, for example, have allocated postcode districts or to have separate teams dedicated to either recruitment or follow up visits. The research nurses also queried whether it was possible to complete some follow up visits over the telephone rather than face to face. In some instances this was completed although face-to-face follow up remained the preferred option.

All of the research nurses reported follow up visits were too frequent and that reducing the frequency to fortnightly or even three weekly would be more suitable for the data collection. It was noted that participants also became less interested in the follow ups, especially once the wound was healed, although the protocol still required photography for three weeks post healing.

The accessibility of equipment proved a problem, especially in the community settings, although equipment did need to be borrowed across both acute and community settings.

*“…I think in a speciality area we always well stocked but in the community it's a different story”*

On one occasion a participant was unable to receive allocated negative pressure wound therapy device as there were no pumps available across the whole area. The research nurses often attempted to anticipate access issues and often knew where to go or who to ask for necessary equipment, however this did impact on the time spent to facilitate the visits. When interviewed some nurses suggested that it would be useful for equipment such as scissors or measurement probes to be included as part of an equipment pack which would reduce the amount of time spent trying to gather equipment for visits.

One nurse highlighted an important issue to be consider would be the potential for delays in the return of equipment due to changes in the procurement of dressings within local Trusts.

*“I took supplies…just in case because the district nurse might not make the appointments…we always made sure we had a spare pack of everything with us in our bags whenever we went for home visit in case the nurses over there didn't have appropriate dressings”.*

It was also highlighted that the increased cost associated with the NPWT dressings potentially influenced the GPs against prescribing them, again limiting availability.

*“…the cost came into it in inner city practices some of the GPs weren't in my opinion… weren't willing to prescribe a more absorbent dressings that's because of the cost”.*

Measurement of the wounds was routine for everyday nursing wound care, however the nurses interviewed expressed uncertainty with regards recording of the deepest point of the wound, particularly if there was tunnelling in the wound. Accurate data collection of the deepest wound point was therefore open to interpretation.

*“…you find from week to week that the deepest bit went different places, sometime it would go up in one place and then go like break down in another so it was never that reference that you'd started with”*

*“ ..wounds heal at different rates so what was once the deepest point a month later would be elsewhere…no accounting for this in the paperwork”*

*“…issue with knowing what to record as the deepest point...deepest point to wound bed of tunnelling?”*

Some nurses interviewed also suggested that that the protocol could have been more specific as to what was expected in relation to wound photographs (i.e. distance from the wound and use of the flash) in order to standardise the photography. There was a concern that some of the pictures didn’t accurately reflect the condition of the wound.

*“Sometimes the pictures don't do it [the wound] justice”.*

**4) Communication and engagement**

Engagement from Trust staff across both Leeds and Hull was inconsistent. The ward and community nurses were happy for the research nurses to screen and join them on joint visits, however there was a perception that if NPWT was involved, then some nurses would be reluctant to engage and would avoid the study.

*“…whilst trying to recruit on the ward rounds, there were a few nurses a bit obstructive”*

*“..quite a struggle really, quite a struggle. I personally found that if a patient was going to have the negative pressure on, that in certain places it was a problem”*

Potential reasons suggested for these attitudes were that some ward and community nurses may have had a lack of confidence with applying NPWT dressings, potentially due to the fact that in some areas this was devolved to tissue viability nurses, or thought it would increase the time required to complete a dressing change.

*“….I do think the barriers there are the lack of expertise with the community nurses, they weren't be keen to identify patients for a more complicated treatment when they can do standard care”*

In Leeds NPWT was already widely used for the management of SWHSI and the research nurses felt this could lead to a potential bias towards negative pressure dressings.

*“…when I overheard the ward staff saying they are very pro VAC as well…it was difficult from the off when it's been sold at all angles and we’re the only ones as the research nurses saying hang on a minute there is no evidence that's what we're trying to find out so we did feel we were the only ones saying this particular thing”.*

As reflected in the findings relating to screening and recruitment, there was also a lack of engagement from some surgical consultants. It was suggested that the PI could spend more time in the initial set up phase meeting with other consultants to explain and promote the trial at a peer level.

*“…a lot of time taken in the first few weeks was basically soothing feathers from consultants who thought that we were trying to step on their toes”.*

*“…I would like the surgeons to be on board a bit more. I think more could have been done to highlight the study prior to starting possibly with some of the district nursing bases, I could have done more in that area, but I certainly think some surgeons here could have got more”.*

Another potential improvement in communication surrounding the trial was to launch the study closer to the introduction to the Trust staff. There was a long delay between the staff being introduced to the study and actually beginning recruitment, it was felt that any potential benefit and momentum in this approach was lost by the time recruitment began.

**5) Safety and Training**

All the research nurses received training in the application of NPWT but as a result of randomisation not all the nurses had the opportunity to apply it. Some research nurses felt that there was a lack of confidence and knowledge of NPWT amongst the ward and community nurses, potentially because in some areas delivery of this treatment was devolved the tissue viability nurses. This concurred with the suggestion that many community and ward nurses felt that they used NPWT so sporadically that further training would help to increase confidence in its use.

*“…they would try and take it off and give a reason why they've taken it off so that they could manage it with normal dressings and I think that had a big impact on our results because if you had nurses that had the training to put negative pressure on and feel comfortable putting it on I think a lot of these wounds would have carried on with it”*

*“…you were asking nurses to apply negative pressure who probably hadn't seen it done in over a year”.*

Safety was also an issue that needed to be considered, especially with patient compliance with the NPWT. Many of the participants had foot wounds and this needed to be considered as it affected mobility. It was therefore suggested that the participant selection should be considered, taking into account the participants’ lifestyle.

*“ ...for example there was one patient who continued to drive with a topical negative pressure…it was alarming and he was calling them out all the time because the seal was going”*

**Discussion**

This study explores the experiences of nurse’s participation in a randomised controlled trial of wound care treatments: the SWHSI pilot, feasibility study. Questionnaire data obtained identified a diversity in opinion with regards study design and conduct. Responses were therefore further explored through semi-structured interviews, and within the five broad themes identified, three key elements; removing barriers to recruitment, time management and engagement strategies, were present across all themes as important to consider for the effective implementation and conduct of research trials.

As in previous research [3] [9] [10], removal of obstacles to recruitment was identified as a key issue in enabling study conduct and research nurse participation. Research nurses felt that trial recruitment could be improved by liaising with individual sites in the early stages of site set up to identify the best methods of recruitment for that specific site, generating appropriate strategies as required. Integral to the remove of barriers, was the need to ensure sufficient equipoise between trial treatments both at participating study sites and with individual recruiters before recruitment commences. This is particularly important to ensure engagement of clinicians who may have treatment preferences which prevent recruitment activity from being conducted [11]. This was identified as a barrier within the SWHSI pilot and feasibility RCT and similar to research by Spilsbury et al [12] it was suggested that further investment could have been made to educate colleagues (both nurses and clinicians) about the trial which may in turn have increased engagement. It was noted that the timing of this intervention was critical to ensure that it was most effective; if conducted well in advance of study green light and recruitment commencing it is possible colleagues would forget about the study subsequently reducing any equipoise generated. Promotional activity should therefore be completed immediately prior to recruitment commencing so as to give potential for best return on this investment. As suggested by Newall et al [5], continued promotional activity should continue to occur through the duration of the study to maintain continued engagement. Input from the Chief Investigator may improve study promotion, increase equipoise and so enhance recruitment, however local research nurses may be best placed to assist with local promotional activity in the initial stages of a trial. The trial management team should work carefully to ensure that this activity does not overburden the local research nurses thus impinging on recruitment activity.

To enhance study recruitment, trials would benefit from discussing proposed recruitment pathways with research nurses, prior to implementation. Follow up rate and methods should also be discussed to ensure that these are appropriate, and feasible for research nurses to manage within the trial setting. This corresponds to previous findings by Newall et al [5], who have suggested that nurses should be involved in the development of study processes, starting with a small group initially and integrating other nurses as processes develop during study preparation.

Whilst proposals made by a Chief Investigator, clinical co-applicants or a research institution are often well intentioned and empirically supported, they may not necessarily be the most practical, or efficient for research nurses to implement on ‘the ground’. In the context of the SWHSI trial, research nurses noted the benefits of utilising allied or affiliated services to help to arrange study follow up appointments. This was found to be a substantial challenge for research nurses, which corresponds to findings by Spilsbury et al [12]. Significant planning is therefore required to generate an effective network to support a study. Promotional activity can assist with generating full understanding of a study, and so increasing support for research activity within routine care settings; however study teams also need to consider how to limit the reported challenges and conflicts of balancing clinical and research activity [18]. This is applicable both to wound care and other research areas and would go some way to increasing understanding of research in the wider nursing community, as has previously been suggested by Newall et al [5], and reduce previously reported barriers to recruitment [3][9].

Research nurses play a vital role, often running the day to day management of a study and more attention should be paid to the knowledge and experience of nursing staff at the trial planning stages and throughout. Their input will help to inform protocol design and ensure appropriate support is available for the conduct of a trial. Given the paucity of literature, across medical specialties, reflecting on research nurse participation in the design and conduct of randomised controlled trials, it is important to continue to learn from the shared experiences of research nurses on the best methods of trial conduct. Utilising the experiences and knowledge of those actively undertaking study activities, in any area, will undoubtedly help to improve study conduct and improve best practice for randomised controlled trials more generally.

***Limitations***

The initial feedback from research nurses was provided directly to the Trial Manager. Therefore, as data collection was not entirely independent of the management team this may have limited the honesty in the responses provided. The addition of the qualitative interviews, conducted by an independent researcher will have helped to limit the impact that this may have had on the information provided.

The vast majority of research nurses who had been involved in study activity provided a response to the Likert questionnaire; however of those who provided a response not all completed a qualitative interview. Those who responded and participated in one or more of these activities may therefore have had differing motivations to those who did not. The collective views of the entire study team may not therefore be represented, but given a response to at least one data collection method was provided by most nurses, it is likely that the views of the wider study team have been captured to some extent, if not fully.

Given that this research was conducted in a pilot, feasibility trial setting, with a specific trial population (patients with surgical wounds healing by secondary intention), and a limited number of sites and research nurses participated in data collection, the generalisability of the findings may be limited. Similar challenges in study conduct are however reported across a wide range of RCTs, and it is noted that challenges and their impacts will naturally differ between studies [4]. Therefore the findings are likely to be generalisable across wound care trials, with some elements also able to be generalised to other study types.

Whilst a researcher, independent to the Trial Management team, completed the interviews, this researcher was affiliated to the lead research site and the study Chief Investigator. This could potentially introduce some outcome bias; however the purpose of this research as a method to inform future research activity should have helped to prevent biased findings.

***Implications for Future Practice***

Research nurses identified that removal of obstacles to recruitment was a key issue in enabling study conduct and participation. It is therefore suggested that research nurses are included in discussions for the initial design and planning stages of a trial to identify appropriate strategies for recruitment. Input in relation to participant retention and follow up completion is also important, to ensure methods proposed are both appropriate and feasible.

This research has also identified the importance of input from both the local and central trial teams, to facilitate clinician equipoise and so support recruitment activity. Future trials should therefore consider how best to publicise study activity to ensure clinical colleagues are sufficiently aware, and educated about current or upcoming research trials in their locality.

**Conclusions**

This study makes a valuable contribution to the limited evidence base of experiences of research nurses involved in the conduct of randomised controlled trials, both in wound care and more generally. The qualitative methods used to elicit detailed experiences of research nurses, has provided a range of suggestions for improvement in both the design and conduct of randomised controlled trials.

Engagement of all members of the research team during the early stages of study set up, and including contributions from research nurses when planning the logistics of study activity are important in ensuring effective study conduct. Further work to explore the experiences of individuals involved in research studies, and the continued sharing of effective techniques, is crucial to evolving research design and conduct in the future.

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## Appendix 15 – Table 24: Pilot and feasibility randomised controlled trial: Wound pain (text message) by randomised group and time point

|  |  |  |  |
| --- | --- | --- | --- |
| **Weekly text message pain scores**  N received/N sent (%)  Mean (SD)  Median (min, max) | **NPWT**  **(n=10)** | **Usual Care**  **(n=10)** | **Total**  **(n=20)** |
| **Week 1** | 6/13 (46.2)  5.0 (1.9)  5 (3, 8) | 9/13 (69.2)  3.3 (3.4)  4 (0, 8) | 15/26 (57.7)  4.0 (3.0)  5 (0, 8) |
| **Week 2** | 10/13 (76.9)  4.9 (3.2)  6 (0, 9) | 9/12 (75.0)  3.0 (3.0)  3 (0, 9) | 19/25 (76.0)  4.0 (3.2)  3 (0, 9) |
| **Week 3** | 9/12 (75.0)  3.4 (2.8)  3 (0, 8) | 8/10 (80.0)  2.6 (3.0)  1.5 (0, 7) | 17/22 (77.3)  3.1 (2.8)  2 (0, 8) |
| **Week 4** | 9/11 (81.8)  3.9 (3.0)  3 (0, 8) | 9/9 (100.0)  2.2 (2.4)  1 (0, 6) | 18/20 (90.0)  3.1 (2.8)  3 (0, 8) |
| **Week 5** | 10/11 (90.9)  3.6 (3.2)  2.5 (0, 9) | 6/8 (75.0)  2.2 (2.5)  1.5 (0, 7) | 16/19 (84.2)  3.1 (3.0)  2 (0, 9) |
| **Week 6** | 9/11 (81.8)  2.6 (3.5)  0 (0, 8) | 7/8 (87.5)  2.7 (2.9)  1 (0, 8) | 16/19 (84.2)  2.6 (3.1)  1 (0, 8) |
| **Week 7** | 7/8 (87.5)  3.6 (3.9)  2 (0, 8) | 7/7 (100.0)  2.1 (2.7)  1 (0, 6) | 14/15 (93.3)  2.9 (3.3)  1 (0, 8) |
| **Week 8** | 6/7 (85.7)  3.7 (3.5)  3.5 (0, 8) | 5/7 (71.4)  1.4 (2.1)  1 (0, 5) | 11/14 (78.6)  2.6 (3.0)  1 (0, 8) |
| **Week 9** | 5/7 (71.4)  2.8 (2.6)  2 (0, 6 | 7/7 (100.0)  1.4 (1.9)  1 (0, 5 | 12/14 (85.7)  2.0 (2.2)  1 (0, 6 |
| **Week 10** | 5/7 (71.4)  3.0 (2.1)  3 (0, 5) | 6/6 (100.0)  1.2 (1.6)  0.5 (0, 4) | 11/13 (84.6)  2.0 (0.2)  2 (0, 5) |
| **Week 11** | 5/5 (100.0)  3.2 (2.4)  3 (0, 6) | 7/7 (100.0)  0.9 (1.2)  0 (0, 3) | 12/12 (100.0)  1.8 (2.1)  1.5 (0, 6) |
| **Week 12** | 5/5 (100.0)  2.4 (2.4)  1 (0, 5) | 6/6 (100.0)  1.0 (1.5)  0.5 (0, 4) | 11/11 (100.0)  1.6 (2.0)  1 (0, 5) |

## Appendix 16 – Pilot feasibility randomised controlled trial: Physical and Mental Health Composite Scale scores (PCS & MCS) derived from the SF-12 by randomised group and time point

Figure 7 - Physical Composite Scale scores derived from the SF-12 by randomised group across time



Figure 8 - Mental Health Composite Scale scores derived from the SF-12 by randomised group across time



## Appendix 17 – Table 25: Unit costs of health care services

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
| **Item** | **Unit of measurement** | **Unit cost** | **Additional notes** | **Source** |
| **Hospital outpatient (doctor)** | Per clinic visit | £131.99 | Based on average of total out-patient attendances | (89) |
| **Hospital outpatient (nurse)** | Per clinic visit | £70.87 |  | (89) |
| **Day case** | Per admission | £720.78 | Based on average of total day case attendances | (89) |
| **GP visit at GP practice** | Per patient contact (surgery) lasting 11.7 mins | £44.00 |  | (90) |
| **GP visit at home** | Per home visit (11.4 mins) plus 12 mins travel time | £88.92 |  | (90) |
| **Nurse visit at GP practice** | Per 15.5 min appointment (based on £43 per hour) | £11.11 |  | (90) |
| **Nurse visit at home** | Per home visit (lasting 25 mins) plus 12 mins travel | £23.33 | Based on average of most commonly reported | (89, 90) |
| **Inpatient admission** | Per night | £359.13 | Based on Elective inpatient excess bed days | (90) |

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## Appendix 18 - Table 26: Completion and missingness of EQ-5D questionnaires

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
| **Follow up** | **Completed EQ-5D** | | **Missing EQ-5D (≥1 dimension missing)** | |
| **NPTW (n =19 )** | **Usual Care (n =21)** | **NPTW (n =19)** | **Usual Care (n = 21 )** |
| **Baseline** | 16 (80%) | 21 (100%) | 4 (20%) | 0 (0%) |
| **3 months** | 15 (%) | 15 (%) | 5 (%) | 6 (%) |

## Appendix 19 – Table 27: Proportion reporting EQ-5D-3L levels 1 to 3 by dimension, group and time point

|  |  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
| **EQ-5D scale** | **Health state Severity\*** | **Baseline** | | | | **3 months** | | | |
| **̃NPTW** | | **̂Usual Care** | | **̃NPTW** | | **̂Usual Care** | |
| **Mobility** | **No problems** | 5 | 31.25% | 6 | 28.57% | 3 | 20.00% | 6 | 40.00% |
| **Some problems** | 8 | 50.00% | 14 | 66.67% | 12 | 80.00% | 9 | 60.00% |
| **Unable/Extreme problems** | 3 | 18.75% | 1 | 4.76% | 0 | 0.00% | 0 | 0.00% |
| **No. reporting any problems** | | 11 | 68.75 % | 15 | 71.43% | 12 | 80 % | 9 | % |
| **Self-care** | **No problems** | 9 | 56.25% | 17 | 80.95% | 8 | 53.33% | 11 | 73.33% |
| **Some problems** | 7 | 43.75% | 4 | 19.05% | 7 | 46.67% | 4 | 26.67% |
| **Unable/Extreme problems** | 0 | 0.00% | 0 | 0.00% | 0 | 0.00% | 0 | 0.00% |
| **No. reporting any problems** | | 7 | 43.75% | 4 | 19.05% | 7 | 46.7 % | 4 | % |
| **Usual activities** | **No problems** | 3 | 18.75% | 6 | 28.57% | 2 | 13.33% | 8 | 53.33% |
| **Some problems** | 4 | 25.00% | 11 | 52.38% | 10 | 66.67% | 6 | 40.00% |
| **Unable/Extreme problems** | 9 | 56.25% | 4 | 19.05% | 3 | 20.0% | 1 | 6.67% |
| **No. reporting any problems** | | 13 | 81.25% | 15 | 71.43 % | 13 | 86.7% | 7 | % |
| **Pain** | **No problems** | 4 | 25.00% | 5 | 23.81% | 2 | 13.33% | 10 | 66.67% |
|  | **Some problems** | 7 | 43.75% | 13 | 61.90% | 10 | 66.67% | 5 | 33.33% |
|  | **Unable/Extreme problems** | 5 | 31.25% | 3 | 14.29% | 3 | 20.0% | 0 | 0.00% |
| **No. reporting any problems** | | 12 | 75 % | 16 | 76.19% | 13 | 86.7% | 5 | % |
| **Anxiety/** | **No problems** | 11 | 68.75% | 14 | 66.67% | 9 | 60.00% | 12 | 80.00% |
|  | **Some problems** | 4 | 25.00% | 5 | 23.81% | 5 | 33.33% | 2 | 13.33% |
|  | **Unable/Extreme problems** | 1 | 6.25% | 2 | 9.52% | 1 | 6.67% | 1 | 6.67% |
| **No. reporting any problems** | | 5 | 31.25 % | 7 | 33.33% | 6 | 40 % | 3 | % |

\* Level 1 - no problems; level 2 – some problems; level 3 – unable/extreme problems.

̃ NPTW – percentages calculated according to valid observations (baseline=16) (3 months=14).

̂ Usual Care – percentages calculated according to valid observations (baseline=21) (3 months=15).