



FIXDT - For patients with a displaced fracture of the distal tibia, is there a clinical and cost-effectiveness difference between 'locking' plate fixation and intramedullary nail fixation

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Amendment 9	24-06-2014	22-07-14	Clarification on how the randomisation is implemented

Amendment 10	26-02-2015	20-04-15	Opt in option for long term follow up at outset of the study. Addendum foot pressure walking study.
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Abbreviations

AE – Adverse Event
CI – Chief Investigator
CRF – Clinical Reporting Form
CTU – Clinical Trials Unit
DEXA - Dual Energy X-ray Absorptiometry
DMC – Data Monitoring Committee
DRI – Disability Rating Index
EQ-5D - EuroQol
FIXDT – Fixation of Distal Tibia Fractures
HE – Health Economy/Economist
HTA- Health Technology Assessment
MCAR – Missing completely at random
MCID – Minimal Clinically Important Difference
OMAS – Olerud and Molander Score
PACS - Picture Archiving and Communications System
PI – Principal Investigator
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
WCTU – Warwick Clinical Trials Unit

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Collaborating Centres – Internal Pilot phase

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- 2) University Hospitals of Leicester NHS trust
Leicester Royal Infirmary
- 3) Nottingham University Hospital NHS Trust
Queen Medical Centre -Nottingham
- 4) North Bristol NHS Trust
Frenchay Hospital, Bristol
- 5) Cambridge University Hospital NHS Foundation Trust
Addenbrooke's Hospital, Cambridge
- 6) South Tees Hospital NHS Foundation Trust
The James Cook University Hospital, Middlesbrough

Collaborating Centres – Main phase

- 7) Oxford University NHS Trust
John Radcliffe Hospital
- 8) NHS Grampian
Aberdeen Royal Infirmary
- 9) Plymouth Hospitals NHS Trust
Plymouth Hospital
- 10) Lothian NHS Board
Royal Infirmary of Edinburgh
- 11) University Hospitals North Midlands NHS Trust
Royal Stoke Hospital
- 12) Brighton & Sussex University Hospitals NHS Trust
Royal Sussex Hospital – Brighton
- 13) The Newcastle Upon Tyne NHS Trust
Royal Victoria Infirmary
- 14) Greater Glasgow and Clyde NHS Board
Glasgow Royal Infirmary
- 15) Poole Hospital NHS Foundation Trust
Poole Hospital
- 16) Royal Berkshire NHS Foundation Trust
Royal Berkshire Hospital
- 17) Portsmouth Hospitals NHS Trust
Queen Alexander Hospital
- 18) King's College Hospital NHS Foundation Trust
Kings College Hospital, London
- 19) Aintree University Hospital
- 20) University Hospitals Birmingham NHS Foundation Trust
Queen Elizabeth Hospital - Birmingham
- 21) University Hospital Southampton NHS Trust
University Hospital Southampton
- 22) The Leeds Teaching Hospitals NHS Trust

- Leeds General Infirmary
- 23) St Georges Hospitals NHS Trust
St Georges Hospital, London
- 24) Hull & East Yorkshire NHS Trust
Hull Royal Infirmary
- 25) Northumbria Healthcare NHS Foundation Trust
North Tyneside General Hospital
Wansbeck General Hospital
- 26) Heart of England NHS Foundation Trust
Birmingham Heartlands Hospital
- 27) City Hospitals Sunderland NHS Foundation Trust
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Trial Steering Committee

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Prof Simon Donell	Independent member
Mr Tim Chesser	Independent member
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2. Background

The tibia is the most commonly broken major bone in the leg. Injuries usually require hospital admission, frequently require surgery and result in prolonged periods (months) away from work and social activities.

The treatment of displaced, extra-articular fractures of the distal tibia (lower third) remains controversial. These injuries are difficult to manage due to the limited soft tissue cover, poor vascularity of the area and proximity of the fracture to the ankle joint. Infections, non-union and malunion are well-recognised complications.

Non-operative treatment is one option and avoids the risks associated with surgery. Sarmiento et al. in 2003, ¹ reviewed 450 closed fractures of the distal tibial following functional bracing: 13.1% developed a malunion (defined as greater than seven degrees of angulation or 12 mm shortening). A further study using a more robust definition of 10 mm shortening and five degrees angulation found a higher rate of malunion (26.4%)². Bostman et al ², treated patients in a long leg cast and failure to maintain reduction lead to surgical treatment with an intramedullary nail. Thirty two of 103 cases required nailing at a mean of nine days following injury. Two patients went on to have a non-union in this group and three in the non-operative group ². Union rates were faster with intramedullary nailing compared with conservative treatment - median values were 12.5 weeks and 14.5 weeks respectively (p0.001) ². Digby et al, ³ also found that non-operative treatment for tibial fractures in the metaphyseal region, leads to unacceptable deformity and ankle stiffness. Therefore, non-operative treatment is not the treatment of choice in the majority of patients with a fracture of the distal tibia.

Surgical treatment options are expanding and include locked intramedullary nails, plate and screw fixation and external fixator systems including the Ilizarov frame and hybrid fixators. External fixators may be beneficial in selected cases – particularly those with severe soft-tissue injuries - but the nail and plate options are the most common in the UK. Mid-shaft fractures of the tibia are generally successfully treated with locked intramedullary nails. However, in the more distal metaphyseal region of the tibia the fixation may be less stable. ⁴ The nail or screws which are inserted into the nail may break ⁵, mal-alignment may occur ⁶ and there is a risk that the nail will penetrate into the ankle joint ^{7 8}.

The development of locking plates (where a thread on the head of the screws locks into the holes in the plate to create a 'fixed-angle' construct) has led to a recent increase in the use of plate fixation. However, plates are not without risks either, they require greater soft tissue dissection which carries a risk of infection, wound breakdown and devitalisation of the surrounding tissue ⁹.

In a retrospective study of 111 patients with extra-articular fractures of the distal tibia (4 to 11 cm proximal to the plafond), a comparison was made between intramedullary nailing and plate fixation. Seventy-six fractures were treated with an intramedullary nail and thirty seven were treated with a medial plate ¹⁰. Nine patients (12%) had a delayed or non-union in the intramedullary nail group and one patient (2.7%) had a non-union after plate fixation (p = 0.10). Angular malalignment of > or = five degrees occurred in 22 patients with nails (29%) and two with plates (5.4%, P = 0.003). The authors concluded that fractures of the distal tibia may be treated successfully with plates or nails, but that delayed union, malunion, and secondary procedures were more frequent after intramedullary nailing. Janssen et al ¹¹ found similar results, delayed union was higher in intramedullary nail group (25%) compared to plate fixation (16.7%), rotational mal-alignment was also higher in the intramedullary nailing group (16.7%) compared with 0% in the plate group. However this was not a randomised controlled trial and the

results do need to be interpreted with some caution. Randomized prospective assessment will be necessary to further clarify these issues and provide information about costs associated with these fractures ¹⁰.

Only two prospective randomised controlled trials have been published to date. In the first, 64 patients were randomised to either intramedullary nail or plate fixation for the treatment of a closed extra-articular fracture ¹². The time to union was found to be similar for the two groups and there was no difference in terms of Olerud and Molander functional scores at two years. However a significant difference was observed in the number of wound complications; one in the intramedullary nail group versus seven in the plate group. This paper concludes that intramedullary nailing is the treatment of choice for this injury. However the method of randomisation was poorly described and so bias in group assignment may have occurred. The study used traditional (non-locking plates) rather than the newer fixed-angle devices. Furthermore, the study included patients with Tschene classification C2 injuries which may have influenced the results. The second trial randomised 111 patients to either intermedullary nail fixation or locking plate fixation ¹³. This trial also showed no difference in the time to union but, one year after the injury there was some evidence of improved American Orthopaedic Foot and Ankle Society functional scores in the nail group. However, this was a single-centre investigation and over 20% of the patients in the trial were lost to follow-up.

In a meta-analysis, Zelle et al ¹⁴ reviewed 1125 extra-articular fractures of the distal tibia. They reported, non-union, mal-union and infection rates are similar for patients undergoing intramedullary nailing and plate fixation. It must be noted none of the studies in the review were randomised controlled trials.

2.1 Pre-pilot data

We performed a pilot study involving 24 patients with, extra-articular fractures of the distal tibia which were closed or Gustilo & Anderson grade 1 ¹⁵. This study was a randomised controlled trial with clinical assessment, functional outcomes and radiological images performed at baseline, 6 weeks, and 3, 6 and 12 months post-surgery. The study was performed to obtain an estimate of the potential effect size to inform the sample size calculation for a larger definitive trial and to assess recruitment rates and study feasibility.

The study had 12 patients in each group. There was no statistically significant difference between the groups six months after the injury but there was a 10 point difference (SD 20) in the Disability Rating Index in favour of the intramedullary nail group. More secondary procedures were required in the locking plate fixation group. There was also a large difference in the cost of the implants.

This pilot study provides compelling evidence to support the development of a definitive randomised trial in multiple centres.

2.2 Good Clinical Practice

The trial will be carried out in accordance with Medical Research council (MRC) Good Clinical Practice and applicable UK legislation using the following protocol.

2.3 Consort

The trial will be reported in line with the CONSORT statement

3. Trial design

3.1 Null hypothesis

There is no difference in the Disability Rating Index (DRI) at 6 months after injury between adults with a displaced fracture of the distal tibia treated with 'locking' -plate fixation versus intramedullary nail fixation.

3.2 Objectives

The primary objective is:

To quantify and draw inferences on observed differences in the Disability Rating Index between the trial treatment groups at 6 months after injury.

The secondary objectives are:

1. To quantify and draw inferences on observed differences early functional status at 3 months and later functional status at 12 months.
2. To quantify and draw inferences on observed differences in the radiological outcomes: nonunion, mal-alignment and shortening.
3. To identify any differences in health-related quality of life between the trial treatment groups in the first year after the injury.
4. To determine the complication rate of intramedullary nail fixation versus 'locking' - plate fixation in the first year after the injury.
5. To investigate, using appropriate statistical and economic analytical methods, the resource use, costs and comparative cost effectiveness of intramedullary nail fixation versus 'locking' - plate fixation.

3.3 Trial summary

The proposed project is a two-phased study. Phase 1 (Internal Pilot) will determine the expected rate of recruitment in a large-scale multi-centre randomised controlled trial in this complicated area of trauma research. Phase 2 (Main phase) will be the proposed randomised controlled trial in a minimum of 18 trauma centres across the UK.

Internal Pilot summary

The pilot will take place in 6 centres over a period of 6 months. The main 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. Screening logs will be kept at each site to determine the number of patients assessed for eligibility and reasons for any exclusion. In addition, the number of eligible and recruited patients, and the number of patients who decline consent/withdraw, will be recorded.

Main RCT summary

All adult patients presenting at the trial centres with an acute fracture of the distal tibia are potentially eligible to take part in the trial. The broad eligibility criteria will ensure that the results of the study can readily be generalised to the wider patient population.

A computer generated randomisation sequence, stratified by centre and age, will be produced and administered independently by a secure web-based service. Randomisation will be on a 1:1 basis to either intramedullary nailing or 'locking'- plate fixation. Both of these operations are widely used within the NHS and all of the surgeons in the chosen centres will be familiar with both techniques.

Baseline demographic data, radiographs and pre-injury functional data using the DRI and the Olerud and Molander Questionnaire will be collected. The patients will also be asked to fill out the EuroQol EQ-5D health-related quality of life questionnaire twice at baseline; one to indicate their typical pre-injury health status and second to indicate their current 'post injury' status i.e how they are feeling today.

A research associate will perform a clinical assessment and make a record of any early complications at 6 weeks and a radiograph will be taken. A further clinical assessment and radiograph will also be taken at 12 months post-operatively to detect late complications. Functional outcome, health-related quality of life and resource use questionnaires will be collected at 3 months, 6 months and 12 months post-operatively.

The results of the trial will be available at the end of the first year of follow-up. However, the long-term function and failure rates of the two interventions are increasingly important. Therefore, at the entry point to the trial, the initial consent form will include an option for the participant to agree to enter our long term follow up for ten years. This involves sending each patient a shortened annual postal questionnaire which includes the Disability Rating Index, EQ-5D and a 'further treatment' question. The completion of these questionnaires should take no more than 5 minutes. For those patients already in the trial but have not reached the 12 month time point they will be re consented, where this is not possible, verbal consent will be sought over the phone using a documented verbal agreement form.

3.4 Outcome measures

The primary outcome measure for this study is the **Disability Rating Index (DRI)** ²⁰. The DRI score is a validated questionnaire which is self-reported (filled out by the patient). It consists of 12 items specifically related to function of the lower limb. This data will be collected at baseline, 3, 6 and 12 months post-operatively. The DRI has been proven to be a robust, practical clinical and research instrument with good responsiveness and acceptability for assessment of disability caused by impairment in the lower limb.

The secondary outcome measures in this trial are:

Olerud and Molander (OMAS) is a self-administered patient questionnaire. It is a good outcome tool for assessing symptoms after an ankle fracture. The score is based on nine different items: pain, stiffness, swelling, stair climbing, running, jumping, squatting, supports and work/activities of daily living ²¹. The scoring system correlates well with parameters considered to summarise the results after this type of injury and is therefore recommended for use in scientific investigations.

EQ-5D; The EQ-5D is a validated, generic health-related quality of life measure consisting of 5 dimensions each with a 3-level answer possibility. Each combination of answers can be converted into a health utility score ²². It has good test-retest reliability, is simple for patients to use, and gives a single preference-based index value for health status that can be used for broader cost-effectiveness comparative purposes.

Complications; all complications will be recorded, including malunion, delayed/non-union, infection, wound complications, vascular and neurological injury and venous thrombo-

embolism. A record will also be kept of any other surgery required in relation to the index fracture, including removal of any metalwork.

Radiographic evaluation; Standard anterior-posterior and lateral radiographs of the tibia and fibula will be taken at baseline, 6-weeks and 12 months after the injury. These radiographs are those routinely used for the investigation of patients with a suspected fracture of the distal tibia and for the follow-up of such patients following any intervention, so there will be no need to request any additional or special investigations.

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 etc.

TIME POINT DATA COLLECTION

Baseline	DRI OMAS, EQ-5D <i>pre-injury</i> , <u>EQ-5D current health status 'as of today'</u> , & radiographs
6 weeks	Complication records, radiographs and operative record
3 months	DRI, OMAS, EQ-5D, record of complications/rehabilitation or other interventions and resource use questionnaire
6 months	DRI, OMAS, EQ-5D, record of complications/rehabilitation or other interventions and resource use questionnaire
12 months	DRI, OMAS, EQ-5D, radiographs, record of complications/rehabilitation or other interventions and resource use questionnaire
Annual	Postal DRI, EQ-D5 and further treatment questionnaire (recording any post-operative Questionnaire problems or treatments)

Table 1 Follow-up measures

3.5 Sample size

The minimum clinically important difference (MCID) is 8 points on the primary outcome (Disability Rating Index: DRI) measurement scale. The DRI is a 12-question, patient reported, functional outcome measure (physical exercise or sports, running, heavy physical work, heavy lifting, carrying a bag, leaning over a wash-stand, making a bed, moderate physical work, walks, mounting stairs, sitting still more than briefly and dressing or undressing) converted to a 100 point scale were '0' represents normal function and '100' is completely disabled. At an individual patient level, a difference of 8 points represents the ability to climb stairs or run with 'some difficulty' versus with 'great difficulty'. At a population level, 8 points represents the difference between a 'healthy patient' and a 'patient with a minor disability'. Eight points also corresponds approximately to the clinically worthwhile benefit identified in other studies and the difference between treatment group means in our pilot study.

The standard deviation (SD) of the DRI in our pilot study was approximately 20 points; the sample size has also been estimated for a larger and smaller standard deviation to obtain an indication of the sensitivity to changes in this parameter. Assuming the distribution of DRI in the study populations to be approximately normal, which is consistent with assumptions made for other reported trials using DRI as the primary outcome measure, the table below shows the total trial sample size with two-sided

significance set at 5% for various scenarios of power and sample SD.

The bold figure of 264 patients represents the most likely scenario, based on our current knowledge, for 90% power to detect the selected MCID. Allowing a margin of 20% loss during follow-up, this gives a figure of **320 patients in total**. Therefore, 160 patients randomized to each group will provide 90% power to detect a difference of 8 points in DRI at 6 months with 90% power at the 5% level.

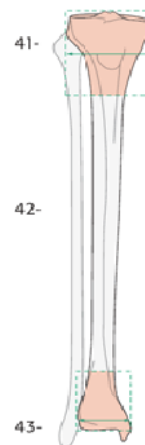
SD	Power	
	80%	90%
15	112	150
20	198	264
25	308	412

3.6 Methodology

3.6.1 Eligibility

Patients will be eligible for this study if:

- Aged 16 years or over
- Any fracture which involves the distal tibial metaphysis – defined as a fracture extending within 2 Muller squares of the ankle joint¹⁷ (see diagram showing Muller square)
- The fracture is closed
- In the opinion of the attending surgeon, the patient would benefit from internal fixation of



Patients will be excluded from participation in this study if:

- In the opinion of the attending surgeon, there is a contraindication to intra-medullary nailing
- The fracture is open
- There is a contra-indication to anaesthesia
- There is evidence that the patient would be unable to adhere to trial procedures or complete questionnaires
- The fracture extends into the ankle joint (i.e Intra-articular fracture)

Contraindications to intramedullary nailing are: that the medullary canal is too narrow OR there is a pre-injury deformity of the medullary canal OR it is not possible to achieve fixation of four cortices with screws distal to the fracture. We feel that this single exclusion criterion will be easily understood by the surgeons and is in keeping with the pragmatic nature of the trial. However, we will include the specific reason in the trial screening data. For those patients withdrawing from the trial after written consent has been obtained, data obtained up until the point of withdrawal will be included in the final analysis.

3.6.2 Recruitment

The internal pilot will specifically inform and test the recruitment rate for the main trial. Recruitment will take place in 6 trial centres over a period of 6 months. The expected rate of recruitment is based upon a pre-pilot study performed at the lead centre. The average recruitment rate for this pre-pilot study, during which 24 patients were recruited, was 1.3 patients per month. The other centres involved in the trial will all be regional trauma units with similar catchment areas to the lead centre. Experience from previous multi-centre trials has however shown that recruitment outside of the lead centre tends to occur at a lower rate. As such, a conservative recruitment rate of 0.75 patient per month per centre is estimated for this trial. If this recruitment rate can be 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 18 centres in total (including the lead centre). The sample of 320 patients will be recruited over a 30 months period.

Screening logs will be collected throughout the trial to assess the main reasons for patient exclusion as well as number of patients unwilling to take part. Patients will be screened by the Research Associates in the Emergency Department and Fracture Clinics at the trial centres. Any patient with a fracture of the distal tibia whom, in the opinion of the treating surgeon would benefit from internal fixation, will potentially be eligible for the trial. The trial will act in accordance with the Mental Capacity Act 2005 and the procedures for undertaking trials in 'emergency settings' will be followed as described in detail below in section 3.6.3 (consent) of this protocol. The consent procedures will be reviewed at the end of the pilot period.

3.6.3 Consent

The clinical team responsible for the patients care will make the decision regarding the patients' capacity.

Informed consent from the patient will be obtained by the local research associate. Patients will be provided with verbal and written information about the study. In general, patients who are admitted with a fracture of the distal tibia will have their surgery on the next available trauma list. Timing and appropriateness of obtaining consent in this setting will be closely monitored during the internal pilot and reviewed by the independent Trial Steering Committee.

For those patients withdrawing from the trial after written consent has been obtained, data obtained up until the point of withdrawal will be included in the final analysis.

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.

3.6.4 Randomisation

The method of fixation will be allocated using a secure, centralised, web-based randomisation service. The randomisation service will be available twenty-four hours each day to facilitate the inclusion of all eligible patients. The allocated treatment will then be reported to the Research Associate who will inform the treating surgeon. The surgeon will then arrange the allocated surgery on the next available trauma operating list, as per standard practice at that institution; this will ensure the integrity of the randomisation process. Randomisation will be implemented using a minimization algorithm (sometimes referred to as *adaptive randomization*) that attempts, at recruitment of each new patient, to balance the marginal totals for each level of the stratification factors identified below. This is the usual practice for trials run at Warwick CTU. Experience indicates that for studies where some centres recruit only a relative small number of patients this method tends to perform better than conventional stratification methods.

Stratification by centre will help to ensure that any clustering effect related to the centre itself will be

equally distributed in the trial arms. The catchment area (the local population served by the hospital) will be similar for all of the hospitals; each hospital being a trauma unit dealing with these fractures on a daily basis. While it is possible that the surgeons at one centre may be more expert in one or other treatment than those at another centre, all of the recruiting hospitals have been/will be chosen on the basis that both techniques are currently routinely available at the centre i.e. theatre staff and surgeons will already be equally familiar with both forms of fixation. This cannot eliminate the surgeon -specific effect of an individual at any one centre ¹⁶. However, fixation of a fracture of the tibia is not an uncommon procedure and many surgeons will be involved in the management of this group of patients; between 10 and 30 surgeons at each centre, including both Consultants and Trainees. Therefore, we anticipate that each individual surgeon will only operate on 2-3 patients enrolled in the trial, greatly reducing the risk of a surgeon-specific effect upon the outcome in any one centre.

Stratification on the basis of age will be used to discriminate between younger patients with normal bone quality sustaining high-energy fractures, and older patients with low-energy (fragility) fractures related to osteoporosis. The stratification will help to identify any effect related to the quality of the patients' bone. The use of DEXA (dual energy x-ray absorptiometry) is widely regarded as the gold-standard for the assessment of bone density. However, such an investigation may be expensive and not routinely available at all centres.

Therefore we propose to use age as a surrogate for bone density. In a large study in Norway involving 7600 participants, it was demonstrated that bone mineral density remains stable up until the age of 50 years. After the age of 50, bone mineral density decreased steadily in males, whilst in females there was an initial decline between the ages of 50 and 65, with a further decline in the age groups thereafter ¹⁸. A recent study by Court-Brown and Caeser ¹⁹, assessed over 1000 patient with a fracture. This study confirmed that there is a clear bimodal distribution according to the age of the patient. The crossover of the two peaks of incidence was around 50 years of age. These studies provide strong evidence that patients over the age of 50 become increasingly vulnerable to fragility fractures. Therefore, we have chosen an age of 50 as the stratification cut-off for this trial.

3.6.5 Post randomization withdrawals

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 record anonymously any relevant hospital data that is recorded as part of normal standard of care; i.e x-rays and further surgery information.

2) or Participants can withdrawal wholly from the study and only 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.

3.6.6 Blinding

As the type of fixation used is 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 assessment of the patients. The functional outcome data will be collected and entered onto the trial central database via postal questionnaire by a research assistant/data clerk in the trial central office. The X-rays collected will be reviewed by an independent assessor.

3.7 Trial treatments

All of the hospitals involved in this trial currently use both of the methods of fixation and all of the consulting surgeons involved will be familiar with both techniques. Operative fixation of fractures of the distal tibia usually takes place under a general anaesthetic but this decision will be made by the attending anaesthetist.

Each patient will undergo the allocated surgery according to the preferred technique of the operating surgeon. Although, the basic principles of Intramedullary nailing and 'locking'- plate fixation are inherent in the technique (see below), there are several different implant systems and several different options for the positioning of the screws. Similarly, each surgeon will make minor modifications to their surgical technique according to preference and the specific pattern of each fracture. In this trial, the details of the surgery will be left entirely to the discretion of the surgeon to ensure that the results of the trial can be generalised to as wide a group of patients as possible. However, a copy of the 'operating record' will form part of the trial dataset.

Although all of the surgeons in the trial will be familiar with both techniques, it is possible that an individual surgeon may have more experience with one technique than the other. We expect that the proficiency of an individual surgeon to perform the procedure may change over time, as the surgeon gains experience and expertise. The term 'learning curve' is often used to describe this process. It will be important to monitor the learning -curve for all surgeons throughout the trial. The operating time recorded on the operative record for each surgery, will be used as a proxy to measure the task efficiency of the surgeons (quality assurance of the clinical process) and the number of complications (e.g. infections) at six weeks after surgery will also be recorded as a patient-based outcome. Given the number of centres and surgeons taking part in this trial, no individual surgeon will perform more than a small number of the procedures. However, where data is available for individual surgeons, temporal variations in operation times and complications at one week will be modelled for each surgeon using a power curve for the trend with appropriate adjustment for confounding factors such as the age of the patients ¹⁶. Also, as this study involves multiple surgeons, in addition to multiple centres, we anticipate that a more complex hierarchical model ¹⁶ that fully accounts for the structure of the data may prove to be useful; therefore we anticipate fitting models of this type in the analysis. Results from the learning curve analysis for each surgeon will inform inferences regarding overall treatment differences and if necessary guide recommendations for implementation and training.

3.7.1 Intramedullary Nailing

The intramedullary nail is inserted at the proximal end of the tibia and passed down the centre of the bone in order to hold the fracture in the correct (anatomical) position. The reduction technique, the surgical approach, the type and size of the nail, the configuration of the proximal and distal inter-locking screws and any supplementary device or technique will be left entirely to the discretion of the surgeon as per standard clinical practice.

3.7.2 'Locking' plate fixation

The 'locking' plate is inserted at the distal end of the tibia and passed under the skin on the surface of the bone. Again, the details of the reduction technique, the surgical approach, the type and position

of the plate, the number and configuration of fixed-angle screws and any supplementary device or technique will be left to the discretion of the surgeon. The only stipulation is that fixed -angle screws must be used in at least some of the distal screw holes – this is standard practice with all distal tibia 'locking' plates.

3.7.3 Rehabilitation

We will ensure that all patients randomised into the two groups will receive the same standardised, written physiotherapy advice detailing the exercises they need to perform for rehabilitation following their injury. All of the patients in both groups will be advised to move their toes, ankle and knee joints fully within the limits of their comfort. Weight-bearing status will be decided by the treating surgeon. In this pragmatic trial, any other rehabilitation input beyond the written physiotherapy advice (including a formal referral to physiotherapy) will be left to the discretion of the treating clinicians. However, a record of any additional rehabilitation input (type of input and number of additional appointments) together with a record of any other investigations/interventions will be requested as part of the 3 month, 6 month and 12 month follow-ups and this will also form part of the trial dataset.

3.7.4 Follow-up

Baseline, standardised radiographs will be copied from the hospital PACs (archiving) system. Copies of the baseline clinical report forms (CRFs) and images will be delivered to the trial co-ordinating centre.

As part of routine clinical practice patients will be seen in clinic on a regular basis after this injury. Any further clinical follow-up in the first year after the injury, will be at the discretion of the surgeon but will not influence the collection of the standard outcome data. For this trial, the primary outcome point will be at six months -when patients with an uncomplicated fracture may expect to return to normal activities but to ensure that all complications and secondary procedures are captured we propose to continue follow-up for one year¹³.

The Research Associate will perform a clinical assessment and make a record of any early complications at 6 weeks. Radiographs will be taken at 6 weeks and 12 months. The radiograph at 6 weeks will be used to assess the quality of the reduction: malalignment will be defined as more than 10mm of shortening and more than 5 degrees of angulation in any plane². An uncomplicated fracture of the distal tibia would be expected to be clinically united at 6 months after the injury. The primary, functional outcome measure will therefore be collected at 6 months. However, radiographic union may lag behind the clinical picture. Therefore, the 12-month radiographs will be used as the definitive radiographic assessment of alignment² and to assess if there are long-term complications including, non-union (failure to show bridging callus on three out of four cortices on orthogonal radiographs) and arthritis of the ankle joint (joint space narrowing with osteophyte formation and peri-articular sclerosis).

The functional outcome data will be collected using questionnaires at 3, 6 and 12 months post-operatively. In addition to the DRI, the patients will be asked to fill out the EuroQol questionnaire, a complications/further surgical interventions and resource use questionnaire. Patients will be asked to complete their 6 and 12 months post-operative questionnaire during their routine follow-up appointments. The 3 months post-operative questionnaires, Short annual questionnaires and any 'missed' questionnaires will be sent to the patients through the post; a process done centrally by a data clerk at the Warwick Clinical Trials Unit. All of the outcome questionnaires can be completed over the phone if postal copies are not returned. Text messages may be sent to patients to inform them that a questionnaire is due or on its way. Text messages will only be sent to those patients who

have given their prior consent to this by initialing the corresponding box on the consent form. Text messages will be sent via the Warwick Clinical Trials Unit Mobile phone from a secure office. The lead site (University of Warwick) will request a copy of the consent form from each patient that is entered into the study to determine if the patient has consented to text messages before a message is sent out.

Thereafter patients that have consented to the 'long-term' follow up will be sent an annual postal questionnaire for ongoing surveillance.

3.8 Adverse event management

3.8.1 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 'FIXDT' central office.

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

1. *Results in death,*
2. *Is life-threatening*
3. *Requires hospitalisation or prolongation of existing inpatients' hospitalisation,*
4. *Results in persistent or significant disability or incapacity,*
5. *Is a congenital anomaly or birth defect*
6. *Any other important medical condition which, although not included in the above, may require medical or surgical intervention to prevent one of the outcomes listed.*

All serious adverse events (SAE) will be entered onto the Serious Adverse Event reporting form and faxed to a dedicated fax machine at Warwick Clinical Trials Unit 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) and sponsor within 15 days. All such events will be reported to the Trial Steering Committee and Data Monitoring Committee at their next meetings.

SAEs that may be expected as part of the surgical interventions, and that do not need to be reported to the main REC are: complications of anaesthesia or surgery (e.g. wound complications, infection, damage to a nerve or blood vessel and thromboembolic events) and secondary operations for or to prevent infection, malunion, non-union or for symptoms related to the metalwork. All participants experiencing SAEs will be followed-up as per protocol until the end of the trial.

3.8.2 Risks and benefits

The risks associated with this study are predominantly the risks associated with 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. There is no data to suggest that the risk is greater in one group or another. We believe that the overall risk profile is similar for the two interventions but assessment of the number of complications in each group is a secondary objective of this trial.

3.9 End of trial

The end of the trial will be defined as the collection of 10 year outcome data from the last

participant.

4. 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 accessible only to essential personnel. Paper forms with patient-identifiable information will be held in secure, locked filing cabinets within a restricted area of Warwick Medical School. Patients will be identified by a code number only. Direct access to source data/documents will be required for trial-related monitoring. All paper and electronic data will be retained for at least five years after completion of the trial.

4.1 Statistical Analysis

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 data 'missingness' 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 completely at random (MCAR). If judged appropriate, missing data will be imputed using the multiple imputation facilities (mice package) available in R (<http://www.r-project.org/>). 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 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.

Standard statistical summaries (e.g. medians and ranges or means and variances, dependent on the assumed distribution of the outcome) 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 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 DRI at 6 months after surgery, between the two treatment groups on an intention-to-treat basis. In addition, early functional status will also be assessed and reported at 3 months and later functional status at 12 months. The differences between treatment groups will be assessed using a Student t-test, based on a Normal approximation for the DRI score at 6 months, and at other occasions. 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). Estimates of treatment effects will be presented with 95% confidence intervals.

As discussed earlier, the stratified randomization procedure will ensure a balance in recruiting centre between test treatments and as we anticipate that any individual surgeon will operate on no more than 2-3 patients enrolled in the trial we do not expect surgeon-specific effects to be important in this study. However, in addition to the unadjusted analysis (t-tests) we will also undertake regression analyses to adjust for any imbalance between test treatment groups in patient age or gender. The fixed effects analysis (linear regression model) will also be generalized by adding a random effect for recruiting centre to allow for possible heterogeneity in patient outcomes due more generally to the recruiting centre. DRI data will be assumed to be normally distributed during modelling, but subsidiary analyses

may also be undertaken after appropriate variance-stabilising transformation. The primary focus will be the comparison of the two treatment groups of patients, and this will be reflected in the analysis which will be reported together with appropriate diagnostic plots that check the underlying model assumptions. Treatment effects will be presented, with appropriate 95% confidence intervals, for both the unadjusted and adjusted analyses.

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 important complications (e.g. infection).

A detailed statistical analysis plan (SAP) will be agreed with the Data management Committee (DMC) at the start of the study. Any subsequent amendments to this initial SAP will be clearly stated and justified. Interim analyses will be performed only where directed by the DMC. The routine statistical analysis will mainly be carried out using R (<http://www.r-project.org/>) and S-PLUS (<http://www.insightful.com/>). Results from this trial will also be compared with results from other trials.

4.2 Health Economic analysis

A prospective economic evaluation, conducted from a NHS and personal social services perspective, will be integrated into the trial design²³. The economic evaluation will estimate the difference in the cost of resource inputs used by participants in the two arms of the trial, allowing comparisons to be made between the two surgical treatment options (intramedullary nail versus 'locking' plate fixation) for patients with a displaced, extra-articular fracture of the distal tibia, and enabling costs and consequences to be compared. The economic assessment method will, as far as possible, adhere to the recommendations of the NICE Reference Case²³. Primary research methods will be followed to estimate the costs of the surgical treatment options, including supplementary devices and rehabilitation inputs. Broader resource utilisation will be captured through two principal sources: (i) routine health service data collection systems; and (ii) patient questionnaires administered at baseline, and three, six and twelve months post-randomisation. Unit costs for health and social care resources will largely be derived from local and national sources and estimated in line with best practice. Primary research using established accounting methods may also be required to estimate unit costs. Costs will be standardised to current prices where possible. Health-related quality of life will be measured at baseline pre-injury status), and three, six and twelve months post-operation using the EuroQol EQ-5D measure; responses will be used to generate quality-adjusted life-years (QALYs). The EQ-5D is a short questionnaire which is widely used in economic evaluation; utility weights will be taken from the UK General Population tariff for the EQ-5D. We will in the first instance use self-reports of the EuroQol EQ-5D measure. Where these data are not available, we will estimate health utilities at each time point using mapping equations between the DRI score and EQ-5D health outcomes on the basis of existing datasets held by the trial team. Multiple imputation methods will be used to impute missing data and avoid biases associated with complete case analysis. The results of the economic evaluation will be expressed in terms of incremental cost per QALY gained. We shall use non-parametric bootstrap estimation to derive 95% confidence intervals for mean cost differences between the trial groups and to calculate 95% confidence intervals for incremental cost effectiveness ratios. A series of sensitivity analyses will be undertaken to explore the implications of uncertainty on the incremental cost-effectiveness ratios and to consider the broader issue of the generalisability of the study results. One such sensitivity analysis will involve adopting a societal perspective for the economic evaluation, which will

incorporate direct costs to trial participants, informal care provided by family and friends, and productivity losses. In the baseline analysis, and for each sensitivity analysis, cost-effectiveness acceptability curves will be constructed using the net benefits approach. Heterogeneity in the trial population will be explored by formulating net-benefit values for trial participants from the observed costs and effects, and then constructing a regression model with an intervention variable and covariates such as age, contemporaneous injuries and experience of surgeons in trial participating centres. The magnitude and significance of the coefficients on the interactions between the covariates and the intervention variable will provide estimates of cost-effectiveness of the surgical options by participant sub-group. More extensive economic modelling using decision-analytic methods will extend the target population, time horizon and decision context, drawing on best available information from the literature together with stakeholder consultations to supplement the trial data. Parameter uncertainty in the decision-analytic model will be explored using probabilistic sensitivity analysis. Longer term costs and consequences will be discounted to present values using discount rates recommended for health technology appraisal in the United Kingdom.

5. Trial Oversight

The day-to-day management of the trial will be the responsibility of the Trial Coordinator, based at Warwick Medical School CTU and 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 coordinator to undertake training of the research associates 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 and Ethics Committee will be set up.

5.1 Trial Supervision

A Trial Steering Committee (TSC) (with an independent Chairman) and Data Monitoring Committee will be set up. 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.

Day-to-day management of the trial will be overseen by a Trial Management Group.

5.2 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 WCTU to ensure integrity of randomisation, study entry procedures and data collection. The WCTU has a quality assurance manager who will monitor this trial by conducting regular (yearly or 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.

5.3 Insurance and Indemnity Arrangements

Standard NHS cover for negligent harm is in place. There will be no cover for non-negligent harm.

5.4 Dissemination

The results of this trial will substantially inform clinical practice on the clinical and cost effectiveness of the treatment of this injury. The results of this project will be disseminated through peer-reviewed journals, conference presentations, the National Library for Health and through local mechanisms at all participating centres.

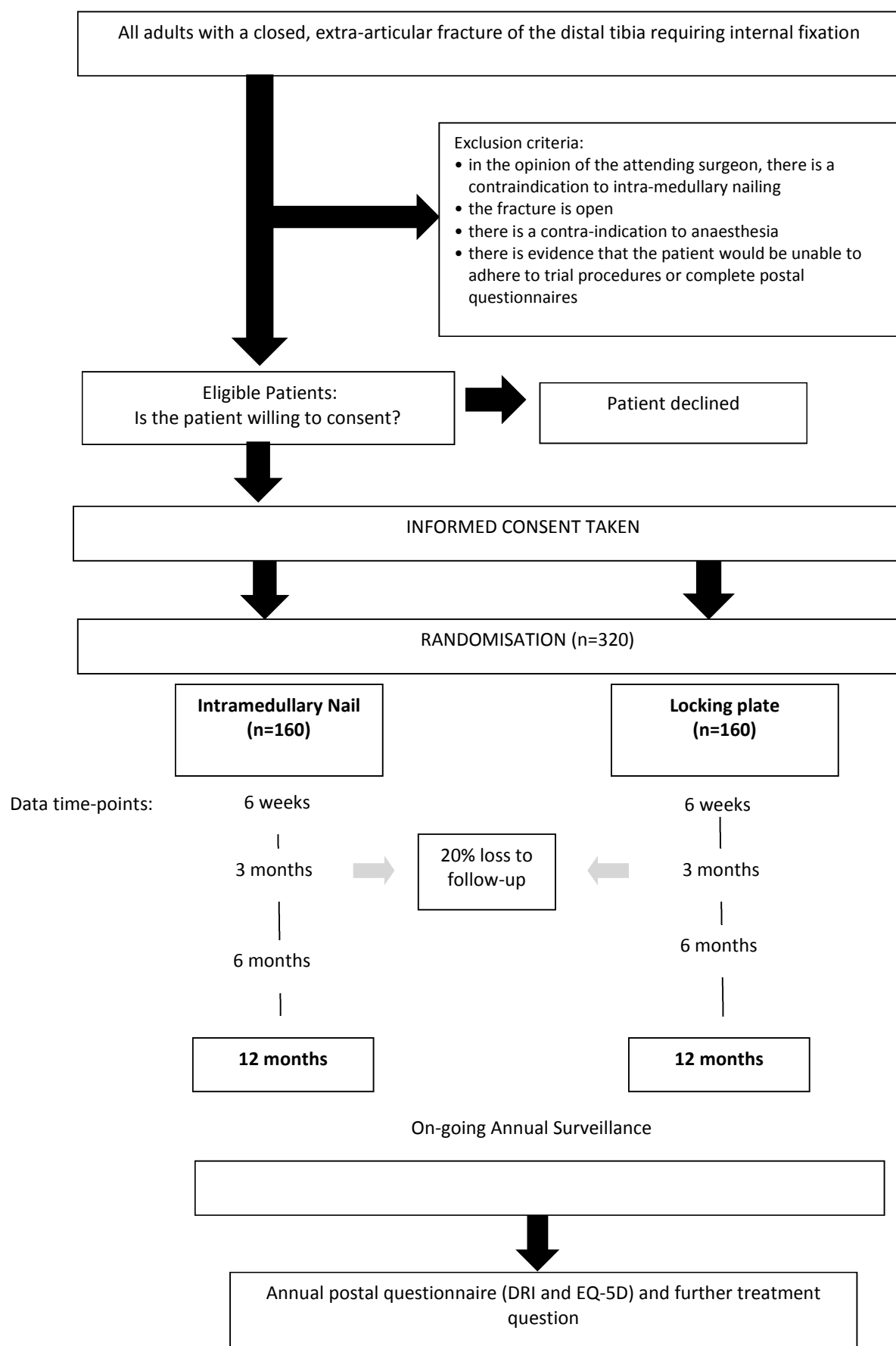
5.5 Project Timetable and Milestones

We propose a 4 year study starting in March 2013. The planned trial timetable is shown below, with key milestones indicated and the responsible parties identified:

Month	By date	Activity	Milestone	Responsibility
-4-0		Ethic submission	REC approval	CI/RF
0-3	March 2013	Start Trial		
	April 2013		1 st TSC/DMC meeting	CI/TC
	May 2013	Finalise trial protocol	Protocol final version	TMG
	May 2013	Complete CRF's	CRF final version	CI/Stat/TC
4-10	June 2013	Start recruitment lead centre + pilot centres 1 & 2	1 st trial site online	TC/CI
	July 2013	Start recruitment at pilot centres 3,4,5 & 6	6 pilot sites online	TC/CI
	Nov 2013	Finish pilot recruitment	33 centre months recruitment	TC/CI
	Dec 2013	Decision on progression of trial	Report to TSC and HTA	TMG
11-16	Jan 2014	Start staggered launch 1-3 centre/month		TC/CI
	May 2014	Start 12/12 follow-up assessments	Initiate follow-up phase	TMG
	June 2014	Complete site initiations	All 18+ sites recruiting	TC/CI
	Nov 2014	50% total recruitment	160 patients enrolled	
17-33	Jan 2015	Data review first 160 patients	DMEC report	DMEC via TSC to HTA
	Feb 2015		2 nd TSC meeting	CI/TC
	Nov 2015	End recruitment	320 patients enrolled	
	Jan 2016	Data review 320 patients	DMEC report	DMEC via TSC to HTA
34-45	Feb 2016		3 rd TSC meeting	CI/TC
	Nov 2016	Complete follow-up all sites	320 patients completed follow-up	
	Dec 2016	Data review		
	Jan 2017	Statistical analysis		Stat
46-48	Jan 2017	Health economics analysis		HE
	Feb 2017		Final TSC meeting	TSC
	May 2017	Final report HTA	HTA report	TMG

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

5.5 Trial flow diagram



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