

BMJ Open Total ankle replacement versus arthrodesis (TARVA): protocol for a multicentre randomised controlled trial

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ABSTRACT

Introduction: Total ankle replacement (TAR) or ankle arthrodesis (fusion) is the main surgical treatments for end-stage ankle osteoarthritis (OA). The popularity of ankle replacement is increasing while ankle fusion rates remain static. Both treatments have efficacy but to date all studies comparing the 2 have been observational without randomisation, and there are no published guidelines as to the most appropriate management. The TAR versus arthrodesis (TARVA) trial aims to compare the clinical and cost-effectiveness of TAR against ankle arthrodesis in the treatment of end-stage ankle OA in patients aged 50–85 years.

Methods and analysis: TARVA is a multicentre randomised controlled trial that will randomise 328 patients aged 50–85 years with end-stage ankle arthritis. The 2 arms of the study will be TAR or ankle arthrodesis with 164 patients in each group. Up to 16 UK centres will participate. Patients will have clinical assessments and complete questionnaires before their operation and at 6, 12, 26 and 52 weeks after surgery. The primary clinical outcome of the study is a validated patient-reported outcome measure, the Manchester Oxford foot questionnaire, captured preoperatively and 12 months after surgery. Secondary outcomes include quality-of-life scores, complications, revision, reoperation and a health economic analysis.

Ethics and dissemination: The protocol has been approved by the National Research Ethics Service Committee (London, Bloomsbury 14/LO/0807). This manuscript is based on V.5.0 of the protocol. The trial findings will be disseminated through peer-reviewed publications and conference presentations.

Trial registration number: NCT02128555.

INTRODUCTION

Every year 29 000 patients with ankle osteoarthritis (OA) seek an opinion from orthopaedic foot and ankle specialists, of which 3000 will choose to undergo surgical treatment on the National Health Service.¹ The main surgical treatments for end-stage ankle OA are total ankle replacement (TAR) or ankle arthrodesis (fusion). The popularity of

Strengths and limitations of this study

- TAR versus arthrodesis is the first randomised controlled trial to compare ankle replacement against arthrodesis.
- Unable to blind any postrandomisation assessments due to the nature of interventions.
- Study is limited to the age 50–85 years.

ankle replacement is increasing among patients while ankle arthrodesis rates remain static.² When deciding whether to undergo ankle replacement or arthrodesis, patients draw on many information resources but the majority of them rely on the advice from their surgeon in order to make a final decision.³ There is a paucity of quality evidence available in order to correctly guide and inform patient care.

To date all studies comparing ankle replacement versus fusion have been observational and lacking randomisation and there are no published guidelines as to the most appropriate management. A meta-analysis of the literature by Haddad *et al*⁴ showed that TAR and fusion have similar intermediate term outcomes in terms of clinical scores, patient satisfaction and revision rate. Both have been shown to improve quality of life at 1 year but with no difference between the two operations.⁵ Another study showed a higher risk of major revision surgery with ankle replacement, but higher risk of adjacent-joint fusion with ankle arthrodesis.⁶ This was a population-based study and patients who received TAR and fusion may not have been comparable.

The TAR versus arthrodesis (TARVA) trial aims to investigate the clinical and cost-effectiveness and complication rates of TAR against ankle arthrodesis in the treatment of end-stage ankle OA in patients aged 50–85 years.



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METHODS AND ANALYSIS

Study design

TARVA is a randomised, multicentre, non-blinded, prospective, parallel group trial of TAR versus ankle arthrodesis in patients with end-stage ankle OA aged 50–85 years, comparing clinical outcomes and cost-effectiveness. An internal feasibility stage (6 months) will be used to ensure adequate recruitment rates are achieved and to establish surgeon willingness to randomise and patient willingness to be randomised. Following the feasibility stage, an Independent Data Monitoring Committee (IDMC) will advise whether to progress to the substantive trial.

Inclusion criteria

Patients with end-stage ankle OA, aged 50–85 years, who the surgeon believes to be suitable for both TAR and arthrodesis are eligible to join the trial (having considered various patient factors including deformity, stability, bone quality, soft tissue envelope and neurovascular status). The patients must be able to read and understand the Patient Information Sheet (PIS) and provide written informed consent. Eligible patients (box 1) will be randomised to a surgery type.

‘End-stage’ OA is defined as a combination of severe unrelenting symptoms sufficient to make the patient consider surgical intervention, radiological changes consistent with OA and failure of at least 6 months of non-operative measures necessitating a definitive surgical procedure.

Recruitment and consent

Patients will be recruited prospectively by the principal investigators in outpatient clinics at participating UK

sites. If eligible for the trial, patients will be shown a short video about the trial (available online at <http://www.anklearthritis.co.uk>) and asked to read the PIS and a generic information booklet about ankle arthritis and its surgical treatment options. The patient can then ask questions about the trial, and have as much time as they need to consider the information. Written informed consent will be obtained and details of participation in the trial will be recorded in the clinical notes by the research nurse.

Confidentiality

All study-related information will be stored securely at the study site. All participant information will be stored in locked filing cabinets in areas with limited access. All reports, data collection, process and case report forms (CRFs) will be identified by a patient identification (ID) number only to maintain patient confidentiality. All records that contain names or other personal identifiers, such as informed consent forms, will be stored separately from study records identified by code number. All local databases will be secured with password-protected access systems. Any listings that link patient ID numbers to other identifying information will be stored in a separate, locked file in an area with limited access.

Patients’ study information will not be released outside of the study without their written permission.

Imaging

All patients will have a preoperative standard ankle MRI scan after providing a written informed consent. Scans will be transferred via the Image Exchange Portal for assessment of presence or absence of OA in the adjacent talonavicular and subtalar joints, by a consultant radiologist at the Royal National Orthopaedic Hospital (RNOH), Stanmore, UK. Scans will be anonymised and stored at RNOH. The purpose of the MRI scan is to determine the presence or absence of adjacent-joint arthritis, as this is deemed by the investigating surgeons to be a confounding factor for prognosis and hence included as a stratifying variable in the randomisation.

No further MRI scans will be performed as part of the study. But a subsequent longer term imaging outcome study may be considered after 5–10 years subject to a further funding application.

Timeline

The 6-month feasibility phase of the trial will start when the first patient is randomised. Recruitment strategies will be reviewed during this phase to ensure that the required sample size can be achieved in a total of 24 months of recruitment, so that the trial will have adequate power. Further sites which treat sufficient numbers of patients with ankle OA may be opened if deemed necessary to achieve target recruitment.

Box 1 Inclusion & exclusion criteria

Inclusion criteria

1. Patients with end-stage ankle osteoarthritis, aged 50–85 years.
2. The surgeon believes they are suitable for both total ankle replacement and arthrodesis (having considered various patient factors including deformity, stability, bone quality, soft tissue envelope and neurovascular status).
3. The patients must be able to read and understand the Patient Information Sheet and provide written informed consent.
4. Patients who are fit for surgery.

Exclusion criteria

1. Previous ipsilateral talonavicular, subtalar or calcaneocuboid fusion or surgery planned within 1 year of index procedure.
2. More than four lower limb joints fused (including contralateral limb, but excluding proximal interphalangeal joint (PIPJ) fusions).
3. Unable to have either an MRI or a CT scan (eg, severe claustrophobia or contraindication for both types of scan).
4. History of local bone or joint infection.
5. Any comorbidity, which, in the opinion of the investigator, is severe enough to; interfere with the patient’s ability to complete the study assessments or; presents an unacceptable risk to the patient’s safety.
6. The patient is participating in another clinical trial that would materially impact on their participation in this study.

Postrecruitment withdrawals and exclusions

Patients may withdraw from the study at any time without prejudice. Those patients who do not wish to participate in the trial following informed consent will be withdrawn. Data and any information about serious adverse events obtained from this group of patients up until the point of withdrawal will be included in the final analysis, in accordance with the intention-to-treat principle, unless they explicitly request the removal of their information from the trial database. The general practitioners of any patients 'lost to follow-up' will be contacted in an attempt to complete follow-up relating to adverse events, complications and prescribed medications. Patients may be withdrawn from the study at the discretion of the site principal investigator due to safety concerns.

Randomisation

A total of 328 patients will be randomised using a minimisation algorithm incorporating a random element, stratifying by surgeon and presence of OA in two adjacent joints (subtalar and talonavicular) as determined by a preoperative standard ankle MRI scan. An independent online randomisation service (<https://www.sealedenvelope.com>) will be used to minimise allocation bias within the trial.

Randomisation will be carried out at each recruiting site once the patient has been found to be fit for surgery at their preoperation assessment visit ~2–6 weeks before surgery. The research nurse or a delegated individual will log on to the online randomisation service and provide basic descriptive information (hospital, surgeon, patient initials and date of birth) and confirmation of eligibility, followed by MRI scan grade:

1. Subtalar joint OA present/absent
2. Talonavicular joint OA present/absent

Once the above details have been supplied, the randomised surgical allocation will be given immediately and the patient will be notified of their allocated surgical treatment.

Blinding

It is not possible to blind patients, surgeons, radiologists and clinical assessors in this trial. Surgeons will know which procedure they are performing and radiologists will be able to identify from radiographs which procedure has taken place. Patients who received ankle arthrodesis will know their ankle is stiff (a known consequence of the surgery), whereas those undergoing TAR will retain motion at the ankle.

Trial treatments

Surgeons involved in the TARVA trial are required to be familiar with both surgical treatments. This is defined as having performed ≥ 10 ankle replacements and ≥ 10 ankle arthrodesis. If a surgeon is using a new CE-marked ankle replacement, they must have completed a minimum of a formal cadaveric training course and

performed a minimum of three surgeries using the implant prior to participation in TARVA. All operation details are recorded on a CRF, including any additional procedures performed at the time of the primary procedure.

Group 1: ankle replacement

The prosthesis will be inserted using the surgeon's standard technique, which essentially involves an anterior approach to the ankle joint avoiding the neurovascular bundle. Once the joint is exposed it will be debrided of osteophytes to aid entry into the joint. The talar and tibial surfaces will be prepared according to the prosthesis used and its instrumentation. Most surgeons will opt to use intraoperative fluoroscopy to confirm position. Once inserted, the wound will be irrigated and closed using the surgeon's standard technique. Use of fluoroscopy and the surgeon's closure technique (such as use of drains or sutures vs clips) will be captured on a CRF. The surgeon's usual postoperative protocol will be followed with respect to method of immobilisation (plaster or walking boot) and weight-bearing status, with details captured for each patient on the CRF.

Group 2: ankle arthrodesis

This can be carried out as an open procedure or arthroscopically depending on the surgeons' preference, ~50% of operations are performed arthroscopically.¹ The technique is generally the same in that the diseased articular cartilage and subchondral bone plate are removed to reveal bleeding cancellous bone surfaces, and the two bone ends are opposed in the most appropriate position (neutral dorsiflexion, 5° valgus and 5° external rotation or to match the contralateral limb) and held with screws or plates until the joints fuse which usually takes between 12 and 16 weeks. If performed as an open procedure, an anterior or lateral incision is normally used. If performed arthroscopically the two portals will be made anteromedially and anterolaterally over the ankle joint for access. If arthroscopic access is not favourable the operation may be converted to an open procedure intraoperatively. The surgical technique will be captured on the CRF. The surgeon's usual postoperative protocol will be followed with respect to use of plaster or walking boot and weight-bearing status. Again the specific details of these will be captured for each patient on the CRF.

Follow-up schedule

Table 1 presents the trial schedule of assessments. Patients will have clinical assessments and complete questionnaires preoperatively, and at 2, 6, 12, 26 and 52 weeks after surgery. All patients will undergo routine clinical review at 2 weeks when the stitches will be removed and plaster assessed. Trial-specific outcome measures including adverse events and postprocedural complications will be recorded from the time of surgery up to the 52-week visit, and costs obtained from the

Table 1 Schedule of assessments

| Visit | Screen/ introduction to study | Follow-up call(s) | Scan | Preoperative assessment (baseline) | Randomisation (inform patient) | Surgery (week 0) | Week 2 follow-up visit 1: clinical review* | Week 6 follow-up visit 2* | Week 12 follow-up visit 3 | Week 26 follow-up visit 4 | Week 52 follow-up visit 5 |
|--|-------------------------------------|----------------------|----------------------------------|--|-----------------------------------|---------------------|--|---------------------------------|--|---------------------------------|--|
| Visit timing | Approximately –12 weeks | | Approximately –6 weeks | –4 weeks | –4 weeks | Day 0 | 2 weeks | 6 weeks | 12 weeks | 26 weeks | 52 weeks |
| Visit window | | | | ±2 weeks | ±2 weeks | | ±2 weeks | ±2 weeks | ±4 weeks | ±4 weeks | ±4 weeks |
| CRF required | 1 and 2 | 3 | | 5, 6, 7, 8, 9 and 20 | 10 | 11 and 20 | 12 and 20 | 13 | 14, 9 and 20 | 15,6,7,8, 9 and 20 | 16,6,7,8, 9 and 20 |
| <i>Procedure</i> | | | | | | | | | | | |
| Patient ID and screening (inclusion/exclusion criteria) | T | | | | | | | | | | |
| Give study information | T | | | | | | | | | | |
| Patient decision | | T | | | | | | | | | |
| Scan booked | | T | | | | | | | | | |
| Surgery slot booked | | R | | | | | | | | | |
| Informed consent | T (or at scan) | | T (if not given at screening) | | | | | | | | |
| Letter to GP | | | T | | | | | | | | |
| MRI (or CT) scan | | | R/T | | | | | | | | |
| Full tibia X-ray | | | R/T (any time preoperative)** | | | | | | T (anytime within 6 months of surgery) | | |
| Physical examination | | | | R | | | R | R | R | R | R |
| EQ-5D | | | | T | | | | | T | T | T |
| MOXFQ | | | | T | | | | | | T | T |
| FAAM | | | | T | | | | | | T | T |
| CSRI | | | | T | | | | | T | T | T |
| ROM (plantar/dorsiflexion) | | | | T | | | | | | | T |
| Randomisation | | | | T | | | | | | | |
| Patient notified of randomisation | | | | | T | | | | | | |
| Order kit | | | | | R | | | | | | |
| Surgery | | | | | | R | | | | | |
| Concomitant medication | | | | | | | | | | | T (update log as required) |
| Record adverse events | | | | | | | | | | | T (record on AE log or report on notification of SAE from consent onwards) |

*In all cases, at the first post-op visit complete the Visit 1 Clinical Review. If this falls within the Visit 2 window report this as a Protocol Deviation. If Visit 2 is then missed report this as a second Protocol Deviation.

**Only request full tibia x-ray at Scan or Pre-Op visit if not already taken as part of routine care.

AE, adverse events; CRF, case report forms; CSRI, Client Service Receipt Inventory; EQ-5D, EuroQol five dimensions; FAAM, foot and ankle ability measure; GP, general practitioner; MOXFQ, Manchester Oxford Foot Questionnaire; R, routine procedure; trial related; ROM, range of movement; SAE, serious adverse events.

Client Service Receipt Inventory questionnaire and patient notes, will be recorded at baseline, 12, 26 and 52 weeks. Longer term follow-up of patients is planned at 2, 5 and 10 years, although the analysis and publication of these results will be subject to a further funding application by the group.

Measures of clinical effectiveness

The primary outcome is the change in the Manchester Oxford Foot Questionnaire (MOXFQ) walking/standing domain scores between preoperative and 52 weeks post-operative. The MOXFQ walking/standing domain score has been validated and is the most sensitive domain to assess improvement in foot and ankle conditions.^{7 8}

Secondary outcomes include the change in MOXFQ walking/standing domain score from preoperative to 26 weeks and change in MOXFQ pain and social interaction domains from preoperative to 26 and 52 weeks. As an additional measure of physical function, the foot and ankle ability measure (FAAM) will be captured preoperative and at 26 and 52 weeks. Quality of life will be captured using the EQ-5D questionnaire preoperative and at 12, 26 and 52 weeks.

Total range of motion of the tibia to the floor will be captured preoperative and at 52 weeks. This will formally assess plantarflexion and dorsiflexion using a goniometer and a standardised technique. This range includes motion at the hindfoot, midfoot and forefoot joints, and is relevant as it reflects the functional range of motion the patient shall experience irrespective of the isolated motion (or absence of) at the tibiotalar (ankle) joint. All adverse events, serious adverse events and complications reported from the date of surgery until the final follow-up visit at 52 weeks (± 4 weeks) will be recorded.

Patients who require further interventions during the study period will be eligible for standard care as if those happened outside of the study. Details of any additional interventions or treatments will be recorded as a (serious) adverse event ((S)AE) and reported under the safety outcome.

Power and sample size

The planned total sample size is 328 patients; 164 patients enrolled to each surgical treatment group. This sample size will give 90% power using the 5% significance level to detect a difference of 12 in the post-operative change in the MOXFQ walking/standing domain score between the two surgical treatment groups assuming a SD of 27,⁹ a surgeon intraclass coefficient of 0.03 (the extent to which the difference between the 2 procedures varies between surgeons), average of 14 patients per surgeon, and a loss to follow-up of 10%.

Statistical analysis

The main analysis will be conducted following the modified intention-to-treat principle. We will analyse the data from all patients who undergo surgery, in accordance with their randomised surgical procedure. Only those

patients who do not undergo surgery of any kind will be excluded from the analysis. We will also conduct a sensitivity analysis for the primary outcome measure where we will analyse the data from all participants who undergo surgery according to the surgical procedure received, if cross-over prior to surgery does occur. Any cross-overs or other treatment deviations, as well as the number of patients who did not undergo surgery of any kind will be specified along with reasons.

For the primary outcome, analysis of the change in MOXFQ walking/standing domain score, we will use a mixed linear regression model that will include a fixed effect for treatment, baseline MOXFQ and presence of OA in two adjacent joints as determined by a preoperative MRI scan, along with a random surgeon effect and random surgeon by treatment interaction to take account of clustering by surgeon. We will include all patients with any follow-up data in these models. Missing covariate data are not anticipated since covariates must be recorded to allocate treatment. Missing outcome data will be assumed to be missing at random, conditional on any variable included in the analysis model (MAR), and so independent of the values of the unobserved data themselves. Any missing outcome data will therefore be handled naturally by the linear mixed model, which is robust to the MAR assumption. Continuous secondary outcome measures will be analysed similarly. Serious adverse events, revision surgery and complication rates in the two groups will be compared using relative risks calculated from a binomial regression model.

An exploratory subgroup analysis will be performed to investigate whether there is any interaction between the effect of treatment and the presence of OA in the two adjacent joints as determined from the preoperative MRI scan. While we may predict that patient reported outcome measure (PROM) scores in patients who had TAR will be better than in patients who had arthrodesis when there is OA in adjacent joints, we accept that this question may only be answered once the 5-year and 10-year follow-up data are available. Based on the findings of SooHoo *et al.*,⁶ it is further hypothesised that patients undergoing arthrodesis may experience more adjacent-joint arthritis than those undergoing TAR.

Long-term continuous outcomes will similarly be analysed with linear mixed regression models. Treatment and time will be modelled along with the interaction between them. The models will include random surgeon effects and fixed effects for the presence of OA in adjacent joints at baseline as determined by the preoperative MRI scan. Long-term binary outcomes (revision surgery, reoperation other than revision and adjacent-joint OA) will be modelled using mixed logit models.

A statistical analysis plan will be agreed before the first substantive statistical analysis and approved by the Independent Trial Steering Committee (TSC). Any confidential interim analyses will be performed at the request of the IDMC. All statistical tests will use a two-sided $p=0.05$, unless otherwise specified. There will be

no formal adjustment of *p* values for any interim analyses performed. All CIs presented will be 95% and two sided. All statistical analysis will be performed using Stata (StataCorp, College Station, Texas, USA).

Health economics analysis

We will undertake a detailed analysis of the cost and cost-effectiveness of TAR versus ankle arthrodesis in patients with end-stage ankle OA. Our analysis will conform to recommended economic evaluation methods such as those from the National Institute for Health and Care Excellence (NICE).¹⁰ For the primary economic analysis costs will be assessed from the perspective of the NHS and personal social services while secondary analysis will consider additional costs borne by the patient as well as societal costs. We will estimate cost and cost-utility for the 'within-trial' period, based on the clinical and health-related quality-of-life results at baseline and follow-up. We will also extrapolate beyond the trial period to estimate cost-effectiveness over the expected lifetime of the patients.

Costs and utilities

Health service costs associated with treatment will include the cost of the surgery by type (including cost of implants), perioperative complications, tests undertaken, boot and plaster changes, revision and reoperation surgery by type and overall hospital length of stay. We will ask patients to tell us about their outpatient attendances, hospital readmissions, primary care contacts, physiotherapy sessions, accident and emergency attendances and prescribed medications. For the broader societal analysis we will also ask the patients to tell us about the costs they would incur as part of their OA treatment, including time and travel costs incurred in the receipt of care, out-of-pocket expenditures and time off work. The volume of resource for each cost component will be measured directly in the trial from both patient records and through patient self-report forms. Unit costs will be taken from standard published sources.

Patient-specific utility profiles will be constructed assuming a linear change in utility values measured at each time point. Utility estimates will be calculated according to the area under the curve approach, adjusting for baseline differences in patients in the trial arms if necessary.

Within-trial and model-based analysis

The cost-effectiveness measures in the 1-year model will be the incremental cost per unit increase in MOXFQ and the incremental cost per quality-adjusted life year (QALY) gained. QALYs will be calculated based on the responses to the EQ-5D collected at baseline and specified follow-up points.

In the lifetime model, cost-effectiveness will be calculated in terms of the incremental cost per QALY gained. A review of previous cost-effectiveness and cost-utility

analyses will be conducted to identify any existing modelling work that may be drawn for developing the model structure and informing model parameters. In the UK, there are no previous studies of the cost-effectiveness of ankle arthrodesis versus ankle replacement, but a number of health technology assessment (HTA)-funded studies have been undertaken on the cost-effectiveness of hip replacement surgery, which may yield relevant economic model structures. The specific details of the data required to populate the model will be determined following the development of the model structure. We will undertake deterministic (one way, two way and multiway) and probabilistic sensitivity analysis, the latter assuming appropriate distributions and parameter values that will also be used to construct cost-effectiveness acceptability curves.

Analysis methods

Both the within-trial and model-based analyses will be undertaken within a Bayesian framework. Methods for conducting economic evaluation using clinical trial data will be applied following O'Hagan and Stevens¹¹ and O'Hagan, Stevens and Montmartin.¹² Monte Carlo simulation methods will be used to construct a cost-effectiveness acceptability curve, based on the expected net benefit statistic, to estimate the probability that the intervention is cost-effective for a range of values of societal willingness to pay per QALY. We will also subject the results to extensive deterministic (one-way, two-way and multiway) sensitivity analysis. Missing EQ-5D and resource use data will be addressed using appropriate statistical methods in consultation with the trial statistician.

Dissemination

The findings of this study will be disseminated through peer-reviewed publications and conference presentations.

Access to data

The Comprehensive Clinical Trials Unit (CCTU) will oversee data sharing, with input from the Trial Management Group.

Data will be stored on a password-protected MACRO database. Site staff will have direct access to their own site's data. No patient identifying information is recorded on the database.

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Collaborators At the time of submission, the following surgeons are screening patients for eligibility and recruiting: Mr Stephen Bendall; Mr Andrew Bing; Mr Chris Blundell; Mr Clifford Butcher; Ms Caroline Chadwick; Mr Tim Clough; Mr Paul Cooke; Mr Nick Cullen; Mr James Davenport; Mr Howard Davies; Mr Mark Davies; Mr Andrew Goldberg; Mr Paul Halliwell; Mr Simon Hill; Mr Rajesh Kakwani; Mr Mike Karski; Mr David Loveday; Mr Nilesh Makwana; Mr Chris Marquis; Mr Steve Milner; Mr Viren Mishra; Mr Andrew Molloy; Mr An Murty; Mr Mark Rogers; Mr Javed Salim; Mr Hemant Sharma; Mr Malik Siddique; Mr Dishan Singh; Mr George Smith; Mr Robert Smith; Mr Rhys Thomas; Mr Paulo Torres; Mr David Townshend. Details of all members of the trial oversight and TARVA Study group can be found on the website <http://www.anklearthritis.co.uk>.

Contributors AJG, RZ, CT, SSS, LK and PC developed the trial protocol and contributed to the writing of the manuscript. CJD, SC, SSS and JR were involved in development of the statistical and health economic analysis facets of the trial and contributed to the writing of the manuscript. AJG is the chief investigator for the study. AM, MD, MK are site principal investigators involved in the trial feasibility phase and the subsequent evolution of the protocol and also contributed to the writing of the manuscript.

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Competing interests None declared.

Ethics approval The National Research Ethics Service Committee (London, Bloomsbury) reviewed the study protocol and materials to be given to the prospective patients (approved 10 June 2014, REC reference number 14/LO/0807). Any subsequent amendments to these documents will be submitted for further approval. Before initiation of the trial at each additional clinical site, the same/amended documents will be submitted for local NHS permissions.

Provenance and peer review Not commissioned; externally peer reviewed.

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