UK WHIST – Wound Healing in Surgery for Trauma

A Randomised Controlled Trial of standard wound management versus negative pressure wound therapy in the treatment of adult patients having surgical incisions for major trauma to the lower limb

Protocol version 3.0
13 October 2016

Ethical approval

MREC approval was obtained on the 16th of February 2016 under reference number 16/WM/0006

Funding

This study is funded by the National Institute of Health Research under reference number 14/199/14

Sponsorship

The University of Oxford is the sponsor of this study.

Registration

The study has been registered with the ISRCTN registry under reference number ISRCTN12702354, and on the NIHR Portfolio PID number 20416

Dates

Study start date: 01/01/2016
Study end date: 30/04/2023

Protocol Amendments:

Amendment Number	Date of Amendment	Date of Approval	Protocol Version
1	02 March 2016	18 March 2016	V2.0
4	18 October 2016	07 November 2016	V3.0

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Abbreviations

AE – Adverse Event
BNF – British National Formulary
CEAC - Cost-Effectiveness Acceptability Curves
CI – Chief Investigator
CRF – Clinical Reporting Form
OCTRU – Oxford Clinical Trials Research Unit
DMC – Data Monitoring Committee
DRI – Disability Rating Index
EQ-5D - EuroQol
HE – Health Economy/Economist
HTA- Health Technology Assessment
ICER – Incremental Cost Effectiveness Ratio
ITT – Intention To Treat
MAU - Multi-Attribute Utility
MCID – Minimal Clinically Important Difference
NPWT – Negative Pressure Wound Therapy
NPWT-EP - International Expert Panel on NPWT
PACS - Picture Archiving and Communications System
PI – Principal Investigator
PSS – Personal Social Services
PSSRU - Personal Social Services Research Unit
QA – Quality Assurance
RCT- Randomised Controlled Trial
REC – Research Ethics Committee
RF – Research Fellow
SAE – Serious Adverse Event
SAP – Statistical Analysis Plan
SD – Standard Deviation
TMG – Trial Management Group
TSC – Trial Steering Committee
QALY – Quality Adjusted Life Year
WHIST – Wound Healing In Surgery for Trauma

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2. Synopsis

Study Title	*WHIST –Wound Healing In Surgery for Trauma - A Randomised Controlled Trial of standard wound management versus negative pressure wound therapy in the treatment of adult patients having surgical incisions for major trauma to the lower limb.*	
Internal ref. no. / short title	WHIST	
Study Design	Multi-centre, multi-surgeon, parallel, two arm, randomised controlled trial	
Study Participants	Participants of 16 years and older, who have sustained a lower limb fracture due to major trauma which requires a surgical incision.	
Planned Sample Size	1540	
Planned Study Period	01/01/2016 – 30/04/2023	
	Objectives	Outcome Measures
Primary	To quantify and draw inferences on differences in the rate of 'deep infection' of the lower limb in the 30 days after major trauma between standard dressing and NPWT.	**Deep Infection**; As per CDC definition (see Section 4.4)
Secondary	i) To quantify and draw inferences on observed differences in the Disability Rating Index and general health-related quality of life in the 6 months after the major trauma. ii) To quantify and draw inferences on the quality of wound healing, using a validated, patient-reported assessment of the scar. iii) To determine the number and nature of further surgical interventions related to the injury, in the first 6 months after the major trauma. iv) To investigate, using appropriate statistical and economic analysis methods, the resource use, and thereby the cost effectiveness, of negative pressure wound therapy versus standard dressing for wounds associated with major trauma to the lower limbs. v) To quantify the long-term (five year) Disability Rating and Health-related Quality of Life in the same group of patients	• *Disability Rating Index* • *EQ-5D-5L* • *Patient-reported assessment of scar* • *Complications*

3. Rationale

3.1 Background

Major Trauma is the leading cause of death in patients under 45 years and a significant cause of short- and long-term morbidity. The National Audit Office (NAO) estimates that there are at least 20,000 cases of Major Trauma each year in England, resulting in 5,400 deaths and many of the survivors suffer permanent disabilities requiring long-term care. The NAO estimate that trauma costs the NHS between £0.3 and £0.4 billion a year for immediate treatment. This does not include the cost of subsequent hospital treatments, rehabilitation, home care support, or informal carers. The NAO estimate that the annual lost economic output as between £3.3 billion and £3.7 billion.

Fractures of the limbs are extremely common injuries in both the civilian and military populations, with 85% of major trauma patients sustaining serious limb injuries. [1] In open fractures, where the broken bone is exposed to the environment by a breach in the skin, the risk of infection is particularly high.[1] This was the area which we investigated in the WOLLF trial (HTA 10/57/20). However, even in closed high-energy injuries associated with major trauma, the rate of infection remains high even in the surgical incisions created during fracture fixation. For example, tibial plateau fractures are associated with average infection rates of up to 27%,[2-6] while pilon fractures have an incidence of deep infections ranging from 5% to 40%[7-10]. If surgical site infection does occur, treatment frequently continues for years after the trauma. This often involves prolonged courses of antibiotics, with attendant risk of antibiotic resistance in chronic wounds, and a huge health care cost associated with such injuries. A US study found that the average cost associated with infection was $163,000 if the limb could be salvaged and $500,000+ if amputation was necessary and these only represent a fraction of the subsequent personal and societal costs[11].

One of the factors which may reduce the risk of surgical site infection in the surgical wounds of major trauma patients is the type of dressing applied over the closed incision at the completion of the operative procedure. The type of dressing will determine whether bacterial ingress into the wound, which for polytrauma patients represents a particularly high risk due to the presence of antibiotic resistant organisms in the ITU and high-dependency environment. Furthermore, the presence of a wound haematoma or oozing from the wound are also likely to predispose to deep infection. Finally, the published literature suggests that the type of dressing applied to the wound influences the healing process itself [12-16]. This proposal concerns the type of dressing that is applied to the closed surgical incision at the end of the operation.

Traditionally, the surgical incision is covered with an adhesive dressing or gauze maintained in place with a bandage to protect the wound from contamination from the outside environment. These ‘standard dressings’ have been used throughout the NHS and in military practice for many years. It is acknowledged that a bandage does not apply sufficient external pressure to reduce blood or serous fluid accumulating in the wound bed and this may be uncomfortable for the patient and may pose an infection risk.

Negative-pressure wound therapy (NPWT) is an alternative form of dressing which may be applied to closed surgical incisions. In this treatment, an ‘open-cell’, solid foam overlies the incision and is covered with a semipermeable membrane which is only permeable to gas. A sealed tube is used to connect the foam to a pump, which creates a partial vacuum over the wound. This negative-pressure therapy provides a sealed environment, preventing bacterial ingress and removes blood and serous fluid exuding the wound. The application of negative pressure to the foam leads to the application of positive pressure to the wound bed and has been shown to reduce the incidence of wound

haematoma[17]. Recent laboratory studies suggest that NPWT shifts the cytokine profile to being less inflammatory, promotes the production of pro-angiogenic growth factors and enzymes responsible for matrix remodeling, leading to improved wound healing.[13-17] [19] Although the principles underlying the use of negative pressure are similar, the NPWT dressings applied to closed surgical wounds are very different from those used in treating wounds which are left open such as ulcers and open fracture wounds; hence the need for this investigation to follow-on from the WOLLF trial (HTA 10/57/20).

NPWT for closed wounds is considerably more expensive than traditional wound dressings, with each NPWT dressing costing c. £120 compared with £4 for a standard dressing. There has been only one randomised trial comparing standard wound dressing with NPWT for patients with closed surgical wounds following major trauma to the limbs[17]. This trial demonstrated a reduction in the rate of late/deep wound infection in the group of patients treated with NPWT (9%) versus the standard dressing group (15%). However, the reduction was of borderline statistical significance (p=0.049) and the study has been criticised in the subsequent Cochrane review for numerous methodological flaws.[19] The trial was funded by a commercial company which produces a NPWT system.

The only other relevant trials registered on the international trials database refer to elective/planned abdominal wounds (ISRCTN44577192), and joint replacement wounds (ISRCTN 92903493).

The very recent Cochrane review for surgical wounds concluded *that "it is still not clear whether NPWT promotes faster healing and reduces complications associated with clean surgery".* "*Given the cost and widespread use of NPWT, there is an urgent need for suitably powered, high-quality trials to evaluate the effects of the newer NPWT products that are designed for use on clean, closed surgical incisions. Such trials should focus initially on wounds that may be difficult to heal".* [19]

In the context of major trauma, the wounds associated with surgery to fractured limbs are notoriously difficult to manage. We propose a multi-centre randomised clinical trial comparing negative-pressure wound therapy with standard dressings for patients with major trauma requiring surgical incisions for the treatment of lower limb fractures.

3.2 Good Clinical Practice

The trial will be conducted in accordance with the Medical Research Council's Good Clinical Practice (MRC GCP) principles and guidelines, the Declaration of Helsinki, Oxford Clinical Trials Research Unit SOPs, relevant UK legislation and this Protocol. GCP-trained personnel will conduct the trial.

3.3 Consort

The trial will be reported in line with the CONSORT statement

4. Trial design

4.1 Trial summary

The proposed project is a two-phased study. Phase 1 (Internal Pilot) will confirm the expected rate of recruitment in a large-scale multi-centre randomised controlled trial. Phase 2 (Main phase) will be the proposed randomised controlled trial in a minimum of 24 trauma centres across the UK.

Internal Pilot summary

The pilot will take place at 5 centres over a period of 6 months. The aim of this initial phase will be to determine the number of eligible and recruited patients in the trauma centres over the course of 6 months.

The trial will be reviewed if the target recruitment during the internal pilot is not achieved. If the trial continues into the main phase, patients from the internal pilot will be included in the final analysis. Should the trial be stopped, those participants already enrolled would continue in the trial and be followed-up as per the protocol.

Main RCT summary

All adult patients presenting at the trial centres within 72 hours of sustaining major trauma and who require a surgical incision to treat a fractured lower limb are potentially eligible for inclusion. Randomisation, stratified by trial centre, open or closed fracture at presentation, and Injury Severity Score (ISS) ≤15 vs ISS ≥16 will be generated and administered via a secure web-based service using minimisation. The random allocation will be to either standard wound management or negative pressure wound therapy.

The patients will have clinical follow-up at the local fracture clinic for a minimum of 6 months, as per standard NHS practice after these injuries. Photographs of the wound and diagnosis of any infection will be taken at 30 days, and a validated patient-reported questionnaire to assess wound healing.[20]. Functional and quality of life outcome data will be collected using the DRI and EQ-5D questionnaires at 30 days, 3 months and 6 months post-injury. Questionnaires will be received centrally by a data administrator at the Kadoorie Centre who will enter the information onto a secure password protected database. In addition, at the same time-points, information will be requested with regards to resource use and any late complications or surgical interventions related to their injury with specific note of continuing treatment for deep infection.

4.2 Null hypothesis

There is no difference in the proportion of wounds healed at 30 days between adult patients treated with standard wound dressings versus negative pressure wound therapy.

4.3 Objectives

The aim of this pragmatic randomised controlled trial is to compare standard dressings with negative-pressure wound therapy for the treatment of surgical incisions associated with major trauma to the lower limb.

The primary objective for the RCT is:

To quantify and draw inferences on differences in the rate of ‘deep infection’ of the lower limb in the 30 days after major trauma between standard dressing and NPWT.

In addition to clinical diagnostic criteria for infection, photographs will be used to assess wound healing. Any infection that requires continuing medical intervention or has already led to amputation at the 30-day review will be considered a 'deep' infection.

The secondary objectives are:
i) To quantify and draw inferences on observed differences in the DRI and general health-related quality of life in the 6 months after the major trauma.
ii) To quantify and draw inferences on the quality of wound healing, using a validated, patient-reported assessment of the scar.
iii) To determine the number and nature of further surgical interventions related to the injury, in the first 6 months after the major trauma.
iv) To investigate, using appropriate statistical and economic analysis methods, the resource use, and thereby the cost effectiveness, of negative pressure wound therapy versus standard dressing for wounds associated with major trauma to the lower limbs.
v) To quantify the long-term (five year) Disability Rating and Health-related Quality of Life in the same group of patients

4.4 Outcome measures

The primary outcome measure for this study is **Deep Infection**; We will use the Center for Disease Control and Prevention definition of a “deep surgical site infection”, that is a wound infection involving the tissues deep to the skin that occurs within 30 days of injury.[21]
The treating clinical team will make the diagnosis of ‘deep infection’, as per routine clinical practice. The treating clinicians will not be part of the research team. Since the prompt diagnosis and treatment of infection is fundamental to the patient’s routine clinical care, the treating surgeon/clinician will always document such a change in management in the patient’s medical record. In addition, an Independent Outcome Classification Group will review the data collected in the Clinical Reporting Forms, which will include the specific criteria used by the CDC to define a “deep surgical site infection”, to confirm/refute the ‘deep infection’ diagnosis.

The diagnostic markers of deep infection (purulent drainage, positive deep wound culture, spontaneous dehiscence (opening up) of the wound) will be supplemented by an objective assessment of wound healing using a standardised photograph of the wound at the 30-day review. The photographs will be reviewed by two independent experienced assessors who are blind to the treatment allocation. Any infection that requires continuing medical intervention or has already led to amputation at or after the 30-day review will be considered a deep infection.
Finally, patients will be asked to self-report (or a consultee on their behalf, in case of continued impaired capacity) at each of the follow-up points on the quality of the wound healing/scar, any treatment for infection and any medical/surgical intervention related to infection associated with their surgical wound.

The secondary outcome measures in this trial are:
Disability Rating Index (DRI) a self-administered, 12-item Visual Analogue Scale questionnaire assessing the patients’ own rating of their disability.[22] This measure was chosen as it addresses “gross body movements” rather than specific joints or body segments. Therefore, it will facilitate the

assessment of patients with different fractures and injuries of the lower limbs. This outcome measure will not be taken for those patients with longer term (more than 4 weeks) impaired capacity.

EuroQol EQ-5D-5L; The EuroQol EQ-5D is a validated measure of health-related quality of life, consisting of a five dimension health status classification system and a separate visual analogue scale. [23] An updated version of the EQ-5D with 5 response levels, the EQ-5D-5L, has recently been developed to enhance the responsiveness of the instrument to changes in patient health.[24] Responses to the health status classification system will be converted into multi-attribute utility (MAU) scores using tariffs currently under development for England.[25] These MAU scores will be combined with survival data to generate QALY profiles for the purposes of the economic evaluation. The EQ-5D has been validated to be completed by a patient's proxy in case of continued impaired capacity.

Complications; all complications and surgical interventions related to the index wound will be recorded.

Resource use will be monitored for the economic analysis. Unit cost data will be obtained from national databases such as the BNF and PSSRU Costs of Health and Social Care.[26] Where these are not available the unit cost will be estimated in consultation with the hospital finance department. The cost consequences following discharge, including NHS costs and patients' out-of-pocket expenses will be recorded via a short questionnaire which will be administered at 3 and 6 months post major trauma. Patient self-reported (or consultee reported) information on service use has been shown to be accurate in terms of the intensity of use of different services.[27]

We will use techniques common in long-term cohort studies to ensure minimum loss to follow-up, such as collection of multiple contact addresses and telephone numbers, mobile telephone numbers and email addresses.

Considerable efforts will be made by the trial team to keep in touch with patients throughout the trial by means of newsletters and social media, which will keep patients informed of the progress of the study and any relevant new information.

TIME POINT	DATA COLLECTION
Baseline	DRI *and* EQ-5D *pre-injury and contemporary*,
30 days	Deep infection, complication records, scar assessment, operative record, photograph of limb wound
3 months	DRI, EQ-5D, scar assessment, record of complications/rehabilitation or other interventions and economics questionnaire
6 months	DRI, EQ-5D, scar assessment, record of complications/rehabilitation or other interventions and economics questionnaire
12 months	DRI, EQ-5D, record of complications/ further interventions
2,3,4,5 years	DRI, EQ-5D, record of complications/ further interventions

Table 1 Follow-up measures

4.5 Sample size

There has only been one previous randomised trial to compare negative pressure wound therapy to standard dressings for surgical incisions associated with major trauma to the lower limb. This trial

indicated that the rate of 'late' (deep) infection was reduced by 6%; from 15% in the standard treatment group to 9% in the NPWT group.[17]
In the absence of a 'Minimum Clinically Important Difference' for deep wound infection, we surveyed surgeons in the UK Orthopaedic Trauma Society who perform surgery for major trauma to the limbs (unpublished data 2015). The survey showed that a 6% reduction in the rate of 'deep infection' would, universally, be sufficient to change clinical practice with regard to the choice of dressing.
Therefore, assuming a reduction in the proportion of patients having a deep infection from 15% to 9%, 615 patients would be required in each group to provide 90% power at the 5% level. Our previous experience in clinical trials of lower limb fracture surgery for major trauma indicates that up to 20% of primary outcome data may be lost during the follow-up period; due to death and loss to follow-up. Therefore, we propose to recruit **1540 patients** in total for this trial.

4.6 Methodology

4.6.1 Eligibility

Patients will be eligible for this study if:

- They are aged 16 years or older
- Present to the trial hospital within 72 hours of injury
- They have major trauma; as defined by eligibility for the UK Trauma Audit Research Network (TARN) database
- They have a limb fracture requiring a surgical incision.

All major trauma patients presenting to a Trauma Centre in England are automatically considered for entry onto the TARN database. We will use the patient's routine imaging on admission, including any 'Major Trauma CT scan', and associated 'secondary survey' to identify the patient's injuries and calculate the Injury Severity Score (15 or less vs 16 or more) before randomisation.
Since payment to Major Trauma Centres is directly linked to the upload of data to TARN, the systems to identify and assess major trauma patients is universally known and routinely used in every centre.

Patients will be excluded from participation in this study if:

- They have an open fracture of the lower limb which cannot be closed primarily.
- There is evidence that the patient would be unable to adhere to trial procedures or complete questionnaires. It is expected that for a small proportion of patients this exclusion criterion will only be determined after randomisation. These patients will then be excluded from the study.

Patients who sustain injuries to areas of the body other than the lower limbs, which may affect the primary outcome measure, will have their injuries documented but the participants will still be included in the analysis. For patients with more than one lower limb injury, only the most severe wound will be included in the trial. It will be up to the surgeons discretion to decide which injury is the most severe.

4.6.2 Recruitment and consenting

The internal pilot will specifically inform and test the recruitment rate for the main trial. Recruitment will take place in 5 trial centres over a period of 6 months. The expected rate of recruitment is based

on recent audit data from two of the centres (Oxford and Coventry). In these centres, an average of 18 potentially eligible patients are admitted with major trauma and a fracture to the lower limb every month. All centres involved in the trial will be Major Trauma Centres or Trauma Units with similar catchment areas as the five initial sites. Experience from previous multi-centre trials has, however, shown that recruitment outside of the lead centre tends to occur at a lower rate. Therefore, a conservative **recruitment rate of 6 patients per month per centre** is estimated for the 6-month pilot phase. If this recruitment rate is achieved by the end of the internal pilot, the trial will progress to the main phase. We intend to recruit patients from a minimum of 24 centres (including the lead centre). Those patients recruited during the internal pilot phase of the study will be included in the main analysis at the end of the study. The remainder of the 1540 patients will then be recruited over a 16 months period.
Patients will be screened from the Emergency Department at the trial centres. All patients with a fracture of the lower limb associated with major trauma will be assessed for eligibility. Throughout the whole study, screening logs will be kept at each site to determine the number of patients assessed for eligibility and reasons for any exclusion. Patients who decline to participate during the pilot phase or withdraw from the study will be given the opportunity to discuss/inform the research team of their reasoning behind their decision not to take part.

The nature of these injuries means that the great majority of patients will be operated on immediately or on the next available trauma operating list, depending on access to an appropriate operating theatre. Some patients may be unconscious, all will be distracted by the injury to their lower limb and its subsequent treatment and all will have had large doses of opiates for pain relief, potentially affecting their ability to process information. Similarly, patients' next of kin, carers and friends are often anxious at this time and may have difficulty in weighing the large amounts of information that they are given about the injury and plan for treatment. In this emergency situation the focus is on obtaining consent for surgery (where possible) and informing the patient and any next of kin about immediate clinical care. The consent procedure for this trial will reflect that of the surgery, with the attending clinician assessing capacity before taking consent for the surgical procedure and this capacity assessment then being used to decide on the proper approach to consenting to the research. The appropriate method, as described below, will then be used to gain either prospective or retrospective consent from the patient or appropriate consultee by a GCP-trained, appropriately delegated member of the research team.

Conducting research in this 'emergency setting' is regulated by the *Mental Capacity Act 2005*. As patients may lack capacity as described above, and because of the urgent nature of the treatment limits access to and appropriate discussion with personal consultees, we propose to act in accordance with section 32, subsection 9b of the MCA following a process approved by the relevant research ethics committee; If we are not able to obtain consent prior to surgery we will approach an appropriate Consultee. Where a Personal Consultee is available, they will be provided with the study information. The Personal Consultee will be given the opportunity to ask questions and discuss the study after which their written agreement will be recorded. Where a Personal Consultee is not available then a Nominated Consultee will be identified to advise the research team. The Nominated consultee will be the patient's treating surgeon. If that surgeon is a member of the research team, another independent surgeon will be identified. The Nominated Consultee will be asked to agree for the patient to be randomised, this will be prospectively recorded during the electronic randomisation process.

Hereafter, at the first appropriate opportunity and when the clinical situation allows, the Nominated Consultee will provide a wet-ink signature on a copy of the electronic recorded agreement. Consent or agreement for further participation into the study after surgery will then be sought by the patient themselves or a Personal/Professional consultee.

Those patients that are able to consent before their operation will always be approached for consent before surgery. For those patients that did not consent prior to surgery, the research associate will provide the patients with all of the study information at the first appropriate time when the patient has regained capacity.
The patients will be given the opportunity to ask questions and discuss the study with their family and friends. They will then be asked to provide written consent for continuation in the study.
Patients will be asked to consent to long-term follow-up and data linkage to routine NHS datasets.
For those patients, who 4 weeks after their major trauma are still lacking capacity, a personal Consultee will be contacted to advise the research team about the patients continued participation in the study. The Personal Consultee will be provided with all the study information and be given the opportunity to ask questions and discuss the study with other relatives and friends. If they agree for the patient to continue to be involved in study, their agreement will be recorded in the patient's notes and on an informed agreement checklist.

On rare occasions, participants may be discharged prior to consent. If this happens the trial team will make every effort to discuss the trial with the patient at their next clinical follow-up appointment. If the patient lacks capacity at this appointment, the trial will be discussed with the patients' personal consultee.

Patients or Personal Consultees who prefer not to be actively involved in the study follow-up, will be asked if they are willing to consent to the research team using their routinely collected NHS data for the study. All original signed consent forms will be kept in the investigator site file. Three copies of the consent forms will be made; one held in the patient's medical notes, one for the patient and one copy for the study team.

Throughout the study, best efforts will be made to involve participants who, temporarily or permanently, lack capacity in the decision to be involved in the study. The clinical team will make a judgement about the amount and complexity of the information that the participant is able to understand and retain on an individual basis. Appropriate information will be communicated to the participant and updated as their understanding changes. At all times the study team will act in accordance with the participants' best interests.

Any new information that arises during the trial that may affect participants' willingness to take part will be reviewed by the Trial Steering Committee; if necessary this will be communicated to all participants. A revised consent form will be completed if necessary.

Responsibility for recording and dating both oral and written informed consent or agreement will be with the investigator, or persons designated by the investigator, who conducted the informed consent discussion. Designated responsibility should be recorded on the site delegation log. Permission will be sought to inform the patients GP of their participation in the study.

4.6.3 Trial ID

When a patient enters the trial, sufficient non-identifiable details will be logged intraoperatively, by the clinical team, on a secure, encrypted, web-based system, provided by Oxford Clinical Trials Research Unit. Basic information including the patient initials, age and eligibility checks will be entered. The patient will then receive a trial ID that will be used on all non-public facing trial documentation.

4.6.4 Randomisation

The treating surgeon will confirm eligibility at the end of the operative procedure but before the wound dressing is applied. Eligible patients will be enrolled into the study via the online randomisation system. The allocation sequence will be generated by an independent centre at the Clinical Trials Unit. Randomisation will be on a 1:1 basis, using a validated computer randomisation program with a minimisation algorithm to ensure balanced allocation of patients across the two treatment groups, stratified by trial centre, open or closed fracture at presentation and Injury Severity Score (ISS) ≤15 vs ISS ≥16. The first 30 participants will be randomised using simple randomisation to seed the minimisation algorithm which will have probabilistic element of 0.8 introduced to ensure unpredictability of the treatment assignment. All modern operating theatres include a computer with web-access, so a secure, 24-hour, web-based randomisation system will be used to generate the treatment allocation intra-operatively.

4.6.5 Post randomisation withdrawals/exclusions

Participants will be excluded in the post-randomisation phase if it is established that they would be unable to adhere to trial procedures or complete questionnaires e.g. no fixed address, history of substance abuse.

Participants may decline to continue to take part in the trial at any time without prejudice. A decision to decline consent or withdraw will not affect the standard of care the patient receives.

Participants have two options for withdrawal;

1) Participants may withdraw from completing any further questionnaires but allow the trial team to still view and retain, anonymously, any relevant hospital data that is recorded as part of normal standard of care e.g. x-rays and further surgery information.
2) Participants can withdraw wholly from the study but data obtained up until the point of withdrawal will be included in the final analysis of the study, thereafter no further data will be collected for that participant.

Once withdrawn, the patient will be advised to discuss their further care plan with their surgeon.

4.6.6 Blinding

As the wound dressings are clearly visible, the patients cannot be blind to their treatment. In addition, the treating surgeons will also not be blind to the treatment, but will take no part in the post-operative research assessment of the patients. The functional outcome data will be collected and entered onto the trial central database via questionnaire administered by a research assistant/data clerk in the trial central office.

In addition, we will use photographs of the wound at the 30-day clinical follow-up to provide an objective assessment of wound healing and infection. Any wound that is not healed at or after the 30-day review will be considered a deep infection. The photographs will be reviewed independently by two experienced assessors who are blind to the treatment allocation. We will supplement this

with a validated, patient-reported assessment of the scar, to provide a subjective assessment of wound healing.

4.7 Technologies assessed

Patients with a fracture of the lower limb associated with major trauma usually have surgery on the next available trauma operating list. Some patients may be transferred to a Major Trauma Centre for definitive care – within the first 48 hours of injury – but will still have their initial surgery as soon as possible. All patients will receive a general or regional anesthetic. At the end of the initial operation, a dressing is applied to the surgical wound. This trial will compare two types of wound dressing; standard dressing versus negative pressure wound therapy.

4.7.1 Treatment options

Standard dressing. The standard dressing for a surgical wound comprises a non-adhesive layer applied directly to the wound which is covered by a sealed dressing or bandage. The standard dressing does not use 'negative pressure'. The exact details of the materials used will be left to the discretion of the treating surgeon as per their routine practice but the details of each dressing applied in the trial will be recorded.

Negative-pressure wound therapy. The NPWT dressing uses an 'open-cell', solid foam which is laid onto the wound as an intrinsic part of a sealed dressing. A sealed tube connects the dressing to a built in mini-pump which creates a partial vacuum over the wound.

In most cases the first dressing applied to the wound at the end of the operation is left in place until the wound is ready for the stitches etc. to be removed – usually one to two weeks after the surgery. However, in some cases, depending upon the specific injury and according to the treating surgeon's normal practice, the wound may be re-dressed again on the ward. Any further wound dressing will be recorded and will follow the allocated treatment unless otherwise clinically indicated.

4.7.2 Rehabilitation

The rehabilitation will be recorded but left entirely to the discretion of the treating surgeon, as the type of injury will vary between patients

4.7.3 Follow-up

Copies of the baseline clinical report forms (CRFs) and images will be delivered to the trial co-ordinating centre by secure email or Royal Mail.

The research associate will make a record of any early complications at the routine 30-day follow-up appointment and take a standardised photograph of the wound. The patient will complete the 'scar assessment' questionnaire. These data will be returned securely to the trial co-ordinating centre. The number and timing of any subsequent follow-up appointments will be at the discretion of the treating surgeon.

All patients will be reviewed at 3 and 6 months as per routine practice after this type of injury. Details of any late complications will be sent securely to the trial co-ordinating centre.

The functional outcome data will be collected using questionnaires at 30 days, 3 months and 6 months post-injury. In addition to the DRI, the patients will be asked to fill out the EQ-5D questionnaire and a complications/further surgical interventions and health economics questionnaire. These questionnaires will be administered centrally by a data clerk at the Kadoorie centre. All of the outcome questionnaires can be completed over the phone if postal copies are not returned. The clinical follow-

up between 3 months and 6 months will be at the discretion of the surgeon and will be recorded, but will not influence the collection of trial outcome data.

Patients will subsequently be contacted on an annual basis to complete the EQ-5D and DRI questionnaires; some patients have long term problems following their injuries. If we have trouble contacting the patient during follow-up we may ask their GP or central NHS organisation to confirm their contact details. A postal cover letter will be provided with each questionnaire and if this is not returned within 2 weeks a postal reminder letter will be sent with an option to withdraw from the study.

4.8 Adverse event management

4.8.1 Adverse event management

Adverse events (AE) are defined as *any untoward medical occurrence in a clinical trial subject and which do not necessarily have a causal relationship with the treatment*. All AEs will be listed on the appropriate Case Report Form for routine return to the 'WHIST' central office.

Serious adverse events are defined as any *untoward and unexpected medical occurrence that: 'Results in death'*, '*Is life-threatening'*, '*Requires hospitalisation or prolongation of existing inpatients´ hospitalisation*', '*Results in persistent or significant disability or incapacity*', '*Is a congenital anomaly or birth defect' or 'any other important medical condition which, although not included in the above, may require medical or surgical intervention to prevent one of the outcomes listed*'.

Some adverse events are expected as part of the surgical interventions, and do not need to be reported immediately, provided they are recorded in the 'Complications' section of the Case Report Forms and/or Patient Questionnaires. These events are: complications of anaesthesia or surgery (wound infection, bleeding or damage to adjacent structures such as nerves, tendons and blood vessels, delayed unions/non-unions, delayed wound healing, further surgery to remove/replace metalwork and thromboembolic events). All participants experiencing SAEs will be followed-up as per protocol until the end of the trial.

All other serious adverse events (SAE) will be entered onto the Serious Adverse Event reporting form and emailed to a secure study nhs.net email account at the Kadoorie Centre within 24 hours of the investigator becoming aware of them. Once received, causality and expectedness will be confirmed by the Chief Investigator. SAEs that are deemed to be unexpected and related to the trial will be notified to the Research Ethics Committee (REC) within 15 days. All such events will also be reported to the Trial Steering Committee and Data Monitoring Committee at their next meetings.

4.8.2 Risks and benefits

The risks associated with this study are predominantly the risks associated with the injury and the surgery: infection, bleeding and damage to the adjacent structures such as nerves, blood vessels and tendons. Participants in both groups will undergo surgery and will potentially be at risk from any/all of these complications. Allocation of the trial intervention will take place at the end of the initial surgery so that there is no difference between the groups in terms of surgical risk.

Both standard wound dressings and NPWT have been used widely in both the civilian and military settings and there are no specific risks associated with the use of either type of wound management - other than a potential reduction in the rate of wound complications which is the focus of this trial.

4.9 End of trial

The end of the trial will be defined as the collection of final 5 year outcome data from the last participant.

5. Data Management

The Case Report Forms will be designed by the trial coordinator in conjunction with the trial management team. All electronic patient-identifiable information will be held on a secure, password-protected database at the Kadoorie Centre, accessible only to the research team. Paper forms with patient-identifiable information will be held in secure, locked filing cabinets within a restricted area. Patients will be identified by a trial identification number only. Direct access to source data/documents will be required for trial-related monitoring and/or audit by the Sponsor, NHS Trust or regulatory authorities as required. All paper and electronic data will be retained for at least five years after completion of the trial.

5.1 Statistical Analysis

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

The main analysis will investigate differences in the primary outcome measure, the proportion of patients with deep infection, at 30 days post operation. Randomisation by minimisation procedure should ensure balance in the recruiting centre, patients presenting with open versus closed fractures and ISS in both treatment groups. Although we have no reason to expect that clustering effects will be important for this study, in reality the data will be hierarchical in nature, with patients naturally clustered into groups by recruiting centre. Therefore, we will account for this by generalizing the conventional linear (fixed-effects) regression approach to a mixed-effects logistic regression analysis. This model will be used to assess differences in deep infection rates between the study intervention groups, with results presented as odds ratios with associated 95% confidence intervals. The mixed-effects model will include a random effect to account for any heterogeneity in response due to the recruitment centre and fixed effects to adjust for open versus closed fractures and the ISS, participant age and gender. An identically structured and formulated mixed-effects linear regression model will be used to assess the effects of the interventions on secondary outcomes DRI and EQ-5D (at both 3 and 6 months, and for the long-term follow-up) that, for the purposes of analysis, will be assumed to be approximately normally distributed. Other dichotomous outcome variables, such as complications related to the trial interventions will be analysed in the same manner as the primary outcome. Temporal patterns of any complications will be presented graphically and if appropriate a time-to-event analysis (Kaplan-Meier survival analysis) will be used to assess the overall risk and risk within individual classes of complications. The main analyses will be conducted using specialist mixed-effects modelling functions available in validated statistical software such as Stata, Stata Corp LP (http://www.stata.com) or the software package R (http://www.r-project.org/) The primary focus will be the comparison of the two treatment groups of patients on an intention-to-treat (ITT) basis, and this will be reflected in the analysis which will be reported together with appropriate diagnostic plots

that check the underlying model assumptions. In addition to the ITT analyses, per-protocol (as treated) analyses will also be undertaken and reported in parallel to, but subsidiary to, the main analyses.
It seems likely that some data may not be available due to voluntary withdrawal of patients, lack of completion of individual data items or general loss to follow-up. Where possible the reasons for missing data will be ascertained and reported. Although missing data is not expected to be a problem for this study, the nature and pattern of the 'missingness' will be carefully considered — including in particular whether data can be treated as missing at random (MAR). If judged appropriate, missing data will be imputed, using multiple imputation. The resulting imputed datasets will be analyzed and reported, together with appropriate sensitivity analyses. Any imputation methods used for scores and other derived variables will be carefully considered and justified. Reasons for ineligibility, non-compliance, withdrawal or other protocol violations will be stated if available and any patterns summarized. More formal analysis, for example using logistic regression with 'protocol violation' as a response, may also be appropriate and aid interpretation. About 1-2% of patients are expected to die during follow-up, so this is unlikely to be a serious cause of bias. However, we will conduct a secondary analysis taking account of the competing risk of death, using methods described by Varadhan et al.[28]
All reported tests will be two-sided and considered to provide evidence for a significant difference if p-values are less than 0.05 (5% significance level). A detailed statistical analysis plan (SAP) will be agreed with the Data Monitoring Committee (DMC) at the commencement of or early in the study. Any subsequent amendments to this initial SAP will be clearly stated and justified in the final report. Interim analyses of efficacy outcomes are not planned and will be performed only where requested by the DMC. Results from this trial will also be compared with results from other trials and reported in accordance with CONSORT guidelines

5.2 Economic evaluation

An economic evaluation will be integrated into the trial design. The economic evaluation will be conducted from the recommended NHS and personal social services (PSS) perspective [26]. Data will be collected on the health and social service resources used in the treatment of each trial participant during the period between randomisation and 6 months post-randomisation. Trial data collection forms will record the duration of each form of hospital care, surgical procedures, adjunctive interventions, medication profiles, tests and procedures. Observational research may be required to detail additional staff and material inputs associated with clinical complications. At 3 and 6 months post-randomisation, trial participants will be asked to complete economic questionnaires profiling hospital (inpatient and outpatient) and community health and social care resource use and, for the purposes of sensitivity analysis, out-of-pocket expenditures and costs associated with lost productivity. Current UK unit costs will be applied to each resource item to value total resource use in each arm of the trial. *Per diem* costs for hospital care, delineated by level or intensity of care, will be calculated by the health economics researcher using data from detailed questionnaires completed by the local finance departments, giving cost data and apportioning these to different categories of patient using a 'top-down' methodology. The unit costs of clinical events that are unique to this trial will be derived from the hospital accounts of the trial participating centres, although primary research that uses established accounting methods may also be required. The unit costs of community health and social services will largely be derived from national sources, although some calculations from first principles using established accounting methods may also be required[29.] Trial participants will be asked to complete the EuroQol EQ-5D-5L[24] measures at 3 and 6 months post-randomisation. Responses to

the EQ-5D-5L will be converted into multi-attribute utility scores using the algorithm currently under development to reflect societal preferences in England.[25] [30 31] Crosswalking algorithms will be employed to generate supplementary utility values comparable with those derived from the EQ-5D-3L instrument.[24]

An incremental cost-effectiveness analysis, expressed in terms of incremental cost per quality-adjusted life year (QALY) gained, will be performed. Results will be presented using incremental cost-effectiveness ratios (ICERs) and cost-effectiveness acceptability curves (CEACs) generated via non-parametric bootstrapping. This accommodates sampling (or stochastic) uncertainty and varying levels of willingness to pay for an additional QALY. Due to the known limitations of within-trial economic evaluations[32], we will construct a decision-analytical model to model beyond the parameters of the proposed trial the cost-effectiveness of negative pressure wound therapy in this clinical population. The model will be informed partly by data collected as part of the proposed trial, but also by data collected from other primary and secondary sources. These sources include published results from relevant observational studies. Specific parameters of interest might be long term costs, health utilities and relapse rates. In addition, registries and trial datasets to which the research team have access might be consulted if they are seen as relevant to informing these parameters. Long term costs and health consequences will be discounted to present values using discount rates recommended for health technology appraisal in the United Kingdom [33] A series of probabilistic sensitivity analyses will be undertaken to explore the implications of parameter uncertainty on the incremental cost-effectiveness ratios. Probabilistic sensitivity analyses will also explore the effects of extending the study perspective, target population, time horizon and decision context on the incremental cost-effectiveness ratios. In addition, cost-effectiveness acceptability curves will be constructed using the net benefits approach.

We recognise from previous experience that missing data can be a particular challenge for health economic analysis. To minimise the impact of this, we will design our HE CRFs, based on previous experience with studies such as WOLLF, so that they are as simple and easy-to-complete as possible. Any remaining issues with missing values will be dealt with within the HE analysis using multiple imputation methods as described in the statistical analysis plan for the main trial.

6. Trial Oversight

The day-to-day management of the trial will be the responsibility of the Trial Manager, supported by the CTU administrative staff. This will be overseen by the Trial Management Group, who will meet monthly to assess progress. It will also be the responsibility of the Trial Manager to undertake training of the research staff at each of the trial centres. The trial statistician and health economist will be closely involved in setting up data capture systems, design of databases and clinical reporting forms. A Trial Steering Committee (TSC) and a Data Monitoring Committee (DMC) will be set up.

6.1 Trial Supervision

Day-to-day management of the trial will be overseen by a Trial Management Group which is made up of the Investigators listed in Section 1 and staff working on the project within OCTRU.
A TSC -with an independent Chairman - and DMC will be set up.

The TSC, which includes independent members provides overall supervision of the trial on behalf of the funder. Its terms of reference will be agreed with the HTA and will be drawn up in a TSC charter which will outline its roles and responsibilities. Meetings of the TSC will take place at least once a year during the recruitment period.

An outline of the remit of the TSC is to:

- monitor and supervise the progress of the trial towards its interim and overall objectives
- review at regular intervals relevant information from other sources
- consider the recommendations of the DMC
- inform the funding body on the progress of the trial.

The DMC is a group of independent experts external to the trial who assess the progress, conduct, participant safety and, if required critical endpoints of a clinical trial.

The study DMC will adopt a DAMOCLES charter which defines its terms of reference and operation in relation to oversight of the trial. They will not be asked to perform any formal interim analyses of effectiveness. They will, however, review accruing data, summaries of the data presented by treatment group, and will assess the screening algorithm against the eligibility criteria. They will also consider emerging evidence from other related trials or research and review related SAEs that have been reported. They may advise the chair of the Trial Steering Committee at any time if, in their view, the trial should be stopped for ethical reasons, including concerns about participant safety. DMC meetings will be held at least annually during the recruitment phase of the study. Full details including names will be included in the DMC charter.

6.2 Quality control

We will institute a rigorous programme of quality control. The research fellow in conjunction with the trial coordinator will be responsible for ensuring adherence to the trial protocols at the trial sites. Quality assurance checks will be undertaken by the CTU to ensure integrity of randomisation, study entry procedures and data collection. The CTU has a quality assurance manager who will monitor this trial by conducting regular (at least once in the lifetime of the study, more if deemed necessary) inspections of the Trial Master File. Furthermore, the processes of consent taking, randomisation, registration, provision of information and provision of treatment will be monitored. Written reports will be produced for the TSC, informing them if any corrective action is required.

6.3 Insurance and Indemnity Arrangements

The Sponsor has a specialist insurance policy in place - Newline Underwriting Management Ltd, at Lloyd's of London - which would operate in the event of any participant suffering harm as a result of their involvement in the research. Standard NHS cover for negligent harm is in place for NHS procedures. There will be no cover for non-negligent harm.

6.4 Dissemination

The study monograph will be prepared by the trial management team within three months of completion of the trial. We will simultaneously prepare a manuscript for a high impact peer-reviewed journal, which will allow for the results to be disseminated across the orthopaedic and rehabilitation communities, the wider medical community, NICE and hence policy makers. In addition, the study will be presented at the British Orthopaedic and Orthopaedic Trauma, and the North American OTA and European EFORT meetings. The lay co-applicants will lead on the dissemination of the trial results to patients and the wider public. To inform patients and the public, we intend to produce a lay summary which will be made available in the trial hospitals and to patients involved in the trial. In addition, we will publicise the work through social media outlets, such as Facebook and Twitter, as well as websites such as Patient.co.uk. This study will produce a clear recommendation for the 'NICE guidelines for complex fractures'. No patient identifiable information will be contained in any form of dissemination of study results.

6.5 Project Timetable and Milestones

We propose a 3 year study starting in Jan 2016 with a planned long-term follow-up of 5 years. The trial timetable is shown below, with key milestones indicated and responsible parties identified:

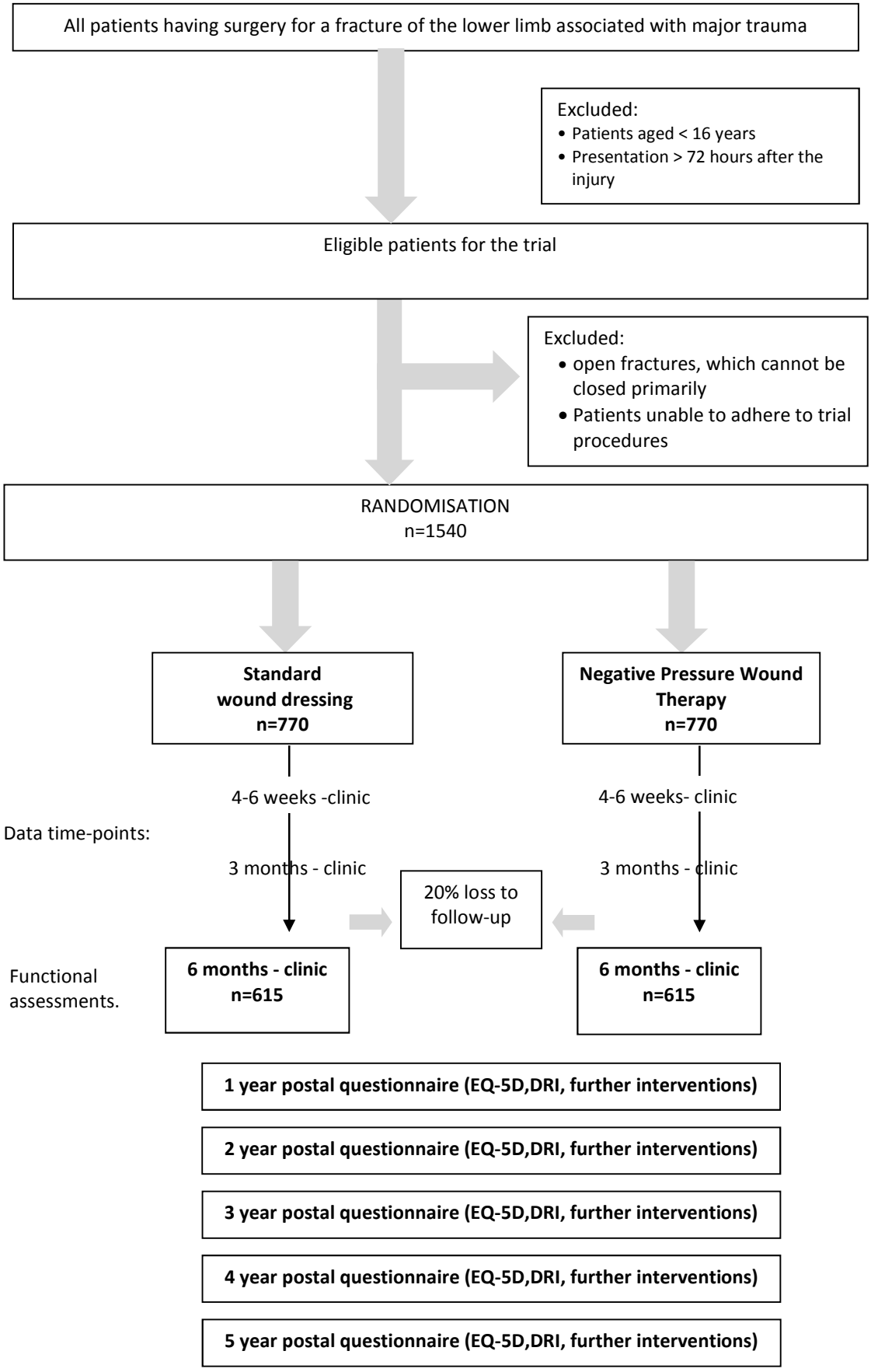
Month	By date	Activity	Milestone	Responsibility
-4-0		Ethic submission	REC approval	CI/RF
0-3	Jan 16	Start Trial		
			1st TSC/DMC meeting	CI/TM
		Finalise trial protocol	Protocol final version	TMG
	Mar 16	Complete CRF's	CRF final version	CI/Stat/TM
4-10	Apr 16	Start recruitment lead centre + pilot centres 1& 2	1st trial site online	TC/CI
	Jun 16	Start recruitment at pilot centres 3,4 &5	5 pilot sites online	TC/CI
	Sep 16	Finish pilot recruitment	24 centre months recruitment	TC/CI
	Oct 16	Decision on progression of trial	Report to TSC and HTA	TMG
11-25	Oct 16	Start staggered launch 2 centres/month		TC/CI
	Jun 17	50% total recruitment	800 patients enrolled	
	Jul 17	Complete site initiations	All 24 sites recruiting	TC/CI
	Aug 17	Data review first 800 patients	DMEC report	DMEC via TSC to HTA
	Sep 17		2nd TSC meeting	CI/TM
	Jan 18	End recruitment	1540 patients enrolled	
26-31	Jul 18	Complete 6 months follow-up all sites	1540 patients completed follow-up	
32-36	Oct 18	Statistical analysis		Stat
		Health economics analysis		HE
	Dec 18	Data review all patients	DMEC report	DMEC via TSC to HTA

			Final TSC meeting	TSC
	Mar 19	Final report HTA	HTA report	TMG

32-37	Jan 19	Complete 1 year postal follow-up		TM/DC
38-49	Jan 20	Complete 2 year postal follow-up		TM/DC
		Interim data review/TMG		TM/DC
50-61	Jan 21	Complete 3 year postal follow-up		TM/DC
62-73	Jan 22	Complete 4 year postal follow-up		TM/DC
		Interim data review/TMG		Stat
74-85	Jan 23	Complete 5 year postal follow-up		TM/DC
87	Mar 23	Statistical analysis		Stat
88	Apr 23	Final report HTA long-term follow-up	HTA report	TMG

CI Chief Investigator, RF Research Fellow, TMG Trial management group, TM Trial Manager, TSC trial steering committee, DMEC Data monitoring and Ethics Committee, Stat statistician, HE Health Economist, DC Data Clerk

7. Trial Flow Diagram



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