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

Health economics analysis plan (HEAP)
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This document provides the economic analysis plan for the SWHSI 2 study, a randomised controlled trial of negative pressure wound therapy (NPWT) versus usual care (standard dressings) for surgical wounds healing by secondary intention. The statistical analysis of clinical effectiveness will be detailed in a separate plan.

The SWHSI 2 protocol specifies that the economic analysis will aim to evaluate the lifetime cost-effectiveness of NPWT, compared to all relevant comparators, in the treatment of SWHSI. The perspective of the cost-effectiveness analysis will be of the UK NHS and the Personal Social Services. The primary economic outcome will be the incremental cost-effectiveness ratio (ICER) for NPWT vs alternatives, expressed as cost per Quality Adjusted Life Years (QALYs) gained.

To best assist decision-making, we aim to build a *de-novo* decision analytic model to establish which of the relevant treatment(s) are most cost-effective, with current information. This decision model will consider all relevant evidence and all relevant comparators. A second economic analysis, agreed with NIHR, will also be conducted where the evidence informing the decision analytic model will be reduced to the findings from the SWHSI 2 trial, including comparators, health-related quality of life (HRQoL), resource consumption and time horizon.

1. *De-novo* decision analytic model

Trials are designed to compare two or more alternative treatments. In general, however, it is not practically possible for one experimental study to compare all available treatment options. This means that for a decision maker, the information provided by head to head trial comparisons can be limited and partial — they still need to know which treatment option is the most cost-effective one amongst all treatments of interest. This limitation of head to head trial comparison can be overcome if available evidence from multiple sources can be used. Decision analytic models provide a structure within which evidence from a range of sources can be synthesised to describe a specific problem, and through this framework overall costs and effects can be estimated. The advantage of using this framework is that the cost effectiveness results can be based on all available evidence, across the full range of possible alternative interventions and clinical strategies, over a relevant time horizon and for specific patient groups (1).

1.1. Decision problem

We will construct a decision analytic model to allow estimation of the cost-effectiveness of all relevant treatments for surgical wounds healing by secondary intention. The analysis will include two main health outcomes: a measure of wound healing (i.e. time to wound healing) and QALYs. A QALY is defined as a year lived with full health, calculated by multiplying quality of life and length of life. Again, the choice of score for HRQoL (or utility) for QALY calculation, for instance scores measured by EQ-5D-5L, is subject to data availability. Cost will be presented in UK pound sterling currency. The last year of the trial, i.e. 2023, will be used as the year of pricing. The time horizon is anticipated to consider the entirety of patients' lifetime though conditional on data availability. If extrapolation is used, relevant assumptions will be evaluated. The study population are patients aged above 16 with a SWHSI; of less than six weeks duration; arising from any surgical specialty and occurring on any part of the body deemed appropriate to receive either NPWT or wound dressing treatment; which is ready for NPWT treatment (i.e. contains at least 80% viable tissue or has only a very thin layer of slough requiring no further debridement); willing and able to give informed consent and provide follow-up data. The analysis will be conducted based on the perspective of the UK NHS and Personal Social Service and findings are expected to inform decision makers on which treatment to adopt for use in the UK NHS, out of a set of alternatives.

1.2. Identifying the treatments of interest

Treatments considered within this evaluation should be those appropriate to treat wounds healing by secondary intention. The traditional approach to treating SWHSI involves daily or more frequent dressing changes, sometimes involving packing of a wound cavity. There are a number of different dressing options, from simple dressings - such as non-adherent dressings - to more modern options such as foam, hydrocolloid and alginate dressings. Usual care, most likely to be a variety of wound dressings, will be that used locally. Given that there is no evidence to suggest any one dressing is more clinically and cost effective than another (2), use of any dressing type will be permitted. The second consideration is that treatments of interest included in this analysis should be relevant to the UK decision making context. However, treatments which are not currently used in general practice may 'possibly' be cost-effective and should be considered in the analysis.

We will identify the relevant treatments firstly through the data collected within the SWHSI 2 trial, but also through the Cochrane reviews by Dumville et al, 2015 (3) and Iheozor-Ejiofor, Z. et al. 2018 (4), where all RCTs investigating the effectiveness of treatments for SWHSI up to then have been recorded. Finally, we will contact clinical experts who might provide relevant alternative treatments for which no data exist, but that should be considered.

1.3. Defining the model structure

A targeted literature review will be conducted to identify published economic evaluations using decision analytic models regarding the treatment of SWHSI. The purpose of the review is to provide information of the current developments in the field in terms of model structure and

assumptions used in the analyses, together with highlighting key areas of uncertainty and potential data gaps. This will prepare us for potential issues which the project might encounter.

The targeted literature review will initially review the trials identified in the Cochrane reviews Dumville et al 2015 (3) and Iheozor-Ejiofor, Z. et al. 2018 (4) (on 'Negative pressure wound therapy for open traumatic wounds') and assess if any economic modelling was performed for any of the identified trials.

The targeted literature review will be conducted by an independent reviewer according to an agreed screening criteria:

- does the study consider SWHSI?
- is the study a full economic evaluation (i.e. includes costs and benefits)?
- does the study employ any kind of model as a method to represent disease progression?

Only studies which meet all the above criteria (agreed by both reviewers) will be extracted and reviewed. The information extracted will include; treatment comparator, study population, model design, model assumptions, effectiveness, utility, cost and uncertainty. The findings of this review will be used to inform the model structure.

1.4. Obtaining data to inform the model

The model will be informed by a variety of parameters, such as data on effectiveness on wound healing, utilities, costs and health resource consumption. Procedures to obtain data and to synthesise available evidence are detailed next.

Effectiveness

Rather than conducting a separate review of effectiveness data we will utilise and update the Cochrane Review Dumville et al 2015 (3) – This review was conducted in 2015 and, to our knowledge, it is planned to be updated in the near future to include additional evidence that may have been published in the last few years. The aim of the review is to evaluate the clinical effectiveness of negative pressure wound therapy on the healing of surgical wounds healing by secondary intention in any care setting. This updated review will serve as the major source of data on the effectiveness of alternative treatments (aggregate data).

Evidence synthesis on effectiveness

At this stage, we know from the Cochrane review Dumville et al 2015 (3), that two trials evaluating the clinical effectiveness of negative pressure wound therapy on the healing of surgical wounds healing by secondary intention exist.

We will combine details of included studies in a narrative review according to type of comparator, possibly by location of or type of wound, and then by outcomes and time period. Where appropriate, we will combine details of included studies quantitatively using meta-analytic methods. Both random and fixed-effect approaches are planned. We will consider clinical and methodological heterogeneity, and anticipate pooling data when studies appear appropriately similar in terms of wound type, intervention type, duration of follow-up and outcome type, in order to ensure any synthesis is valid.

In the presence of multiple treatments, we plan to use a mixed treatment comparisons (MTC) / network meta-analysis (NMA) approach (5, 6) to estimate the relative effectiveness of multiple treatments by synthesising the existing evidence base of trials. Where trials have common comparators, this process allows relative effectiveness estimates to be made for treatments not compared in head to head trials (i.e. indirect evidence), whilst maintaining the randomisation of each trial. In this way, all available evidence can be used to estimate treatment effects for pairs of treatments that have, at least, indirect evidence (i.e. for comparisons that have not been examined in any trial).

We will aim to combine data from studies for which individual patient data (IPD) is available to the authors (e.g. SWHSI 1) with aggregate data identified from studies in the Cochrane review. We also aim to incorporate (instead of exclude) trials that report alternative measures of healing (e.g. proportion of patients healed or time to wound healing), by appropriately modelling these within the NMA. Inferences will be obtained using Bayesian methods. If necessary, the sensitivity to prior distributions and the validity and consistency of the NMA will be explored.(7)

Participants for whom the event of interest (wound healing) was not observed (hard to heal)
In SWHSI 1, approximately 20% of the sample did not heal within the study. With an average follow-up of 416 days (compared to an average time to healing in those that healed of 99 days), the data suggested that these were 'hard-to-heal' participants of different baseline characteristics to the patients that healed.(8) This phenomenon is likely to happen in SWHSI 2. As in the economic analysis of SWHSI 1, we will explore different scenarios around the censoring of the hard to heal participants, considering imputation and expert elicitation. This exercise will be useful to externally validate the temporal extrapolations on the time to wound healing analysis.

Health-Related Quality-of-Life
We will be conducting a systematic review of health-related quality of life data. Key data of interest will be the health-related quality of life/utility and data regarding possible changes to health-related quality of life/utility for a patient whose surgical wound heals. Studies will be included if they: a) included or related to people with, or who had previously had, SWHSI; and b) presented quantitative health-related quality-of-life/utility data for people with SWHSI or a history of SWHSI.

In addition to the findings of the systematic review, we will have access to the SWHSI 2 trial data on health-related quality of life, obtained via the EQ-5D-5L questionnaire.
The EQ-5D-5L is a validated instrument for assessing HRQoL, comprised of 5 items, with 5 levels of response and a single general health status VAS.(9, 10) The EQ-5D-5L measures HRQoL in terms of 5 dimensions: mobility, self-care, usual activities, pain and discomfort, anxiety and depression. For each dimension, participants rate the extent of their problem as 'no problems', 'slight problems', 'moderate problems', 'severe problems' and 'extreme problems/unable'. Participants will complete the EQ-5D-5L at baseline, 3, 6 and 12 months post-treatment. According to the responses to the EQ-5D classification system, a health status can be defined, and a single index utility assigned. The EQ-5D-5L will be used to estimate the impact of both treatments on HRQoL as per quality-adjusted-life years (QALYs).

The raw EQ-5D-5L scores by domain will be presented to examine the movements between levels for each domain by trial arm. A value set for the EQ-5D-5L is now available that reflects the preference of members of the public in England for health states that are defined by the EQ-5D-5L descriptive system (11). However, this value set is currently under revision. A new value set is currently under development. NICE current recommendation (12-16) on the use of the EQ-5D advises that utilities for the 5L are derived using the mapping function developed by NICE DSU which maps the 5L descriptive system data onto the 3L valuation set. Therefore, unless the NICE guidance is changed by the time of our analysis, this mapping model will be used to derive utilities for the participants in the SWHSI-2 trial.

The overall difference in EQ-5D index scores between the arms will be examined through regression methods (e.g. mixed effect models), consistent with the model selected in the statistical analysis and the decision analytic model structure. EQ-5D index scores will be conditional on healing status and it is anticipated that while unhealed (unhealed health state(s)), patients will be assigned a utility decrement. A covariate selection process will be implemented to include covariates that are deemed relevant to explain the variability of EQ-5D index scores. Comparisons between healed EQ-5D index scores and adjusted population utility norms will be performed.

Health outcomes will be expressed in terms of the QALY, which captures the impact of treatment on both mortality and morbidity by 'weighting' each period of follow up time by the value corresponding to the quality of life (using the EQ-5D-5L) during that period. Utility scores will be converted into QALYs using area under the curve analysis (17). The summary of QALYs at each time point and total QALYs will be presented. The difference in QALYs gained between the arms will be adjusted for baseline utility weights to allow for any differences between the groups at baseline.

Resource use and costs

We will be conducting a systematic review on costs and resource use data. Key data of interest will be the resource use and the data regarding the costs incurred by patients with an unhealed surgical wound. Studies will be included if they: a) included or related to people with SWHSI; and b) presented costs/resource use data for people with SWHSI in the UK.

In addition to the findings of the systematic review, we will have access to the SWHSI 2 trial data on resource use/costs. Resource use will be collected using both investigator and participant forms. Resource use i.e. wound-related NHS consultations, support (e.g. occupational therapy, in home adaptations) and out-of-pocket medication costs will be completed by the participant at baseline, 3, 6 and 12 months. Details of wound dressing changes (frequency and type) will be collected at weekly follow-up. Information on resources provided by the recruiting centre will be collected via a retrospective review of medical records at 12 months post-randomisation.

The primary perspective of the analysis will be that of the NHS and Personal Social Services, however, given the implication of the surgical wound for the patient in terms of loss of earnings and days loss of normal activities, a secondary analysis from a broader perspective will be conducted.

The total NHS cost (e.g. base-case analysis) and total wider cost (e.g. secondary analysis) will be calculated by multiplying resource data by their unit cost. Unit costs will be sourced from published sources relevant to the UK costs (e.g. BNF (18) list prices for pharmaceuticals and PSSRU unit costs (19) and/or NHS reference costs for healthcare resource use). The unit cost items will be summarised and presented in the report/publication. All costs will be evaluated in pounds sterling (£) for the appropriate year (e.g. 2023). In cases where costs are sourced from previously published data, costs will be inflated to the appropriate year figures. The productivity costs will be derived assuming an average workday of 7.5 hours and the average hourly wage across all UK residents as estimated by the Office for National Statistics (20).
Health care resource use results will be presented for both arms in terms of mean value, standard error and mean difference (with 95% confidence intervals) between the groups. Costs will be divided into two components for the analysis: costs associated with the interventions and all other costs. Regression analysis will be used to relate costs to baseline characteristics.

Other model parameters

We will be conducting a systematic review on mortality data. Key data of interest will be the evidence regarding a relationship between having an unhealed surgical wound and increased mortality risk. Studies will be included if they: a) included or related to people with, or who previously had, SWHSI; and b) reported mortality data.

For all the model input parameters listed above, data from IPD sources, such as the SWHSI 1 cohort study, may be used to inform these.

1.5. Methods of analysis

To address several of the elements included in decision analytic modelling (i.e. evidence synthesis, estimation of other model inputs and evaluation of uncertainty) we will construct a comprehensive probabilistic decision analytic model evaluated using Monte Carlo simulation implemented in either the software R or Excel, using WinBUGS to perform any quantitative synthesis and regression analyses. The model outputs will be the estimated expected mean costs, effectiveness, and QALYs associated with each alternative treatment. Estimated total costs and outcomes will be discounted properly according to the latest NICE guidance of health technology appraisal. These cost-effectiveness estimates will be compared across treatment options by estimating the Incremental Cost Effectiveness Ratio (ICER) as appropriate. A cost-effectiveness threshold of £20,000/QALY will be used as the base-case value to estimate the net health benefit (NHB) of each of the treatment options (21). A threshold of £13,000/QALY will be also used as suggested by recent research (22, 23). The NHB will be estimated as the increase in effectiveness multiplied by the amount that the decision maker is willing to pay per unit of increased effectiveness (i.e. the cost-effectiveness threshold) minus the increase in cost.

Decision uncertainty

Uncertainty regarding cost-effectiveness will be evaluated using probabilistic sensitivity analysis (PSA), where inputs into the analysis are defined as probability distributions which reflect uncertainty. PSA explicitly incorporates the uncertainty in parameter estimates by using the range of values over which these estimates exist (characterised by an informative distribution), rather than single point estimates, as inputs into the models. The choice of

distribution to describe the uncertainty in individual parameters will be guided by the form of the data, the type of parameter and the estimation process for the parameter (24, 25). The estimated mean QALYs and costs associated with each treatment option will be combined with a feasible range of values for decision makers' willingness to pay (λ), to obtain distribution of net benefits at different levels of λ. The uncertainty surrounding the decision to adopt a given treatment option as a cost-effective treatment as different levels of willingness to pay will be represented in cost-effectiveness acceptability curves (CEACs). CEACs are a graphical representation of the probability of an intervention being cost-effective (on the vertical axis) for a range of willingness-to-pay values λ (on the horizontal axis) associated with the health outcome of interest.

Population and patient heterogeneity

The population considered in the extrapolated model will be consistent with the SWHSI 2 trial. There is likely to be considerable heterogeneity in the baseline surgical wound risk, HRQoL and costs, which will impact the absolute benefit and costs of treatment and subsequently influence the cost-effectiveness results. Heterogeneity will be captured by including baseline prognostic factors in regressions (baseline, costs, HRQoL) that will inform the economic model. Selection of regression covariates will be in line with the statistical analyses.

Missing data

We anticipate that there may be reasonably high levels of missing data for resource use and HRQoL. We will explore the amount of missing data on costs and quality of life at each follow-up period and whether missing data is restricted to individual items of resource use or HRQoL, or is missing for all items at specific visits. We will conduct a comprehensive investigation of missing data pattern following missing data guidelines.(26) Under the *missing at random* assumption, a mixed effect model for repeated measures will be used to address the missing data and derive incremental estimates for QALYs and costs.(27)

Scenarios and sensitivity analysis

Scenario analyses – as per agreed with the NIHR HTA, we will be conducting a scenario analysis where the evidence informing the decision analytic model will be reduced to the findings from the SWHSI 2 trial, including HRQoL, resource consumption and time horizon. This scenario will provide results which will be considered as a proxy to the results of a standard within-trial economic analysis on SWHSI 2.

Sensitivity analysis – The impact of assumptions undertaken in the analysis regarding the evidence over parameters or relating to the decision model (such as extrapolation) will be evaluated, if possible.

Value of further research

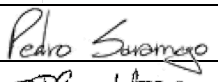
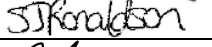
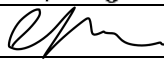
As part of this analysis we will conduct a value of information analysis. Uncertainty around treatment decisions means that in many cases there is always a chance that the "wrong" decision will be made (28). With estimates of probability of error and the opportunity cost of error, the expected cost of uncertainty or the expected opportunity loss surrounding the decisions can be calculated. This is also known as the expected value of perfect information (EVPI) and can be used to indicate whether further research is potentially worthwhile. It would also be useful to have an indication of what type of additional evidence would be most valuable. Therefore, the

expected value of partially perfect information for parameters (EVPPI) is calculated to identify those parameters for which more precise estimates would be most valuable.

2. Data, data storage and data verification

The analysis of trial-based data will use the dataset that has been finalised by the Trial Statistician, with any data queries raised and resolved with the Data Manager.

3. Signatures of approval

Name	Trial Role	Signature	Date
Ian Chetter	Chief Investigator		20.12.2022
Pedro Saramago	Senior Health Economist		14.12.2022
Sarah Ronaldson	Health Economist		14.12.22
Catherine Arundel	Trial Manager		14.12.22
Caroline Fairhurst	Statistician		20/12/2022

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