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Total ankle replacement versus ankle arthrodesis for patients aged 50–85 years with end-stage ankle osteoarthritis: the TARVA RCT

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Disclosure of interests

Full disclosure of interests: Completed ICMJE forms for all authors, including all related interests, are available in the toolkit on the NIHR Journals Library report publication page at https://doi.org/10.3310/PTYJ1146.

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Abstract

Total ankle replacement versus ankle arthrodesis for patients aged 50–85 years with end-stage ankle osteoarthritis: the TARVA RCT

Andrew J Goldberg,[1,2,3*] Kashfia Chowdhury,[4] Ekaterina Bordea,[4] James Blackstone,[4] Deirdre Brooking,[2] Elizabeth L Deane,[4] Iva Hauptmannova,[2] Paul Cooke,[5] Marion Cumbers,[2] Simon S Skene[6] and Caroline J Doré[4] on behalf of the TARVA Study Group[†]

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Background: We aimed to compare the clinical effectiveness, cost-effectiveness and complication rates of total ankle replacement with those of arthrodesis (i.e. ankle fusion) in the treatment of end-stage ankle osteoarthritis.

Methods: This was a pragmatic, multicentre, parallel-group, non-blinded randomised controlled trial. Patients with end-stage ankle osteoarthritis who were aged 50–85 years and were suitable for both procedures were recruited from 17 UK hospitals and randomised using minimisation. The primary outcome was the change in the Manchester–Oxford Foot Questionnaire walking/standing domain scores between the preoperative baseline and 52 weeks post surgery.

Results: Between March 2015 and January 2019, 303 participants were randomised using a minimisation algorithm: 152 to total ankle replacement and 151 to ankle fusion. At 52 weeks, the mean (standard deviation) Manchester–Oxford Foot Questionnaire walking/standing domain score was 31.4 (30.4) in the total ankle replacement arm (n = 136) and 36.8 (30.6) in the ankle fusion arm (n = 140); the adjusted difference in the change was −5.6 (95% confidence interval −12.5 to 1.4; p = 0.12) in the intention-to-treat analysis. By week 52, one patient in the total ankle replacement arm required revision. Rates of wound-healing issues (13.4% vs. 5.7%) and nerve injuries (4.2% vs. < 1%) were higher and the rate of thromboembolic events was lower (2.9% vs. 4.9%) in the total ankle replacement arm than in the ankle fusion arm. The bone non-union rate (based on plain radiographs) in the ankle fusion arm was 12.1%, but only 7.1% of patients had symptoms. A post hoc analysis of fixed-bearing total ankle replacement showed a statistically significant improvement over ankle fusion in Manchester–Oxford Foot Questionnaire walking/standing domain score (−11.1, 95% confidence interval −19.3 to −2.9; p = 0.008). We estimate a 69% likelihood that total ankle replacement is cost-effective compared with ankle fusion at the National Institute for Health and Care Excellence's cost-effectiveness threshold of £20,000 per quality-adjusted life-year gained over the patient's lifetime.

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Limitations: This initial report contains only 52-week data, which must therefore be interpreted with caution. In addition, the pragmatic nature of the study means that there was heterogeneity between surgical implants and techniques. The trial was run across 17 NHS centres to ensure that decision-making streams reflected the standard of care in the NHS as closely as possible.

Conclusions: Both total ankle replacement and ankle fusion improved patients' quality of life at 1 year, and both appear to be safe. When total ankle replacement was compared with ankle fusion overall, we were unable to show a statistically significant difference between the two arms in terms of our primary outcome measure. The total ankle replacement versus ankle arthrodesis (TARVA) trial is inconclusive in terms of superiority of total ankle replacement, as the 95% confidence interval for the adjusted treatment effect includes both a difference of zero and the minimal important difference of 12, but it can rule out the superiority of ankle fusion. A post hoc analysis comparing fixed-bearing total ankle replacement with ankle fusion showed a statistically significant improvement of total ankle replacement over ankle fusion in Manchester–Oxford Foot Questionnaire walking/standing domain score. Total ankle replacement appears to be cost-effective compared with ankle fusion at the National Institute for Health and Care Excellence's cost-effectiveness threshold of £20,000 per quality-adjusted life-year gained over a patient's lifetime based on long-term economic modelling.

Future work: We recommend long-term follow-up of this important cohort, in particular radiological and clinical progress. We also recommend studies to explore the sensitivity of clinical scores to detect clinically important differences between arms when both have already achieved a significant improvement from baseline.

Trial registration: This trial is registered as ISRCTN60672307 and ClinicalTrials.gov NCT02128555.

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Contents

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List of tables

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List of figures

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List of abbreviations

AE	adverse event
ASA	American Society of Anesthesiologists
CEAC	cost-effectiveness acceptability curve
CI	confidence interval
CONSORT	Consolidated Standards of Reporting Trials
CRF	case report form
CSRI	Client Service Receipt Inventory
CT	computerised tomography
EQ-5D-3L	EuroQol 5-Dimensions, three-level version
EQ-5D-5L	EuroQol 5-Dimensions, five-level version
FAAM	Foot and Ankle Ability Measure
FAAM-ADL	Foot and Ankle Ability Measure – Activities of Daily Living
GP	general practitioner
HRQoL	health-related quality of life
ICC	intraclass correlation coefficient
ICER	incremental cost-effectiveness ratio
ICF	informed consent form
IDMC	Independent Data Monitoring Committee
ITT	intention to treat
MID	minimal important difference
MOXFQ	Manchester–Oxford Foot Questionnaire
MRI	magnetic resonance imaging
NICE	National Institute for Health and Care Excellence
NJR	National Joint Registry
PIS	patient information sheet
PSA	probabilistic sensitivity analysis
PSS	personal social services
QALY	quality-adjusted life-year
QoL	quality of life
RCT	randomised controlled trial
REC	Research Ethics Committee
ROM	range of motion
SAE	serious adverse event
SAP	statistical analysis plan
SD	standard deviation
SF-12	Short Form questionnaire-12 items
SF-36	Short Form questionnaire-36 items
SF-6D	Short Form questionnaire-6 Dimensions
TAR	total ankle replacement
TARVA	total ankle replacement versus ankle arthrodesis
TSC	Trial Steering Committee
UCL CCTU	University College London Comprehensive Clinical Trials Unit
VAS	visual analogue scale

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Plain language summary

Each year, over 29,000 patients with ankle osteoarthritis seek a specialist opinion, of whom 4000 undergo NHS surgical treatment. The main surgical treatments for severe ankle osteoarthritis are total ankle replacement or arthrodesis (i.e. ankle fusion). Both are known to be good treatments to relieve pain, and each has its advantages. Total ankle replacement is a more popular patient choice than ankle fusion. When deciding whether to undergo ankle replacement or fusion, patients consult various sources, but the majority of them rely on the advice of their surgeon to make a final decision. To the best of our knowledge, there has never been a high-quality randomised clinical trial comparing these two treatments and there are no published guidelines on the most suitable management.

In this study, 303 patients were randomised to a type of ankle surgery: 138 in the total ankle replacement arm and 144 in the ankle fusion arm received surgery. We found that both total ankle replacement and ankle fusion improved patients' walking ability, but we did not find a statistically significant difference between the treatment arms based on our primary outcome measure at 1 year. When we considered the type of total ankle replacement implant, we found that the implant most commonly used in the NHS (a fixed-bearing two-component implant) had better outcomes at 1 year than ankle fusion. Both total ankle replacement and ankle fusion appear to be safe. However, there were more wound-healing issues and nerve injuries in the total ankle replacement arm than in the ankle fusion arm. Twelve per cent of patients experienced bone non-union in the ankle fusion arm, but only 7.1% experienced symptoms.

We estimate that there is a 69% chance that total ankle replacement would be cost-effective compared with ankle fusion at the National Institute for Health and Care Excellence's cost-effectiveness threshold of £20,000 per quality-adjusted life-year gained over a patient's lifetime. This study provides the NHS with important information that could help to obtain the best possible outcome for patients with severe ankle arthritis.

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Scientific summary

Background

More than 29,000 patients in the UK present to specialists each year with symptomatic end-stage ankle osteoarthritis, a condition in which the cartilage lining the ankle joint has worn away, causing progressive pain and stiffness. Ankle osteoarthritis causes major disability and has a similar impact on quality of life (QoL) as end-stage hip osteoarthritis and cardiac failure. The demand incidence for ankle osteoarthritis has been estimated at 47.7 per 100,000. The majority of this is secondary to trauma caused by fractures or severe sprains, both of which are increasing; hence, ankle osteoarthritis is likely to become an increasingly important health problem, especially among working adults. Other causes of ankle osteoarthritis include long-standing inflammatory arthropathies (e.g. rheumatoid arthritis, haemochromatosis and haemophiliac arthropathy).

In the early stages of disease, non-operative measures such as a change in activity levels, weight loss, physiotherapy, painkillers and ankle braces should be used. When these conservative measures have failed, and a surgeon confirms the diagnosis of end-stage osteoarthritis on the basis of radiological and clinical evidence (i.e. plain radiographs and unrelenting symptoms, respectively), surgery might then be considered.

Although arthrodesis (i.e. ankle fusion) is the most common surgical treatment for end-stage ankle osteoarthritis, in response to patient demand, more and more surgeons are performing total ankle replacement (TAR). At least 4000 patients are treated with ankle fusion or TAR each year in the NHS. The TARs implanted in England, Wales, Northern Ireland, the Isle of Man and Guernsey are captured on the National Joint Registry, which has revision surgery as its end point. The British Orthopaedic Foot & Ankle Society only recently started capturing outcome data on ankle fusion patients. All studies comparing TAR with ankle fusion to date have been observational and, to the best of our knowledge, there have been no high-quality prospective randomised trials reported.

Objectives

The total ankle replacement versus ankle arthrodesis (TARVA) trial aimed to compare the clinical effectiveness and cost-effectiveness of TAR with that of ankle fusion for the treatment of end-stage ankle osteoarthritis in patients aged 50–85 years. Clinical effectiveness was measured through self-reported pain-free function using a standardised questionnaire of walking and standing ability 52 weeks post surgery. We also aimed to determine whether or not there was a difference in physical function [measured using the Foot and Ankle Ability Measure – Activities of Daily Living (FAAM-ADL)], QoL [measured using the EuroQol 5-Dimensions, five-level version (EQ-5D-5L)] and range of ankle motion at 26 and 52 weeks post surgery. We investigated the cost-effectiveness and cost–utility of TAR and ankle fusion.

Methods

Design

We conducted a pragmatic prospective, multicentre, parallel-group, non-blinded randomised controlled trial (RCT). Participants were randomised equally between two arms: TAR and ankle fusion. The study protocol [Goldberg AJ, Zaidi R, Thomson C, Doré CJ, Skene SS, Cro S, *et al.* Total ankle replacement versus arthrodesis (TARVA): protocol for a multicentre randomised controlled trial. *BMJ Open* 2016;**6**:e012716] was developed before recruitment commenced and detailed the design, interventions and study procedures.

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Setting and participants

The trial was conducted across 17 participating UK sites. Patients with end-stage ankle osteoarthritis who were aged 50–85 years and who the surgeon believed were suitable for both TAR and ankle fusion were eligible to join the trial. Patients had to be able to read and understand the patient information sheet (PIS) and provide written consent on an informed consent form (ICF).

Interventions and follow-up

At randomisation patients were allocated to receive either TAR or ankle fusion. For TAR, the remaining damaged cartilage was removed and the joints resurfaced with metal implants and an intervening polyethylene liner, either fixed or mobile bearing, to act as a gliding surface. All prostheses were Conformité Européenne marked. For ankle fusion, the remaining damaged cartilage was removed from the ends of the bone and the two bones held together in compression using screws or plates to join them as one bone (bone fusion) so that there was no longer any movement at the tibiotalar joint. Participants were seen at recruitment, randomisation, surgery visit and at 2, 6, 12, 26 and 52 weeks post surgery.

Blinding

This was an open (non-blinded) trial. It was not possible to blind patients, surgeons, radiologists or clinical assessors.

Randomisation

Participants were randomised in a 1 : 1 ratio to either TAR or ankle fusion. Randomisation was carried out using minimisation incorporating a random element, with surgeon and whether osteoarthritis was present in the subtalar or the talonavicular joint as minimisation factors. A secure online service (Sealed Envelope™; Sealed Envelope Ltd, London, UK) provided the treatment arm allocations.

Outcome measures

The primary outcome was the change in the Manchester–Oxford Foot Questionnaire (MOXFQ) walking/standing domain scores (0–100, where low scores are better) between the preoperative baseline and 52 weeks post surgery. The secondary outcomes were change in MOXFQ walking/standing domain score from preoperative baseline to 26 weeks and change in MOXFQ pain and social interaction domain scores from baseline to 26 and 52 weeks. An additional measure of physical function, the Foot and Ankle Ability Measure (FAAM), was captured at baseline and at 26 and 52 weeks. The changes in FAAM-ADL (0–100, where higher scores are better) and FAAM sport subscale scores from baseline were compared between arms. We also compared changes in QoL from baseline to 12, 26 and 52 weeks using the EQ-5D-5L questionnaire. Longer-term follow-up at 2, 5 and 10 years post surgery is planned.

Total range of motion (ROM) of the tibia to the floor was captured at baseline and 52 weeks. All adverse events (AEs), serious adverse events (SAEs) and complications reported from the date of consent until 52 weeks were compared between arms. Secondary outcomes that related to the economic evaluation included quality-adjusted life-years (QALYs), health-care resource use collected from patient files and a modified version of the Client Service Receipt Inventory (CSRI), and mean incremental cost per QALY gained.

Sample size

The sample size calculation for the primary outcome (change in MOXFQ walking/standing domain score by 52 weeks) was performed using Stata/IC®, version 12.1 (StataCorp LP, College Station, TX, USA). It was based on achieving 90% power to detect an estimated minimal important difference (MID) in the primary outcome at the 5% level of significance, accounting for expected loss to follow-up.

The sample size calculation was based on previous observational studies and determined it was important to detect a difference of 12 in the change from baseline in the MOXFQ walking/standing domain score between the two treatment arms. The standard deviation (SD) of the MOXFQ walking/standing domain score was estimated to be 27, and loss to follow-up was estimated to be 10% (attrition in similar RCTs has been 5–7%). Based on these quantities, the required sample size was estimated to be

118 patients per arm. The sample size was adjusted to account for clustering by surgeon. The intraclass correlation coefficient (ICC) was estimated based on previous studies, and the initially computed sample size was inflated by a factor of $f = 1 + (m - 1) \times ICC$. Assuming an average cluster size (m) of 14 (patients per surgeon) and an ICC of 0.03, an inflation factor of $f = 1.39$ was estimated, leading to a final required sample size of 164 per arm or 328 patients in total.

Data collection and management

Data were entered into a central MACRO v4 database (Elsevier, Amsterdam, the Netherlands) by sites, with internal validation checks to improve data quality; data queries were resolved by site staff before database lock and final analysis.

Statistical methods

As per the statistical analysis plan, all the analyses were conducted on an intention-to-treat (ITT) basis, meaning that all randomised participants with at least one postsurgery follow-up visit were included in the analysis, regardless of their adherence to treatment. In addition, a per-protocol analysis was performed for the primary outcome that included outcome data from only those patients who received their randomised surgical procedure within the time window specified in the protocol.

The primary analysis involved fitting a multilevel repeated-measures linear regression model to estimate the difference between treatment arms in the change in MOXFQ walking/standing domain score from baseline to 52 weeks. This analysis model used all available visit data (from 26 weeks and 52 weeks) to strengthen confidence in the missing at random assumption and provide greater power to detect differences at individual visits. The model was adjusted for baseline MOXFQ walking/standing domain score and presence of osteoarthritis in each of the two adjacent joints. A random surgeon effect was also included in the model to account for clustering by surgeon. Similar models were used for other continuous secondary outcomes to estimate differences at 26 and 52 weeks post surgery.

Economic evaluation

The aim of the economic evaluation was to assess the cost-effectiveness of TAR compared with ankle fusion in patients with end-stage osteoarthritis. We compared the costs and outcomes of the two arms over the time horizon of 52 weeks. Outcomes were QALYs, calculated using utility index values obtained from the EQ-5D-5L. The primary within-trial analysis was conducted according to the ITT principle from the NHS and personal social services (PSS) perspective. Costs included cost of surgery, cost of health-care resource use (collected using the CSRI) and cost of concomitant medications. Sensitivity analyses included per-protocol analysis and analysis from a societal perspective. The societal perspective included additional out-of-pocket costs incurred by the participants and any productivity loss. The analytical approach is a cost–utility analysis as it estimates the mean incremental cost per QALY gained of TAR compared with ankle fusion.

We built a decision model to extrapolate the trial results to a lifetime horizon. We constructed a simple Markov model, which simulates participants' pathways after TAR or ankle fusion. Monte Carlo simulations were used to account for uncertainty. We estimated the probability of the intervention being cost-effective at the cost-effectiveness thresholds of £20,000–30,000 per QALY gained, recommended by the National Institute for Health and Care Excellence (NICE).

Results

Baseline characteristics

Between March 2015 and January 2019, 303 participants were randomised; 282 participants had surgery and 281 attended at least one follow-up visit. The mean age was 68 years, 71% of participants were male and 43% had arthritis in one or more adjacent joints. The arms were well balanced at baseline, as observed from the baseline characteristics.

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Primary outcome

The mean (SD) MOXFQ walking/standing domain score at 52 weeks was 31.4 (30.4) in the TAR arm and 36.8 (30.6) in the ankle fusion arm. Patients improved in both arms, but the adjusted mean [95% confidence interval (CI)] difference of −5.56 (−12.49 to 1.37) suggests that, on average, patients who received TAR had a MOXFQ walking/standing score 5.56 points lower than those who received ankle fusion at 52 weeks post surgery. This difference was not statistically significant ($p = 0.12$). The 95% CI included the MID of −12, so the trial was not able to exclude the MID. After 52 weeks, more patients achieved the MID in the TAR arm (82%) than in the ankle fusion arm (80%).

In a post hoc analysis, when each of the two TAR subtypes (fixed- and mobile-bearing implants) were compared with ankle fusion, the mean (SD) MOXFQ walking/standing domain score at 52 weeks was 25.9 (28.3) in the fixed-bearing TAR arm and 36.8 (30.6) in the ankle fusion arm. The adjusted difference of −11.1 (95% CI −19.3 to −2.9) suggests that, on average, patients who received a fixed-bearing TAR had a MOXFQ walking/standing score 11.1 points lower than those who received ankle fusion at 52 weeks post surgery. This difference was statistically significant ($p = 0.008$).

Secondary outcomes

The MOXFQ pain and social interaction domain scores also suggested improvement in patients in both arms, but the adjusted difference of −4.20 (95% CI −9.80 to 1.39) for pain and −5.06 (95% CI −10.37 to 0.26) for social interaction at 52 weeks post surgery were not statistically significant ($p = 0.14$ and $p = 0.06$, respectively). The difference between the TAR and ankle fusion arms in the change in MOXFQ walking/standing domain score at 26 weeks was statistically significant ($p = 0.02$).

The difference between the TAR and ankle fusion arms in the change in FAAM-ADL scores at 52 weeks was statistically significant ($p = 0.01$). There were improvements from baseline in both arms, but a difference of 6.16 (95% CI 1.54 to 10.78) between arms. The change in the EQ-5D-5L visual analogue scale value was statistically significant at 26 weeks ($p = 0.03$), but the change in the EQ-5D-5L index value was not significantly different at 26 weeks ($p = 0.08$) and 52 weeks ($p = 0.32$) between the two treatment arms.

At 52 weeks from baseline, the ROM (dorsiflexion and plantarflexion) improved for patients with TAR and decreased for those with ankle fusion; the difference between arms was statistically significant ($p < 0.001$). One or more SAE occurred in 17.8% of TAR and 23.8% of ankle fusion patients ($p = 0.19$). One or more AE occurred in 54.3% of TAR and 52.6% of ankle fusion patients ($p = 0.84$). The risks of patients experiencing any SAE or AE during the course of the trial were not statistically significantly different between the two arms.

Economic evaluation

Total ankle replacement generated more QALYs than ankle fusion, but this difference was not statistically significant (adjusted difference 0.02, 95% CI −0.008 to 0.05; $p = 0.14$). The CI was generated using the bootstrapping technique (1000 iterations). The total cost of TAR from the NHS and PSS perspective was £2576 higher than the total cost of ankle fusion (95% CI £1181 to £3988; $p < 0.01$). The difference was due to the difference in the cost of surgery (£2230, 95% CI £1024 to £3103; $p < 0.01$), as other differences in other cost components were not statistically significant. The incremental cost-effectiveness ratio (ICER) was £127,931 per QALY gained at 52 weeks.

Model-based analysis suggested that TAR is cost-saving compared with ankle fusion when extrapolated to a lifetime horizon. As the population of interest is aged 50–85 years, the average life expectancy was 17 years; therefore, the model was run for 17 cycles. Over the lifetime horizon, there was a 69% probability that TAR would be cost-effective compared with ankle fusion at the cost-effectiveness threshold of £20,000 per QALY gained.

Conclusions

Both TAR and ankle fusion improved patients' QoL at 1 year, but we did not show one to be superior in terms of clinical scores at 52 weeks when using either ITT or per-protocol analysis. The TARVA trial is inconclusive in terms of the superiority of TAR, as the 95% CI for the adjusted treatment effect includes both a difference of zero and the MID of 12. However, we can rule out the superiority of ankle fusion. Both operations appear to be safe. A post hoc analysis of the most common type of implant in the UK, the fixed-bearing TAR, did show a statistically significant improvement of TAR over ankle fusion, suggesting that fixed-bearing TAR may outperform ankle fusion. There is a 69% probability of TAR being cost-effective compared with ankle fusion at the NICE cost-effectiveness threshold £20,000 per QALY gained over patients' lifetime.

Future research

There is a strong case for continuing follow-up, in particular to study the radiological and clinical progress of these patients, and the need for revision surgery. There is also a need for studies to explore the sensitivity of clinically important differences between arms when both have already improved significantly from their baseline scores.

Trial registration

This trial is registered as ISRCTN60672307 and ClinicalTrials.gov NCT02128555.

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Chapter 1 Introduction

Background

Ankle osteoarthritis is a condition in which the cartilage lining the ankle joint has worn away. The cartilage acts as a shock absorber and allows smooth, gliding motion. Absence of the cartilage and the resultant bone spurs that form (bony projections or osteophytes), and calcification and scarring of the capsule, lead to progressive pain and stiffness.

More than 29,000 patients in the UK present to specialists each year with symptomatic ankle osteoarthritis, a condition that causes major disability and has a similar impact on quality of life (QoL) as end-stage cardiac failure[1] and end-stage hip arthritis.[2] The current demand incidence of ankle osteoarthritis has been estimated to be 47.7 per 100,000 per year.[3]

The most common aetiological factor in the development of osteoarthritis of the ankle is previous trauma, often following fractures or severe sprains of the ankle.[4] The incidence of both of these is rising; hence, post-traumatic osteoarthritis of the ankle is likely to become an increasing health burden. Indeed, ankle sprains are one of the most common reasons for attendance at emergency departments. Other causes of ankle osteoarthritis include long-standing inflammatory arthropathies (e.g. rheumatoid arthritis, haemochromatosis and haemophiliac arthropathy).

In the early stages of disease, non-operative measures such as a change in activity levels, weight loss, physiotherapy, painkillers and ankle braces should be used. When these conservative management measures have failed for at least 6 months, and providing the surgeon confirms the diagnosis of osteoarthritis (now termed 'end-stage osteoarthritis') on the basis of radiological and clinical evidence (i.e. plain radiographs and unrelenting symptoms, respectively), surgery might then be considered.

Although ankle fusion is the most common surgical treatment for end-stage ankle osteoarthritis, surgeons are increasingly performing total ankle replacement (TAR), also known as arthroplasty, in response to patient demand. TAR started in the 1970s, with initial poor results. However, over the last 50 years, several new generations of implants have been developed with far improved results and its use is increasing globally. At least 4000 patients are treated with ankle fusion or TAR each year in the NHS.[5] Every TAR implanted in England, Wales, Northern Ireland, the Isle of Man and Guernsey is captured on the National Joint Registry (NJR), which has revision surgery as its only end point. No comprehensive outcome data are captured for ankle fusion patients. All studies comparing TAR with ankle fusion to date are observational and, to the best of our knowledge, there are no prospective randomised trials.

Many studies have shown that ankle fusion provides good short- and medium-term results. However, in the long term, it poses major risk (> 80%) of the development of adjacent joint arthritis owing to the transfer of stresses and motion to other joints.[6,7] Other complications following ankle fusion include pain, dysfunction, non-union and malalignment.[8]

On the other hand, TAR can preserve the functional range of ankle motion, relieve pain and might avoid potential osteoarthritis in the adjacent joints. However, it may also result in revision surgery for aseptic loosening, intraoperative fracture, malalignment, impingement and heterotopic ossification.[9–11]

To the best of our knowledge, there is no high-quality study comparing the two procedures, and the literature on this subject does not provide conclusive differentiation of the treatments, with varying length of follow-up, sample size and types of technique and implants.[12–19] The studies use a wide range of patient-reported outcome measures, without consistency of reporting or statistical analysis. Many

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of them have missing data, which makes the interpretation and comparison of results from individual studies next to impossible.

More recently, Daniels *et al.*[20] looked at 281 TARs and 107 ankle fusions and found comparable outcome scores between the two surgeries at a mean follow-up of 5.5 years. In their study, which was not randomised, patients who received ankle fusion were younger, more likely to be diabetic, less likely to have inflammatory arthritis and more likely to be smokers than those who received TAR. Veljkovic *et al.*[21] analysed 88 TARs and 150 ankle fusions at a follow-up of 3.6 years and found comparable clinical outcomes between ankle fusion and TAR in patients with non-deformed end-stage ankle arthritis.

In the NJR, which covers England, Wales, Northern Ireland, the Isle of Man and Guernsey, the most commonly used ankle replacement implants drastically changed between 2014 and 2019.[22] Prior to 2014, the majority of implants used in the UK were mobile bearing. In 2014, the Mobility™ Total Ankle System (DePuy Synthes Companies, Raynham, MA, USA) was withdrawn from the market. By 2019, the majority of implants used in the UK were fixed bearing. In 2019, the most commonly used implant was the Infinity™ Total Ankle System (Stryker, MI, USA) with the STAR™ (DJO, LLC, Vista, CA, USA) and Box® Total Ankle Replacement (MatOrtho Limited, Leatherhead, UK) implants the second and third most popular, respectively.[22] With regard to ankle fusion, there were a heterogeneity of techniques used to perform the ankle fusion, including arthroscopic and open techniques.

Esparragoza *et al.*[17] conducted a 2-year follow-up study of 30 patients [ankle fusion, *n* = 16; TAR with Ankle Evolutive System prosthesis (Transystème JMT Implants SA, Nîmes, France), *n* = 14], comparing their QoL before and after the procedure. They showed that the third-generation TAR provided greater improvement in QoL (physical conditions, and perception of general health and QoL) at 2 years post surgery.[17] On the other hand, Krause *et al.*,[18] in their 3 year-follow up study of 161 patients [ankle fusion, *n* = 27; TAR with Agility™ (DePuy Synthes Companies), HINTEGRA® (DT MedTech, LLC, TN, USA), STAR or Mobility Total Ankle System implants, *n* = 114], found no significant difference in the mean improvement between the two groups, although the rate of complication was significantly higher after TAR than after ankle fusion. In another short-term follow-up study, Slobogean *et al.*[16] assessed QoL 1 year after TAR or ankle fusion in 107 patients and demonstrated that preference-based QoL was improved following TAR and ankle fusion, but the improvement was not significantly different between the two procedures.[16]

Two systematic reviews comparing outcomes from TAR with ankle fusion, using second-generation prostheses[13] or third-generation three-component meniscal-bearing prostheses,[12] showed no significant differences in short-, mid- or long-term outcomes between the two treatments. Haddad *et al.*[13] reported that ankle fusion resulted in a higher risk of lower limb amputation, although they did not include any studies that directly compared TAR with ankle fusion. A systematic review and meta-analysis of 7942 modern TARs by Zaidi *et al.*[23] reported that TAR has a positive impact on patients' lives, with benefits lasting 10 years, as judged by improvement in pain and function, and improved gait and increased range of movement. Zaidi *et al.*[23] reported an overall survivorship at 10 years of 89%, with an annual failure rate of 1.2% [95% confidence interval (CI) 0.7% to 1.6%]. The same authors reported improvements in clinical scores, although the scores used were heterogeneous and without consistency. Radiolucency was identified in up to 23% of TARs after a mean of 4.4 years (95% CI 2.3 to 9.6 years).

Gougouilas *et al.*[15] also performed a systematic review of the outcome of seven TAR implants that are currently in use [Agility, STAR, Buechel-Pappas™ (Endotec, Inc., Orlando, FL, USA), HINTEGRA, Salto Talaris® Total Ankle Prosthesis (Integra LifeSciences Corporation, Boston, MA, USA), TNK (Kyocera Corporation, Kyoto, Japan) and Mobility implants] and showed that most patients experienced significant improvement, as assessed by the clinical score. In contrast to Zaidi *et al.*,[23] Gougouilas *et al.*[15] suggested that the postoperative improvement in the range of ankle motion was relatively small (0–14°). A decision analysis using a Markov model showed that TAR was a better treatment than ankle fusion, as assessed by the quality well-being index score.[19] These systematic reviews have exposed significant bias and a lack of prospective controlled data for either procedure.

A cost-effectiveness evaluation conducted in the USA concluded that TAR has the potential to be a cost-effective alternative to ankle fusion, but reaffirmed the poor quality of the supporting evidence.[24] To the best of our knowledge, there have been no level 1 randomised controlled trials (RCTs) to inform this important subject.

Objectives

The total ankle replacement versus ankle arthrodesis (TARVA) trial was a pragmatic, multicentre, parallel-group, non-blinded RCT that compared the two existing NHS treatment options: TAR and ankle fusion. The trial compared any current TAR implant with any isolated tibiotalar ankle fusion procedure. As a pragmatic trial should reflect the real-world situation, procedures varied in terms of technique owing to the specific requirements of each case and the preference of the operating surgeon. Thus, no surgical technique or type of ankle fusion was specified, although details were captured. Surgeons performing TAR were free to adopt their usual technique within each treatment arm, allowing the results of the trial to be extrapolated across the NHS. All surgeons included in this trial used implants and prostheses commonly used in the NHS only.

The trial assessed the comparative efficacy of the two main surgical treatments for end-stage ankle osteoarthritis: TAR and ankle fusion. It investigated the clinical effectiveness and complication rates of the two procedures in patients aged 50–85 years, measured through self-reported pain-free function using a standardised questionnaire of walking and standing ability at 52 weeks after the surgical intervention. It also aimed to determine whether or not there was a difference in physical function [measured using the Foot and Ankle Ability Measure – Activities of Daily Living (FAAM-ADL)], QoL [measured using the EuroQol 5-Dimensions, five-level version (EQ-5D-5L)] and range of motion (ROM) at 26 and 52 weeks post surgery. Last, we investigated the cost-effectiveness and cost–utility of TAR and ankle fusion. The adoption of a pragmatic trial design with broad entry criteria for the comparison of the two topical therapies means that the results can be generalised to the large number of patients presenting with ankle osteoarthritis who are treated each year.

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Chapter 2 Methods

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Design

The TARVA trial was a randomised, multicentre, non-blinded, prospective, parallel-group trial of TAR versus ankle fusion in patients with end-stage ankle osteoarthritis who were aged between 50 and 85 years, comparing clinical outcomes (i.e. pain-free function, QoL, ROM and rate of postoperative complications) and cost-effectiveness.

The trial incorporated an internal feasibility phase to ensure the surgeons' willingness to randomise and the patients' willingness to be randomised. The feasibility phase involved four centres and took place over a 6-month period following randomisation of the first patient (24 cumulative months across all centres) to closely monitor eligibility, consent and randomisation rates and ensure that they were adequate. In addition, this provided 5 months' information on whether or not patients accepted their randomised surgery, and whether or not the surgery took place.

The final protocol has been published previously.[25] All trial analyses were performed in accordance with a predefined SAP.[26]

Ethics

London Bloomsbury Research Ethics Committee (REC) reviewed and approved (14/LO/0807) the trial protocol and all material given to prospective participants, including the informed consent forms (ICFs). Subsequent amendments to these documents were submitted for further approval. Before initiation of the trial at each additional clinical site, the same/amended documents were reviewed and approved by local Research and Development.

Patient and public involvement

Patients and the public were involved at all stages of the trial, from the development of the research questions and protocol to the running of the trial. This was important to ensure the salience of the research question and that the methods proposed were acceptable to potential participants, including the frequency of visits and relevance of outcome measures. One patient representative was part of the TARVA Trial Management Group, and one patient and public representative sat on the Trial Steering Committee (TSC). We will involve patient organisations and charities such as Versus Arthritis (Chesterfield, UK) and the Arthritis and Musculoskeletal Alliance (London, UK) in the dissemination of

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the findings to a wider audience, both professionals and patients, through their newsletters, at their annual members' meetings and on their websites.

Setting

The trial was carried out in 17 UK hospitals, in a mixture of district general hospitals, university teaching hospitals and specialist orthopaedic hospitals (including their adjoining private hospitals) with adequate facilities to carry out the surgical procedures and trial assessments (see *Acknowledgements* for a list of participating sites).

Participants

The eligibility criteria for participation were patients with end-stage ankle osteoarthritis, aged 50–85 years, who the surgeon believed to be suitable for both TAR and ankle fusion (having considered various patient factors including deformity, stability, bone quality, soft tissue envelope and neurovascular status). The patients had to be able to read and understand the patient information sheet (PIS) and provide written informed consent. Eligible patients were randomised to a surgery type. 'End-stage' osteoarthritis is defined as a combination of severe unrelenting symptoms sufficient to make the patient consider surgical intervention, radiological changes consistent with osteoarthritis and failure of at least 6 months of non-operative measures, necessitating a definitive surgical procedure.

Exclusion criteria included patients with previous ipsilateral talonavicular, subtalar or calcaneocuboid fusion or surgery planned within 1 year of index procedure; those with more than four lower-limb joints fused; and those who were unable to undergo magnetic resonance imaging (MRI) or computerised tomography (CT). Those with a history of local bone or joint infection and those who had severe osteoporosis (T-score of < −2.5) with recent fracture (< 12 months previously) were not included in the trial. Patients with any comorbidity that, in the opinion of the investigator, was severe enough to interfere with the patient's ability to complete the trial assessments or present an unacceptable risk to the patient's safety were also excluded from the trial.

Interventions

In the UK, two broad types of prostheses are currently used in TAR: a two-component fixed-bearing prosthesis and a three-component mobile-bearing prosthesis. As both are commonly used, no restriction on the type of prosthesis used was stipulated, although data on prosthesis type were captured. The surgical technique followed the standard operative procedure, which involved an anterior approach to the ankle joint, protection of the neurovascular bundle, and talar and tibial preparation according to the prosthesis used and its instrumentation. Intraoperative fluoroscopy was used as required to confirm position, and final implantation used an uncemented technique. Thorough washout was followed by wound closure using the surgeon's standard technique. Details of the surgeon's technique were captured on a case report form (CRF). The surgeon's usual postoperative protocol was followed with respect to method of immobilisation (plaster or walking boot) and weight-bearing status.

Ankle fusion was performed either as an open procedure or arthroscopically, depending on the surgeon's preference. Tibial and talar joint surfaces were prepared to avoid bleeding from the cancellous bone, any deformity correction was addressed, and the surfaces were opposed and held with screws and/or plates as required to ensure that the foot was plantigrade and appropriately positioned to match the contralateral ankle in axial orientation. If performed arthroscopically, two portals were made, one anteromedially and one anterolaterally, over the ankle joint for access. If arthroscopic access was not favourable, the operation was performed using an open procedure, which involved either a standard anterior approach, two mini anterior incisions or a lateral approach. The surgical technique and implants

used were captured on the CRF. The surgeon's usual postoperative protocol was followed with respect to use of plaster or walking boot and weight-bearing status, and the specific details of these were captured for each patient on the CRF.

Magnetic resonance imaging

Each participant was booked to undergo MRI of the affected ankle, if this had not already been performed as part of routine care, once they had given written informed consent to take part in the trial. If the participant was ineligible for MRI, CT was booked instead. The grade of MRI/CT was determined by an independent radiologist using a methodology published by our group,[27] the report of which was sent to the local principal investigator, and a preoperative assessment appointment was scheduled for the participant.

Randomisation

The randomisation process was based on a minimisation algorithm. The algorithm gave an overall chance of 85% of allocating the patient to the treatment arm that was under-represented with respect to three stratifying variables: surgeon, presence of osteoarthritis in subtalar joint and presence of osteoarthritis in talonavicular joint (as determined by preoperative MRI). The research nurse or delegated individual logged on to the Sealed Envelope randomisation service and provided patient information (including information on minimisation variables), and the surgical treatment to be received was supplied immediately. Patients were allocated in a 1 : 1 ratio to the TAR and ankle fusion arms. To protect against allocation bias, the person recruiting the patient to the trial was not aware of the allocation to be assigned prior to contacting the randomisation service. All surgeons were proficient in both surgical procedures, having independently performed ≥ 10 procedures of each type prior to participation.

Blinding

The trial was open (i.e. non-blinded). It was not possible to blind patients, surgeons, radiologists and clinical assessors for the following reasons:

- Surgeons would have known which procedure they were performing.
- Radiologists and patients would be able to identify which procedure had taken place from the radiographs.
- Patients who received ankle fusion would tend to have stiffer ankles and the incisions may also provide clues to the surgery type.

Recruitment and consent

All patients with ankle osteoarthritis who were considering surgery were screened prospectively by principal investigators at 17 UK hospitals. Potentially eligible participants were identified during routine clinic appointments to assess treatment need, or through screening of referral letters/clinic lists. Those identified through screening were sent a study information pack in the post prior to their appointment.

If considered eligible for the TARVA trial, the patient watched a bespoke trial video, and read the PIS and a generic factsheet about ankle arthritis and its treatment options. Participants either consented at that stage or received a follow-up telephone call from the research team to discuss participation. Reasons for non-enrolment in the trial (including lack of equipoise) were recorded. All participants provided written informed consent using an ICF.

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Following consent, participants underwent MRI (or, where contraindicated, CT) (if this had not been performed as part of standard care within the previous 6 months), followed by a preoperative assessment 14–30 days prior to surgery. If declared fit for surgery, participants were randomised to one of the two surgical treatments. Participants who were found to be unsuitable for surgery at the preoperative assessment appointment were passed back to their general practitioner (GP) to be re-referred for surgery when they were considered fit.

Baseline visit

Baseline measures were recorded at the point of randomisation, once the participant had been found to be fit for surgery, at their preoperative assessment. Baseline measures included the EQ-5D-5L, MOXFQ, Foot and Ankle Ability Measure (FAAM), Client Service Receipt Inventory (CSRI), ROM and concomitant medication.

Follow-up assessments and treatment

All participants attended routine follow-up, which consisted of visits at 2, 6, 12, 26 and 52 weeks post surgery. These visits were standard care. Patients underwent routine clinical review at 2 weeks, during which the stitches were removed and plaster casts changed. Trial-specific outcome measures, including adverse events (AEs) and postprocedural complications, were recorded at 6, 12, 26 and 52 weeks. Concomitant medications were recorded from preoperative assessment to the 52-week visit. Participants underwent routine physical examination, as per standard care. Participants completed additional questionnaires (the MOXFQ, EQ-5D-5L and FAAM) at 26- and 52-week routine follow-up visits, with the EQ-5D-5L and CSRI additionally completed at 12 weeks. ROM (total floor to tibial shaft plantarflexion and dorsiflexion) was assessed using a goniometer at the preoperative assessment visit and 52 weeks post surgery.[28]

To avoid bias, operating surgeons were not involved in measuring ROM. Preoperative and postoperative hindfoot deformity was measured using weight-bearing anteroposterior and lateral radiographs of the ankle and tibia at baseline, and on a postoperative radiograph (between 0 and 26 weeks post surgery) using the methods described by Knupp *et al.*[29] Plain radiographs were sent to the Royal National Orthopaedic Hospital via the NHS Image Exchange Portal (Sectra Ltd, Stevenage, UK) in one batch (containing preoperative and postoperative radiographs) after the second (postoperative) radiograph was taken. Investigators were blinded to participant treatment allocation when reviewing the preoperative radiographs. Each participant was in the trial from consent until the final 52-week follow-up visit, although long-term follow-up at 2, 5 and 10 years post surgery was part of their informed consent.

Safety

All medical device deficiencies, AEs and serious adverse events (SAEs) occurring during the trial that were observed by the investigator or reported by the participant (whether or not they were attributed to the surgery, surgery-related medications, device or other trial-specific procedures) were recorded in the participants' medical records. Related AEs over and above what would normally be expected after ankle surgery were recorded on the relevant CRFs. SAEs were reported in line with procedures set out in the protocol.[25]

The severity of all AEs (serious and non-serious) was graded using the TARVA trial safety management plan for expected AEs, in conjunction with the most recent version of the Common Terminology Criteria for Adverse Events (at the time the protocol was written, this was version 4.0[30]) for other (unexpected) AEs. The 'expectedness' was determined by the list of expected events in the TARVA trial safety management plan.

Outcomes

Primary outcome

The primary outcome measure was the absolute difference between the two treatment arms in self-reported pain-free function, as measured by the Manchester–Oxford Foot Questionnaire (MOXFQ) walking/standing domain score at 52 weeks post surgery (0–100, where lower scores are better).[31] The 52-week score was used if it was taken in the window from 48 to 56 weeks post surgery.

The MOXFQ walking/standing domain score has been found to be a valid and responsive measure to evaluate all types of foot and ankle surgery and it has also been shown to be more responsive for the outcomes of foot and ankle surgery patients than generic QoL measures such as the EQ-5D-5L quality-of-life instrument.[32] The MOXFQ walking/standing domain score was selected by patients as the most important outcome measure.[32]

Secondary outcomes

The secondary outcome measures for the trial were the absolute differences between the two treatment arms in:

- the MOXFQ walking/standing domain score at 26 weeks post surgery
- self-reported pain and social interaction, measured using the MOXFQ pain and social interaction domain scores at 26 weeks and 52 weeks post surgery
- physical function, measured using the FAAM-ADL questionnaire at 26 weeks and 52 weeks post surgery (0–100, higher scores better)
- physical function for patients involved in sport, measured using the FAAM sport subscale score at 26 weeks and 52 weeks post surgery
- QoL, assessed using the EQ-5D-5L [EQ-5D-5L index value and EQ-5D-5L visual analogue scale (VAS)] at 26 weeks and 52 weeks post surgery
- total ROM (degrees plantarflexion and dorsiflexion) at 52 weeks post surgery, assessed using a goniometer
- the proportion of patients experiencing at least one AE
- the proportion of patients experiencing at least one SAE
- the proportion of patients with recorded complications (including revision surgery and reoperations other than revision).

Additional outcomes were also collected for a detailed cost and cost-effectiveness analysis of TAR compared with ankle fusion.

The Manchester–Oxford Foot Questionnaire

Responses to each MOXFQ questionnaire item consist of a five-point Likert scale ranging from no limitation (scoring 0) to maximum limitation (scoring 4). Items are grouped into three domains: walking/standing (seven items), pain (five items), and social interaction (four items). Domain scores are computed by summing the patient's responses to each item within the domain and converting to a 0–100 metric, where higher scores represent greater severity.

If a single item within any domain is unanswered, it will be imputed with the mean of the respondent's answers to the other items within that domain. If two or more questions on any domain are unanswered, the overall score for that domain will not be calculated and its value will be set to missing.[33] If the entire questionnaire has not been completed, all MOXFQ domain scores for that visit will be set to missing.

The Foot and Ankle Ability Measure – Activities of Daily Living

Each of the 21 items on the FAAM-ADL is scored from 4 (no difficulty) to 0 (difficulty).[34] The overall FAAM-ADL score is then calculated by summing the responses to each completed item, dividing this by the maximum score achievable based on the number of items completed (e.g. 84 if all 21 items are

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completed), and then multiplying the resulting fraction by 100 to return a 0–100 metric, where higher scores indicate a higher level of physical function. If an answer for one item is missing, its value will be imputed as the mode of the other items; if more than one item is missing, the overall score will be set to missing.

The FAAM sport subscale score provides a complementary, specific assessment of ability to participate in sports based on eight questionnaire items, each also scored from 0–4. A 0–100 metric is then generated using the same approach as for the FAAM-ADL; higher scores indicate a higher level of ability to participate in sports. Missing items will be handled using the same approach as for the FAAM-ADL.

EuroQol-5 Dimensions, five-level version, quality-of-life instrument

The EQ-5D-5L is a generic measure of health-related quality of life (HRQoL) developed by the EuroQol group in 2009. It was introduced to improve on the sensitivity of its predecessor, the EuroQol 5-Dimensions, three-level version (EQ-5D-3L). It is a five-dimension, five-level questionnaire scored 1 (no problem) to 5 (extreme problem). The dimensions are mobility, self-care, usual activities, pain/discomfort and anxiety/depression. It also includes a VAS scored from 0 (worst imaginable health) to 100 (best imaginable health). The EQ-5D-5L was translated into > 130 languages and is available in various modes of administration.[35]

The EQ-5D-5L is a descriptive system that defines a unique health state by combining one level from each of the five dimensions.[36] The descriptive system can be converted into a single index value using a value set.[37] The value set was derived from a study that elicited preferences from the general population (n = 3395).[37] The index value can take values from 0 (death) to 1 (perfect health). Currently, a value set is available for the EQ-5D-3L, which was derived directly from the population responses. For the EQ-5D-5L, the National Institute for Health and Care Excellence (NICE) recommends using a 'crosswalk' calculator,[38] which is a link function that allows researchers to obtain index values using value sets for the EQ-5D-3L. The index values are also used in the calculation of quality-adjusted life-years (QALYs) in the economic evaluation of health interventions.

Another generic measure of HRQoL is the Short Form questionnaire-36 items (SF-36). The SF-36 is a standardised questionnaire comprising 36 items across eight domains. The domains of the SF-36 are physical functioning (10 items), physical role limitations (four items), bodily pain (two items), general health perceptions (five items), energy/vitality (four items), social functioning (two items), emotional role limitations (three items) and mental health (five items). The last item is called 'self-report health transition'; it is answered by the respondent, but is not included in the scoring system. The SF-36 has a scoring algorithm that generates a score for each of the eight domains and two summary scores (a physical component summary and mental health component summary), but it is not preference based. A study was conducted to create a preference-based measure from the SF-36, which is called the Short Form questionnaire-6 Dimensions (SF-6D).[39] A value set was created by interviewing a representative sample of 611 members of the UK population. There is also a short version of the questionnaire, called the Short Form questionnaire-12 items (SF-12). It is often preferred for routine follow-up.[40]

Both measures are widely used in joint replacement registries.[41] The EQ-5D-5L[42,43] and SF-36[44] were validated to use in patients with osteoarthritis. There are no recommendations as to which one is preferred.[40] There is a mapping function available to convert the SF-12 to EQ-5D-5L index values, which facilitates comparison between the two measures.[45]

If any dimension score is missing, the EQ-5D-5L index value will be set to missing. If the entirety of one component of the questionnaire (dimension score or VAS) has not been completed, the associated component score will be set to missing. If the entire questionnaire has not been completed, both the EQ-5D-5L index value and EQ-5D-5L VAS at that visit will be set to missing.

Sample size

The sample size calculation for the primary outcome (change in MOXFQ walking/standing domain score by 52 weeks post surgery) was performed using Stata/IC®, version 12.1 (StataCorp LP, College Station, TX, USA). It was based on achieving 90% power to detect the minimal important difference (MID) in the primary outcome at the 5% level of significance, accounting for expected loss to follow-up.

Dawson *et al.*[46] previously defined the MID in the MOXFQ when evaluating outcomes following surgery for hallux valgus as the mean change in MOXFQ score of those patients who reported feeling at least 'slightly better'. They found the MID to be 16, 12 and 24 for the walking/standing, pain and social interaction domains, respectively.[46]

A later paper by Dawson *et al.*[47] discussed the minimal detectable change, which is the smallest change for an individual that is beyond the measurement of error of a given instrument and therefore likely to represent a true change. Although Dawson *et al.*'s 2007 paper[46] looked at hallux valgus, their later paper[47] specifically studied ankle procedures as a subgroup and estimated the MID to be 10.67.

For this trial, we determined that it was important to detect a difference of 12 in the change in the MOXFQ walking/standing domain scores from baseline between the two treatment arms.

The standard deviation (SD) of the MOXFQ walking/standing domain score was estimated to be 27.[46] We took into account an anticipated 10% dropout rate (attrition in orthopaedic trials is about 5–7%, as shown by other similar UK RCTs[48]). Based on these quantities, the required sample size was estimated to be 118 patients per arm.

However, the trial was multicentre and the outcome was assumed to vary by surgeon, so the sample size was increased to account for clustering by surgeon. The intraclass correlation coefficient (ICC) was estimated from the median of 10 previous surgical studies reporting patient-reported disease-specific measures 12 months post surgery,[49] and the initial sample size estimate was inflated by a factor of $f = 1 + (m - 1) \times \text{ICC}$. Assuming an average cluster size (m) of 14 (patients per surgeon) and an ICC of 0.03, an inflation factor of $f = 1.39$ was estimated, leading to a final required sample size of 164 patients per arm or 328 patients in total.

Data collection and management

A member of the research team captured data from patients on paper using the TARVA trial CRFs. The data were entered onto the main trial database (MACRO v4.1; Elsevier, Amsterdam, the Netherlands) by a delegated member of site staff.

The site retained the original paper copies of patient CRFs to allow monitoring and audit by the University College London Comprehensive Clinical Trials Unit (UCL CCTU) trial team. All data queries were resolved prior to trial closure and analysis.

At sites where electronic records were available, the site may have captured some of the data electronically, which were then transcribed onto the paper CRFs to ensure a complete record.

Statistical methods

All trial analyses were performed according to a predefined SAP.[26] All efficacy analyses were conducted following the intention-to-treat (ITT) principle, in which all randomised patients were analysed according to their randomised surgical procedure, irrespective of the type of surgery they received.

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In addition, a per-protocol analysis was carried out for the primary outcome, which included only the outcome data that were collected within the protocol-specified time window from patients who underwent surgery according to their randomised surgical procedure, excluding crossover patients.

The baseline characteristics were summarised by randomised treatment arm. The categorical variables were summarised by number and percentage in each category; continuous variables were summarised by mean and SD, or median and interquartile range, as appropriate. No statistical tests of differences in baseline characteristics between arms were undertaken, as in a randomised trial any differences between treatment arms must be due to chance.

Primary outcome analysis

A multilevel repeated-measures linear regression model was used to estimate the difference between the treatment arms in the change in MOXFQ walking/standing domain score from before the operation to 52 weeks post surgery. The model included fixed effects for time, treatment, treatment-by-time interaction, baseline MOXFQ walking/standing domain score and presence of osteoarthritis in each of the two adjacent joints (subtalar and talonavicular). A random patient effect was included to account for clustering by patient. A random surgeon effect was also included to account for clustering by surgeon.

Owing to the heterogeneity of the surgeon cluster sizes, the planned model (which included an additional, random surgeon by-treatment-coefficient) encountered convergence problems. Although randomisation was stratified by surgeon, many of the surgeons treated only a few patients, leading to insufficient data to estimate the random surgeon-by-treatment coefficient. As the primary analysis model failed to converge, the model was refitted after excluding the random surgeon-by-treatment coefficient.

The model used an unstructured covariance structure and was fitted using restricted maximum likelihood. The model makes assumptions about random effects distributions, correlation structure and residuals, which were investigated using appropriate plots.

Secondary outcome analysis: continuous secondary outcomes

Each of the following continuous secondary outcome measures were analysed using a separate multilevel repeated-measures linear regression model:

- change in MOXFQ pain domain score
- change in MOXFQ social interaction domain score
- change in FAAM-ADL
- change in FAAM sport subscale (for patients involved in sport)
- change in EQ-5D-5L index value
- change in EQ-5D-5L VAS
- change in ROM dorsiflexion
- change in ROM plantarflexion.

Similar to the primary analysis model, each model included fixed effects for treatment, time, treatment by time, baseline value of the associated score and presence of osteoarthritis in each of the two adjacent joints. A random patient effect and a random surgeon effect were also included in each of the models.

The outcomes ROM dorsiflexion and ROM plantarflexion were measured at baseline and 52 weeks only. Hence, the analyses models included fixed effects for treatment, baseline value of the associated score and presence of osteoarthritis in each of the two adjacent joints, and a random surgeon effect.

Adverse events, serious adverse events and complications

The following absolute differences in proportions were estimated using the treatment coefficient obtained using a binomial regression model with the identity link function:

- proportion of patients experiencing at least one AE
- proportion of patients experiencing at least one SAE.

Relative risks were obtained using a binomial regression model with the log link.

The distribution of the AEs and SAEs per patient have also been presented descriptively, but no formal analysis was performed. The descriptive statistics of complications, revisions and reoperations were also presented.

Subgroup analyses

An exploratory subgroup analysis was performed to investigate whether there was any interaction between the effect of treatment and the presence of osteoarthritis in the two adjacent joints on the primary outcome.

The fitted primary analysis model was extended to include the interactions between treatment and presence/absence of osteoarthritis in adjacent joints. As the trial was not powered to detect this, the analysis had limited power and is exploratory.

Further exploratory subgroup analyses were undertaken to investigate whether or not there was any interaction between age and the randomised treatment.

Post hoc analysis

At the time of developing the protocol, only mobile-bearing TAR implants were on the UK market. Between 2014 and 2019, after the study had begun, fixed-bearing implants became the most commonly used implants in the UK. Therefore, a post hoc analysis was carried out as a sensitivity analysis, comparing the most common type of implant in the UK (fixed-bearing TAR) with ankle fusion. The subtypes of TAR patients (those who received fixed-bearing TAR and those who received mobile-bearing TAR) were used as separate groups in the post hoc model and compared with the ankle fusion arm (including both open and arthroscopic ankle fusion patients).

Study oversight

A TSC was established, comprising seven independent members, including a patient and public representative, the chief investigator and representatives from among the principal investigators. The trial health economist and senior trial statistician attended meetings as observers. The committee provided advice to the chief investigator, UCL CCTU, the funder and the sponsor on all aspects of the trial.

The UCL CCTU was responsible for the day-to-day management of the trial, with oversight from a Trial Management Group on the design, co-ordination and strategic management of the trial. The Trial Management Group was chaired by the chief investigator.

An Independent Data Monitoring Committee (IDMC) monitored the accumulating data and made recommendations to the TSC on whether or not the trial should continue as planned. The committee consisted of three independent members: a professor of medical statistics, a professor of rehabilitation sciences and a professor of orthopaedic surgery (the chairperson).

All oversight committees had agreed terms of reference.

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During the trial, the TSC and IDMC each met six times between August 2014 and July 2019, one of which was a joint meeting of the two committees. The joint meeting led to the abbreviation of the exclusion criteria so that the surgeons' checklist was shorter. The committees also reviewed the impact of the withdrawal of the Mobility TAR implant, which occurred after the study began but prior to any recruitment. The IDMC and TSC also advised on a recovery plan for slow recruitment, including increasing the number of recruitment sites, extending the recruitment period and a qualitative study to provide insight into recruitment difficulties.

Chapter 3 Trial results

Recruitment

Participants were randomised between 6 March 2015 and 10 January 2019. A total of 1604 patients were screened for eligibility, of whom 303 were randomised: 152 to TAR and 151 to ankle fusion. The numbers of participants recruited and included in the ITT analysis are summarised in the Consolidated Standards of Reporting Trials (CONSORT) flow diagram in *Figure 1*. Of the 303 patients randomised, 21 withdrew from the trial before receiving surgery, one withdrew before the 26-week follow-up and a further five withdrew/had missing data at week 52. Six of those who received surgery were missing primary outcome measure data at 52 weeks. All patients who received surgery and attended either the 26-week or 52-week visit were included in the ITT analysis. Four patients randomised to arthrodesis did not receive their allocated surgery and crossed over to the TAR arm. All observed outcome data from these patients were analysed according to their randomised surgical procedure.

Of the 282 patients who received surgery, one patient who withdrew before the 26-week follow-up could not contribute data to the primary outcome but was included in the baseline characteristics table. All 281 patients who received surgery and attended at least one follow-up were included in the mixed model for the primary outcome analysis (ITT analysis).

Table 1 lists the 17 sites in order of the date the site opened to recruitment. The first site to open was the Royal National Orthopaedic Hospital in December 2014. This site randomised the largest number of patients (24% of the total randomised).

Table 2 summarises the losses and exclusions after randomisation, with reasons, for each arm. There have been no losses to follow-up in the trial.

A total of 21 randomised patients withdrew from the trial prior to surgery – 14 (9%) in the TAR arm and seven (5%) in the ankle fusion arm. Of the patients who received surgery, four (two in each arm) withdrew from the trial prior to the 52-week follow-up. One patient in the TAR arm died after their 52-week follow-up visit.

Baseline characteristics of participants

The baseline characteristics of participants are presented in *Table 3*.

The mean (SD) age of the participants was similar in each treatment arm: 68.0 (8.1) years in the TAR arm and 67.7 (8.0) in the ankle fusion arm. In total, 81 (29%) participants were female. The rate of obesity (body mass index of ≥ 30 kg/m^2) was 37% in the TAR arm and 51% in the ankle fusion arm.

The proportion of patients with respiratory pathology, diabetes or obesity was lower in the ankle fusion arm than in the TAR arm at baseline. However, there was more deformity in the TAR arm than in the ankle fusion arm (see *Table 3*). Overall, the two randomised arms were considered generally similar with regard to medical history factors and smoking habits. In terms of American Society of Anesthesiologists (ASA) grade (*Table 4*), there were slightly more ASA grade 3 patients (severe systemic disease) in the ankle fusion arm than in the TAR arm (17.4% vs. 14.5%, respectively).

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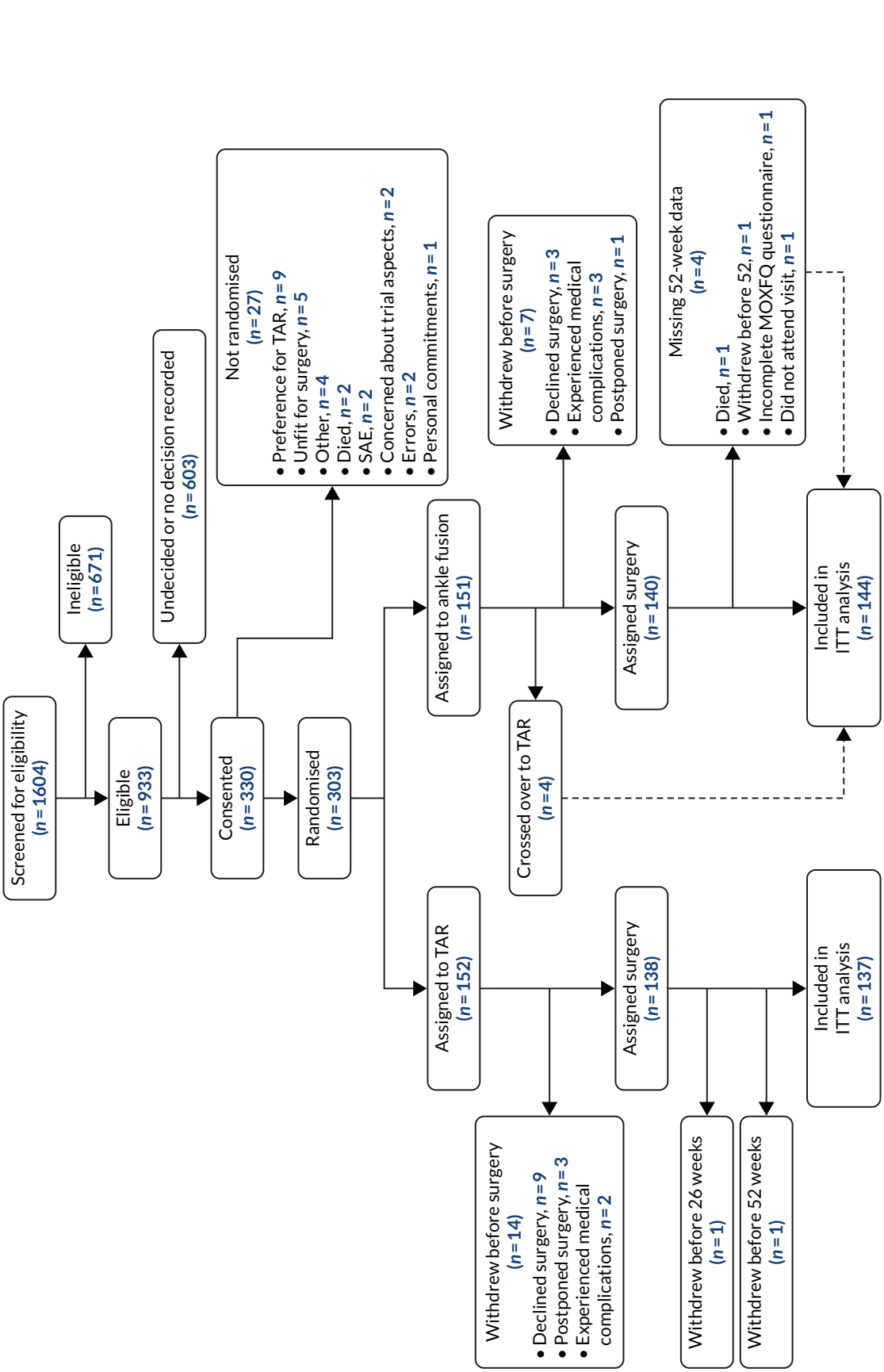

FIGURE 1 Trial profile: CONSORT flow diagram.

TABLE 1 Number screened and randomised by site

Site (site identification number)	Date opened[a]	Number of patients			
		Screened	Eligible	Randomised	Per centre per month
Royal National Orthopaedic Hospital (10)	23 December 2014	287	136	73	1.7
Aintree University Hospital (11)	10 February 2015	109	37	17	0.4
Northern General Hospital (Sheffield) (13)	13 February 2015	101	51	10	0.2
Wrightington Hospital (24)	21 April 2015	147	100	10	0.2
Freeman Hospital (Newcastle) (18)	19 May 2015	116	73	19	0.4
Royal Derby Hospital (28)	11 June 2015	103	72	30	0.7
Royal Surrey County Hospital (27)	9 July 2015	34	14	12	0.3
Cardiff and Vale University Local Health Board (16)	20 November 2015	67	27	3	0.1
Hull and East Yorkshire Hospitals NHS Trust (30)	1 December 2015	51	36	9	0.2
Northumbria Healthcare NHS Foundation Trust (25)	15 January 2016	105	73	26	0.7
Norfolk and Norwich University Hospital NHS Foundation Trust (19)	15 January 2016	99	58	11	0.3
Robert Jones and Agnes Hunt Orthopaedic Hospital NHS Foundation Trust (21)	29 January 2016	128	93	23	0.6
Brighton and Sussex University Hospitals NHS Trust (26)	4 March 2016	37	25	18	0.5
Oxford University Hospitals NHS Foundation Trust (22)	3 May 2016	32	17	9	0.3
Nottingham University Hospitals NHS Trust (20)	20 May 2016	75	61	16	0.5
Royal Cornwall Hospitals NHS Trust (33)	28 September 2016	16	14	1	0.0
North Bristol NHS Trust (14)	23 January 2017	97	46	16	0.7
Total		1604	933	303	

a Ordered according to date site opened.

Participants appeared to be equally distributed between treatment arms with regard to the minimisation factors, that is the presence of osteoarthritis in the two adjacent joints (subtalar and talonavicular). A total of 122 patients (34%) had osteoarthritis in the adjacent joints. For 25 (9%) of these patients, the osteoarthritis was in both adjacent joints.

Prior to their surgery, 44% of patients reported that they used assistive devices. The majority of those using an assistive device used a stick or cane. Patients also reported using other forms of assistive devices such as crutches (9%) and ankle braces (8%).

The majority of patients (77%) did not express a treatment preference, 17% of patients stated a preference for TAR and 6% expressed a preference for ankle fusion.

The baseline mean (SD) MOXFQ walking/standing score was 82 (16.6) in TAR and 82 (16.8) in ankle fusion patients. The baseline values for the outcome measures were similar in the two treatment arms.

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TABLE 2 Withdrawals from trial

Reasons for withdrawal	Number of patients	
	TAR arm	Ankle fusion arm
Withdrawal pre surgery	14	7
Declined surgery	9	3
Patient experienced medical complication	2	3
Postponed surgery	3	1
Withdrawal post surgery	2	2
Unable to commit to treatment schedule	1	0
Patient experienced SAE	1	0
Patient died	0	1
Reason not given	0	1
Withdrawal after 52 weeks	1	0
Patient died	1	0

TABLE 3 Baseline characteristics

Baseline characteristics	TAR arm (*N* = 138)	Ankle fusion arm (*N* = 144)	Total (*N* = 282)
Age (years), mean (SD)	68.0 (8.1)	67.7 (8.0)	67.9 (8.0)
Sex, *n* (%)			
Female	34 (25)	47 (33)	81 (29)
Male	104 (75)	97 (67)	201 (71)
Height (m), mean (SD)	1.7 (0.1)	1.7 (0.1)	1.7 (0.1)
Weight (kg), mean (SD)	85.8 (13.2)	88.3 (17.4)	87.1 (15.5)
Body mass index (kg/m^2), *n* (%)			
< 30	87 (64)	70 (49)	157 (56)
≥ 30	50 (37)	74 (51)	124 (44)
Smoking status			
Current smoker, *n* (%)	5 (4)	5 (4)	10 (4)
Cigarettes/day, mean (SD)	5.8 (2.4)	10.4 (7.4)	8.1 (5.7)
Ex-smoker, *n* (%)	53 (38)	57 (40)	110 (39)
Time since cessation (years), mean (SD)	25.5 (16.0)	25.9 (15.6)	25.7 (15.7)
Patients' treatment preference, *n* (%)			
No preference expressed	100 (75)	112 (79)	212 (77)
TAR	26 (19)	20 (14)	46 (17)
Ankle fusion	8 (6)	9 (6)	17 (6)
Aetiology of osteoarthritis, *n* (%)			
Post traumatic	83 (60)	73 (50)	156 (55)
Primary	46 (33)	56 (38)	102 (36)

TABLE 3 Baseline characteristics (*continued*)

Baseline characteristics	TAR arm (*N* = 138)	Ankle fusion arm (*N* = 144)	Total (*N* = 282)
Rheumatoid arthritis	6 (4)	7 (5)	13 (5)
Other inflammatory	2 (2)	5 (4)	7 (3)
Other	1 (1)	4 (3)	5 (2)
Presence/absence of osteoarthritis, *n* (%)			
Healthy adjacent joint	81 (59)	79 (55)	160 (57)
Osteoarthritis in subtalar or talonavicular	45 (32)	52 (36)	97 (34)
Osteoarthritis in both adjacent joints	12 (9)	13 (9)	25 (9)
User of assistive device, *n* (%)			
No	80 (58)	79 (55)	159 (56)
Yes	58 (42)	65 (45)	123 (44)
Assistive device, *n* (%)			
Crutches	12 (9)	14 (10)	26 (9)
Ankle brace	16 (12)	7 (5)	23 (8)
Frame	2 (2)	1 (1)	3 (1)
Wheelchair	3 (3)	3 (2)	6 (2)
Stick/cane	33 (24)	46 (32)	79 (28)
Wheeled walker	1 (1)	4 (3)	5 (2)
Knee scooter	1 (1)	1 (1)	2 (1)
Other	8 (6)	4 (3)	12 (4)
Medical history, *n* (%)			
Anticoagulants	24 (17)	24 (17)	48 (17)
History of cancer	13 (9)	20 (14)	33 (12)
Chronic pain	40 (29)	46 (32)	86 (31)
Connective tissue disorder	1 (1)	4 (3)	5 (2)
Diabetes	9 (7)	16 (11)	25 (9)
Gastrointestinal disease	17 (12)	22 (15)	39 (14)
Hypertension/hypercholesterolaemia	61 (44)	62 (43)	123 (44)
Inflammatory disorder	8 (6)	12 (8)	20 (7)
Metabolic disorder	5 (4)	3 (2)	8 (3)
Neurological disorder	2 (2)	6 (4)	8 (3)
Obesity	8 (6)	15 (10)	23 (8)
Peripheral nervous system disorder	0 (0)	5 (4)	5 (2)
Peripheral vascular disease	2 (2)	3 (2)	5 (2)
Renal pathology	7 (5)	3 (2)	10 (4)
Respiratory pathology	12 (9)	20 (14)	32 (11)
Thromboembolic disease	7 (5)	7 (5)	14 (5)
Other condition affecting mobility	39 (28)	43 (30)	82 (29)

continued

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TABLE 3 Baseline characteristics (*continued*)

Baseline characteristics	TAR arm (*N* = 138)	Ankle fusion arm (*N* = 144)	Total (*N* = 282)
Degree of deformity, *n* (%)			
16–30° varus	13 (10)	7 (5)	20 (7)
5–15° varus	36 (26)	43 (30)	79 (28)
Physiological neutral	47 (34)	51 (35)	98 (35)
5–15° valgus	20 (15)	18 (13)	38 (14)
16–30° valgus	10 (7)	6 (4)	16 (6)
Not available	11 (8)	19 (13)	30 (11)
Fixed flexion deformity of knee, *n* (%)	2 (1.4)	3 (2.1)	5 (1.8)
Fixed equinus, *n* (%)	7 (5.1)	5 (3.5)	12 (4.3)
ROM dorsiflexion (degrees), mean (SD)	14.3 (9.5)	14.2 (9.3)	14.2 (9.4)
ROM plantarflexion (degrees), mean (SD)	25.4 (8.3)	26.3 (10.5)	25.9 (9.5)
Outcome measures at baseline, mean (SD)			
MOXFQ walking/standing	81.6 (16.6)	81.5 (16.8)	81.5 (16.7)
MOXFQ pain	66.7 (16.8)	67.6 (17.5)	67.2 (17.1)
MOXFQ social interaction	54.4 (26.1)	56.3 (21.7)	55.4 (24.0)
MOXFQ summary index[a]	70.1 (15.4)	70.9 (14.8)	70.5 (15.1)
FAAM-ADL	47.0 (16.7)	44.1 (16.6)	45.5 (16.7)
FAAM sport subscale	28.3 (19.7)	25.6 (21.3)	27.3 (20.2)
EQ-5D-5L index value	0.5 (0.2)	0.5 (0.2)	0.5 (0.2)
EQ-5D-5L VAS	72.7 (20.2)	67.5 (21.4)	70.0 (21.0)

a Post hoc analysis.

TABLE 4 Details of surgery by randomised treatment arm

Surgery characteristic	TAR arm (*N* = 138)	Ankle fusion arm (*N* = 144)	Total (*N* = 282)
Surgery type,[a] *n* (%)			
Mobile-bearing TAR	65 (47.1)	1 (25.0)[a]	66 (46.5)
Fixed-bearing TAR	73 (52.9)	3 (75.0)[a]	76 (53.5)
Arthroscopic ankle fusion	–	85 (60.7)	–
Open ankle fusion	–	55 (39.3)	–
Tourniquet duration (minutes),[b] mean (SD)	117 (23.8)	92 (28.0)	105 (28.8)
Operation duration (minutes), mean (SD)	121 (31.6)	103 (36.2)	112 (35.2)
Drain used, *n* (%)			
No	125 (92.6)	139 (98.6)	264 (95.6)
Yes	10 (7.4)	2 (1.4)	12 (4.4)

TABLE 4 Details of surgery by randomised treatment arm (*continued*)

Surgery characteristic	TAR arm (*N* = 138)	Ankle fusion arm (*N* = 144)	Total (*N* = 282)
Post surgery weight-bearing recommendation, *n* (%)			
Full weight-bearing	9 (6.6)	1 (0.7)	10 (3.6)
Partial weight-bearing	17 (12.4)	6 (4.2)	23 (8.2)
Non-weight-bearing until 2 weeks	81 (59.1)	40 (28.0)	121 (43.2)
Non-weight-bearing until 6 weeks	13 (9.5)	69 (48.3)	82 (29.3)
Other	17 (12.4)	27 (18.9)	44 (15.7)
Immobilisation type, *n* (%)			
Backslab	104 (75.9)	114 (79.2)	218 (77.6)
Walker boot	11 (8.1)	13 (9.0)	24 (8.6)
Other	21 (15.4)	19 (13.2)	40 (14.3)
ASA grade, *n* (%)			
Healthy patient	18 (13.0)	25 (17.4)	43 (15.3)
Mild systemic disease	100 (72.5)	94 (65.3)	194 (68.8)
Severe systemic disease	20 (14.5)	25 (17.4)	45 (16.0)
Prior fracture around index joint, *n* (%)			
No	87 (63.0)	111 (77.1)	198 (70.2)
Yes	45 (32.6)	28 (19.4)	73 (25.9)
Not available	6 (4.4)	5 (3.5)	11 (3.9)
Previous surgery on index joint, *n* (%)			
None	92 (66.7)	92 (63.9)	184 (65.3)
Internal fixation	22 (16.0)	18 (12.5)	40 (14.2)
Other	14 (10.4)	16 (11.1)	30 (10.6)
Thromboprophylaxis given, *n* (%)			
None	2 (1.5)	3 (2.1)	5 (1.8)
Chemical	31 (22.5)	34 (23.6)	65 (23.1)
Mechanical	2 (1.5)	0 (0.0)	2 (0.7)
Both	103 (74.6)	107 (74.3)	210 (74.5)

a Includes four ankle fusion patients who crossed over to TAR.
b Some surgeons did not inflate a tourniquet during the arthroscopic phase of the arthroscopic fusion.

Surgery details

The duration of the procedure was slightly longer for TAR (121 minutes) than ankle fusion (103 minutes). Patients were immobilised for longer in the ankle fusion arm than in the TAR arm: 26 (19%) patients in the TAR arm compared with seven (5%) in the ankle fusion arm were allowed to weight bear within 2 weeks of the surgery.

The arms were broadly similar in terms of previous surgery, although the TAR arm had slightly more patients who had previously had internal fixation on the index joint than the ankle fusion arm (16% vs. 12.5%, respectively).

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For those patients who underwent TAR, 76 (53.5%) had a fixed-bearing TAR and 66 (46.5%) had a mobile-bearing TAR (*Table 5*). In the ankle fusion arm, 60% of the procedures were performed arthroscopically. For those patients who underwent an open ankle fusion, seven (14%) received a lateral approach (*Table 6*).

The proportion of patients who had an associated procedure was higher in the TAR arm than in the ankle fusion arm (35% vs. 18%, respectively). The most common procedure was Achilles tendon lengthening, which was undertaken in 17 (12.3%) patients in the TAR arm (*Table 7*). Six patients (4.3%) in the TAR arm required a lateral ligament repair. No patients in the ankle fusion arm underwent ligament repair.

The distribution of procedures by surgeon is shown in *Table 8*. Recruitment ended at the Royal National Orthopaedic Hospital in June 2018, 6 months prior to closure of recruitment.

TABLE 5 Total ankle replacement: implant usage

Type of implant	*n* (*N* = 142)	Percentage
Infinity Total Ankle System	76	53.5
STAR	24	16.9
BOX Total Ankle Replacement	23	16.2
Zenith (Corin Group, Circencester, UK)	18	12.7
Salto Talaris Total Ankle Replacement	1	0.7

TABLE 6 Ankle fusion: procedure type

Procedure type	*n* (*N* = 140)	Percentage
Arthroscopic	85	60.7
Open anterior/anteromedial	48	34.3
Open lateral	7	5.0

TABLE 7 Associated procedures

Procedure	TAR arm (*N* = 138), *n* (%)	Ankle fusion arm (*N* = 144), *n* (%)	Total, *n* (%)
None	90 (65.2)	118 (81.9)	208 (73.8)
Calcaneal osteotomy	1 (0.7)	0 (0.0)	1 (0.4)
Achilles tendon lengthening	17 (12.3)	2 (1.4)	19 (6.7)
Fibula osteotomy	0 (0.0)	6 (4.2)	6 (2.1)
Lateral ligament repair	6 (4.3)	0 (0.0)	6 (2.1)
Bone grafting	2 (1.4)	5 (3.5)	7 (2.5)
Removal of metalwork	4 (2.9)	2 (1.4)	6 (2.1)
Other	18 (13.0)	11 (7.6)	29 (10.3)

TABLE 8 Number of operations performed by surgeon

Surgeon number	Site	Type of surgery (*n*)		Total (*n*)
		TAR	Ankle fusion	
1	Aintree	2	3	5
2	Aintree	4	6	10
3	Brighton	10	8	18
4	Bristol	4	3	7
5	Bristol	1	1	2
6	Bristol	3	4	7
7	Cardiff	1	2	3
8	Cornwall[a]	0	2	2
9	Derby	14	15	29
10	Guildford	5	4	9
11	Hull	4	4	8
12	Newcastle	5	6	11
13	Newcastle	3	4	7
14	Northumbria	6	3	9
15	Northumbria	4	1	5
16	Northumbria	6	4	10
17	Norwich	2	6	8
18	Norwich	1	0	1
19	Nottingham	5	6	11
20	Nottingham	2	3	5
21	Oswestry	10	9	19
22	Oswestry	3	1	4
23	Oxford	4	2	6
24	Oxford	1	1	2
25	Oxford	1	0	1
26	Sheffield	4	4	8
27	Stanmore	5	3	8
28	Stanmore	24	24	48
29	Stanmore	1	1	2
30	Stanmore	4	4	8
31	Wigan	0	2	2
32	Wigan	0	1	1
33	Wigan	3	2	5
34	Wigan	0	1	1
Total		142	140	282

a Screened at Stanmore but referred to local centre, Cornwall, where surgery took place.

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Numbers analysed

Owing to the nature of the model used in the analysis of primary and secondary continuous outcomes (i.e. a mixed model), all patients with a baseline visit and at least one follow-up visit were included in the analysis. Therefore, the final primary outcome analysis was based on 281 patients: 137 in TAR and 144 in ankle fusion (*Table 9*).

Primary outcome

Findings for the primary outcome, MOXFQ (walking/standing domain), are presented in *Table 10*.

TABLE 9 Number of patients analysed in each outcome model

Analysis	TAR arm (*N* = 138)[a]	Ankle fusion arm (*N* = 144)
Primary outcome (ITT)	137	144
Sensitivity of primary outcome (per protocol)	135	134
Secondary outcome		
MOXFQ pain	137	144
MOXFQ social interaction	137	144
EQ-5D-5L index value	137	144
EQ-5D-5L VAS	137	144
FAAM-ADL	137	143
FAAM sport subscale	43	24
ROM dorsiflexion	132	131
ROM plantarflexion	132	131

a One patient randomised to the TAR arm did not have an outcome score.

TABLE 10 The MOXFQ walking/standing scores at 52 weeks post surgery, by treatment arm

	TAR arm			Ankle fusion arm				
Outcome	*n*	Value at 52 weeks, mean (SD)	Change from baseline, mean (SD)	*n*	Value at 52 weeks, mean (SD)	Change from baseline, mean (SD)	Adjusted difference in change from baseline (95% CI)[a]	*p*-value
Primary outcome (ITT)								
MOXFQ walking/standing score	136	31.4 (30.4)	−49.9 (30.7)	140	36.8 (30.6)	−44.4 (31.9)	−5.56 (−12.49 to 1.37)	0.12
Sensitivity analysis of primary outcome (per protocol)								
MOXFQ walking/standing score	135	31.4 (30.5)	−49.9 (30.8)	134	36.4 (30.8)	−45.0 (32.4)	−4.84 (−11.96 to 2.28)	0.18

a Adjusted difference is based on 281 patients in the mixed ITT model who had baseline MOXFQ (walking/standing) scores and at least one follow-up. The per-protocol analysis is based on 269 patients; it excludes crossovers and those missing the 52-week visit.

The mean (SD) MOXFQ walking/standing domain score at 52 weeks was 31 (30.4) in the TAR arm and 37 (30.6) in the ankle fusion arm. The mean (SD) change in scores between pre-surgery baseline and 52 weeks was −50 (30.7) in the TAR arm and −44 (31.9) in the ankle fusion arm. The adjusted difference in change score of −5.56 (95% CI −12.49 to 1.37) suggests that, on average, the improvement in the MOXFQ score from baseline to 52 weeks post surgery was 5.56 points greater in TAR patients than in ankle fusion patients (p = 0.12). The 95% CI for this difference includes both a difference of zero and the MID of 12. The MOXFQ scores improved following surgery in both arms (TAR: mean change −50, 95% CI −55 to −45; ankle fusion: mean change −44, 95% CI −50 to −39), but there was not a statistically significantly greater improvement in the TAR arm than in the ankle fusion arm. The proportion of patients with a reduction in MOXFQ score of at least 12 points from baseline at 52 weeks was very similar in the two arms: 82% of TAR patients compared with 80% of ankle fusion patients.

Four patients crossed over from ankle fusion to TAR after randomisation. Three patients had their 52-week visit outside of the protocol window and an additional five patients had missing 52-week scores. We carried out a per-protocol analysis as a sensitivity analysis for the primary outcome by excluding these 12 patients. The per-protocol analysis did not change the ITT conclusions.

Secondary outcomes

Findings for the secondary outcomes are presented in *Table 11*.

On average, patients in both arms reported an improvement in the MOXFQ pain and social interaction domains at 26 weeks, and on all MOXFQ domains at 52 weeks, but improvement was not greater in the TAR arm than in the ankle fusion arm. The difference between the TAR and ankle fusion arms in the change in MOXFQ walking/standing domain score at 26 weeks was statistically significant (p = 0.02).

The difference between the TAR and ankle fusion arms in the change in FAAM-ADL scores at 52 weeks was statistically significant (p = 0.01). There were substantial improvements from baseline in both arms, with a difference of 6.16 (95% CI 1.54 to 10.78) between the two arms.

The change in EQ-5D-5L index values between the two treatment arms was not significantly different at 26 weeks (p = 0.08) or 52 weeks (p = 0.32). The change in EQ-5D-5L VAS was statistically significant at 26 weeks (p = 0.03), but not at 52 weeks (p = 0.07).

Changes from baseline in ROM dorsiflexion and ROM plantarflexion were greater in the ankle fusion arm than in the TAR arm. Although ROM (dorsiflexion and plantarflexion) improved from baseline to 52 weeks in the TAR arm, it decreased in ankle fusion patients and the difference between arms was statistically significant (p < 0.001).

Subgroup analyses

A total of 45 patients (33%) in the TAR arm and 50 (36%) in the ankle fusion arm had osteoarthritis in one adjacent joint at baseline; 11 patients (8%) in the TAR arm and 12 patients (9%) in the ankle fusion arm had osteoarthritis in both the subtalar and talonavicular joints. Adjusted MOXFQ scores were lower in the TAR arm than in the ankle fusion arm at 52 weeks in the subgroup analyses (*Table 12*). However, we did not find a significant interaction caused by this factor. There was also no evidence to suggest that the effect of treatment was moderated by age. The subgroup analyses are presented in *Figure 2*.

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TABLE 11 Secondary outcomes at 52 weeks and 26 weeks, by treatment arm

Secondary outcomes	TAR arm			Ankle fusion arm			Adjusted difference in change from baseline (95% CI)	*p*-value
	n	Value at follow-up, mean (SD)	Change from baseline, mean (SD)	*n*	Value at follow-up, mean (SD)	Change from baseline, mean (SD)		
52 weeks								
MOXFQ pain	136	26.7 (24.7)	−40.2 (28.0)	140	30.6 (25.7)	−36.7 (24.6)	−4.20 (−9.80 to 1.39)	0.14
MOXFQ social interaction	136	17.0 (20.1)	−37.0 (30.0)	140	22.4 (24.4)	−33.7 (28.0)	−5.06 (−10.37 to 0.26	0.06
MOXFQ summary index[a]	136	26.4 (24.5)	−43.7 (26.1)	140	31.2 (25.5)	−39.3 (25.6)	−4.95 (−10.61 to 0.72)	0.09
FAAM-ADL	135	81.2 (20.5)	33.8 (22.7)	141	73.8 (20.7)	29.7 (20.7)	6.16 (1.54 to 10.78)	0.01
FAAM sport subscale	37	71.3 (28.8)	41.9 (31.8)	22	75.6 (23.2)	52.7 (26.8)	−4.98 (−18.60 to 8.64)	0.47
EQ-5D-5L index value	136	0.7 (0.2)	0.3 (0.3)	140	0.7 (0.2)	0.2 (0.2)	0.02 (−0.02 to 0.07)	0.32
EQ-5D-5L VAS	136	81.9 (15.2)	9.1 (19.9)	141	77.0 (17.3)	9.4 (22.3)	3.41 (−0.30 to 7.11)	0.07
ROM dorsiflexion	132	15.3 (7.2)	1.1 (10.1)	131	9.1 (5.8)	−4.9 (7.9)	6.09 (4.61 to 7.57)	< 0.001
ROM plantarflexion	132	27.3 (7.9)	1.9 (9.8)	131	14.4 (7.2)	−11.7 (11.1)	13.01 (11.24 to 14.77)	< 0.001
26 weeks								
MOXFQ walking/standing	134	35.8 (29.9)	−45.8 (31.0)	141	44.6 (29.6)	−36.9 (31.2)	−8.21 (−15.14 to −1.27)	0.02
MOXFQ pain	134	32.9 (24.3)	−33.8 (25.9)	140	36.2 (24.8)	−31.4 (23.8)	−2.45 (−8.06 to 3.16)	0.39
MOXFQ social interaction	134	22.3 (24.7)	−32.1 (29.5)	140	26.5 (24.4)	−29.6 (26.9)	−3.38 (−8.71 to 1.95)	0.21
MOXFQ summary index[a]	134	31.5 (25.0)	−38.6 (25.6)	140	37.5 (24.9)	−33.2 (24.9)	−5.13 (−10.80 to 0.55)	0.08
FAAM-ADL	132	77.1 (20.0)	30.0 (21.4)	140	70.9 (22.1)	26.8 (21.9)	4.56 (−0.08 to 9.20)	0.05
FAAM sport subscale	39	56.6 (28.1)	27.7 (26.2)	19	62.9 (28.7)	37.3 (35.7)	−7.17 (−21.11 to 6.76)	0.31
EQ-5D-5L index value	134	0.7 (0.2)	0.2 (0.2)	141	0.7 (0.2)	0.2 (0.2)	0.04 (−0.004 to 0.09)	0.08
EQ-5D-5L VAS	134	81.3 (14.8)	8.7 (21.5)	142	76.0 (19.2)	8.1 (22.2)	4.14 (0.43 to 7.85)	0.03

a Post hoc analysis.

Adverse events

A total of 20.8% of randomised patients experienced at least one SAE and 53.5% of patients experienced at least one AE during the course of their trial pathway (*Table 13*). The risks of patients experiencing a SAE or an AE were not significantly different between the two arms ($p = 0.19$ and $p = 0.84$, respectively).

All the AEs and SAEs reported during the trial have been summarised as postoperative complications in *Table 14*. One patient in the ankle fusion arm died during the follow-up period and one patient in the TAR arm died after the 52-week visit (not presented in *Table 14*). Both events were unrelated to surgery.

TABLE 12 The MOXFQ walking/standing scores at 52 weeks post surgery, by treatment arm

Subgroup analyses	TAR arm (*n*)	Ankle fusion arm (*n*)	Difference	95% CI	*p*-value
Change in walking/standing score					
Overall effect	136	140	−5.56	−12.49 to 1.37	0.12
Age (years)					
≤ 65	45	46	1.36	−9.82 to 12.53	0.13
> 65	91	94	−7.95	−17.79 to 1.88	
Adjacent osteoarthritis					
Healthy adjacent joint	80	78	−3.78	−12.64 to 5.09	
Osteoarthritis in subtalar or talonavicular	45	50	−9.56	−22.14 to 3.03	0.92
Osteoarthritis in both adjacent joints	11	12	−22.75	−46.77 to 1.27	0.11

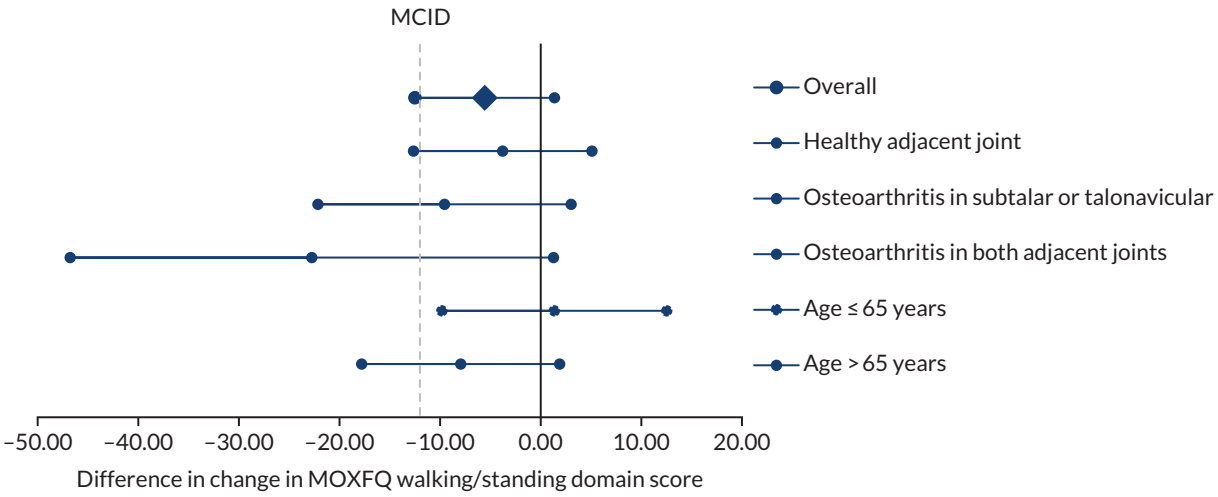

FIGURE 2 Forest plot showing subgroup analysis by treatment arm.

TABLE 13 Number of AEs and SAEs by treatment arm

Event	TAR arm (*N* = 152)	Ankle fusion arm (*N* = 151)	Total (*N* = 303)	Difference in proportion (95% CI)	*p*-value
Number (%) of patients experiencing a SAE	27 (17.8)	36 (23.8)	63 (20.8)	0.74 (0.48 to 1.16)	0.19
Total SAEs (*n*)	31	43	75		
Number (%) of patients experiencing an AE	82 (54.3)	80 (52.6)	162 (53.5)	1.02 (0.83 to 1.26)	0.84
Total AEs (*n*)	162	168	330		

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TABLE 14 Postoperative complications by treatment arm[a]

Complication	TAR arm, *n* (*N* = 152)	Ankle fusion arm, *n* (*N* = 151)	Total, *n* (*N* = 303)
Total surgeries (by procedure, not randomisation)	142	140	282
Complications (1–11, larger numbers thought to lead to worse outcome)			
1: Intraoperative bone fracture	3	0	3
2: Wound-healing problems[b]	20	8	28
A: Not requiring antibiotics	3	3	6
B: Requiring antibiotics	17	4	21
C: Requiring debridement	0	1	1
3: Pain undiagnosed[c]	17	23	40
4: Nerve injury[c]	8	1	9
5: Postoperative bone fracture	3	0	3
6: Technical error	0	0	0
7: Reoperation other than revision	5	4	9
8: Bone union issues	0	4	4
A: Aseptic loosening for TAR	0	–	0
B: Non-union for ankle fusion	–	17	17
9: Subsidence	0	0	0
10: Deep infection	0	0	0
11: Implant failure[d]	1	0	1
Not related to implant[c]			
Medical complication unrelated to implant (including cardiopulmonary)	73	92	165
Worsening of pre-existing musculoskeletal issue	35	35	70
Death	0	1	1
Thromboembolic events			
1: Deep-vein thrombosis[e]	2	5	7
2: Pulmonary embolism[e]	2	4	6
Otherc			
Trauma	1	3	4
Stiffness	3	1	4
Plaster/immobilisation/mobility issues	11	8	19
Tendon complications after surgery	2	2	4
Swelling	8	7	15

a Events reported for all 303 randomised patients.
b In the TAR arm, one patient had two relevant events.
c Some patients experienced more than one event and some events were reported more than once.
d All revision events took place after the 52-week window (some of the revisions also underwent a prior reoperation other than revision).
e In the ankle fusion arm, one patient had two relevant events.

There were 20 wound-healing problems in 19 (13.4%) patients in the TAR arm and eight wound-healing problems in eight (5.7%) patients in the ankle fusion arm. One patient in the ankle fusion arm and none in the TAR arm required debridement for the infection, although the majority of TAR patients were administered prophylactic antibiotics to treat the superficial wound infections.

There were eight nerve injury events reported in six patients (4.2%) in the TAR arm and one nerve injury event reported in one (< 1%) patient in the ankle fusion arm. Two events were reported twice.

There were 17 non-unions (12.1%) in the ankle fusion arm, which were diagnosed through the presence of a lucent line on plain radiographs at the 52-week follow-up. Of the 17 patients, eight were expected to be revised (47%), two (12%) were symptomatic but not planning to be revised due to serious comorbidities and seven (41%) were completely asymptomatic. Hence, 10 (7.1%) of 140 patients who received ankle fusion went on to symptomatic non-union.

There were 13 thromboembolic events in 11 patients: four (2.9%) patients in the TAR arm and seven (4.9%) in the ankle fusion arm. Two (1.4%) patients in the TAR arm experienced deep-vein thrombosis events and there were five events in four (2.8%) patients in the ankle fusion arm. Two (1.4%) patients experienced pulmonary embolism events in the TAR arm and there were four events in three (2.1%) patients in the ankle fusion arm. None of these events was fatal.

At 52 weeks' follow-up, nine patients (3.2%) required further unplanned reoperation other than revisions: five in the TAR arm and four in the ankle fusion arm. In the TAR arm, one revision took place within the 52-week window. This was due to a traumatic fall, leading to a fracture and conversion to a tibiotalocalcaneal fusion. We are aware of several other revisions that will take place outside the 52-week window and these data will be reported in the 2-year results. *Table 15* lists reoperations and revisions.

TABLE 15 Reoperation and revision, by treatment arm

Reoperation/revision	TAR arm (*N* = 152)	Ankle fusion arm (*N* = 151)
Total surgery (*n*) (by procedure, not randomisation)	142	140
Cases with no reoperations or revision, *n* (%)	136 (95.8)	136 (97.1)
Cases with reoperation, *n* (%)	5 (3.5)	4 (2.9)
Cases with revision, *n* (%)	1 (0.7)	0
Reoperations/revisions by type (n)		
Type 2: hardware removal	0	2
Type 3: unplanned procedures related to the TAR	2	2
Type 4: debridement of gutters or heterotopic ossification	3	0
Type 5: exchange of polyethylene bearing	0	0
Type 6: debridement of osteolytic cysts	0	0
Type 7: deep infection requiring debridement, no metal component removal	0	0
Type 9: revision of metal components for aseptic loosening, fracture or malposition	1	0
Type 10: revision of metal components secondary to infection	0	0
Type 11: amputation above the level of the ankle	0	0

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Post hoc analysis

The baseline characteristics of each of the subtypes of TAR (fixed and mobile bearing) and ankle fusion (open and arthroscopic) are reported in *Appendix 3*. Of those who received TAR, 53.5% received fixed-bearing TAR and 46.5% received mobile-bearing TAR. Of the ankle fusion patients, 61% received arthroscopic ankle fusion and 39% received open ankle fusion. Overall, all four subtypes of patients appeared similar with respect to baseline factors and baseline outcome measures. We carried out a post hoc comparison of each TAR subtype (those who received fixed-bearing TAR and those who received mobile-bearing TAR) with the ankle fusion arm (including both open and arthroscopic ankle fusion patients).

The mean (SD) MOXFQ walking/standing domain score at 52 weeks was 25.9 (28.3) in the fixed-bearing TAR group, compared with 36.8 (30.6) in the ankle fusion arm (*Table 16*). The adjusted difference of −11.1 (95% CI −19.3 to −2.9) suggests that, on average, the MOXFQ score at 52 weeks post surgery was 11.1 points lower in those who received fixed-bearing TAR than in those who underwent ankle fusion. This difference is statistically significant (p = 0.008). Comparing mobile-bearing TAR patients with ankle fusion patients, the adjusted difference is 2.1 (95% CI −6.6 to 10.8). This difference is not statistically significant (p = 0.64). There was no difference in the change in MOXFQ score at 52 weeks (p = 0.83) between open and arthroscopic patients in the ankle fusion arm (see *Appendix 4*).

The subgroup analyses by subtype of TAR patients (fixed and mobile bearing) compared with ankle fusion patients are shown in *Figure 3*.

TABLE 16 The MOXFQ walking/standing scores at 52 weeks post surgery, by treatment arm and TAR subtype

		TAR arm	
	Ankle fusion arm (n = 136)	Fixed bearing (*n* = 75)	Mobile bearing (*n* = 64)
Operation duration (minutes), mean (SD)	103 (36.2)	121 (30.6)	122 (32.7)
MOXFQ at 52 weeks, mean (SD)	36.8 (30.6)	25.9 (28.3)	38.5 (31.6)
Change from baseline at 52 weeks, mean (SD)	−44.4 (31.9)	−55.9 (27.7)	−42.0 (32.1)
Adjusted difference in change from baseline (95% CI)	–	−11.1 (−19.3 to −2.9)	2.1 (−6.6 to 10.8)
p-value	–	0.008	0.64

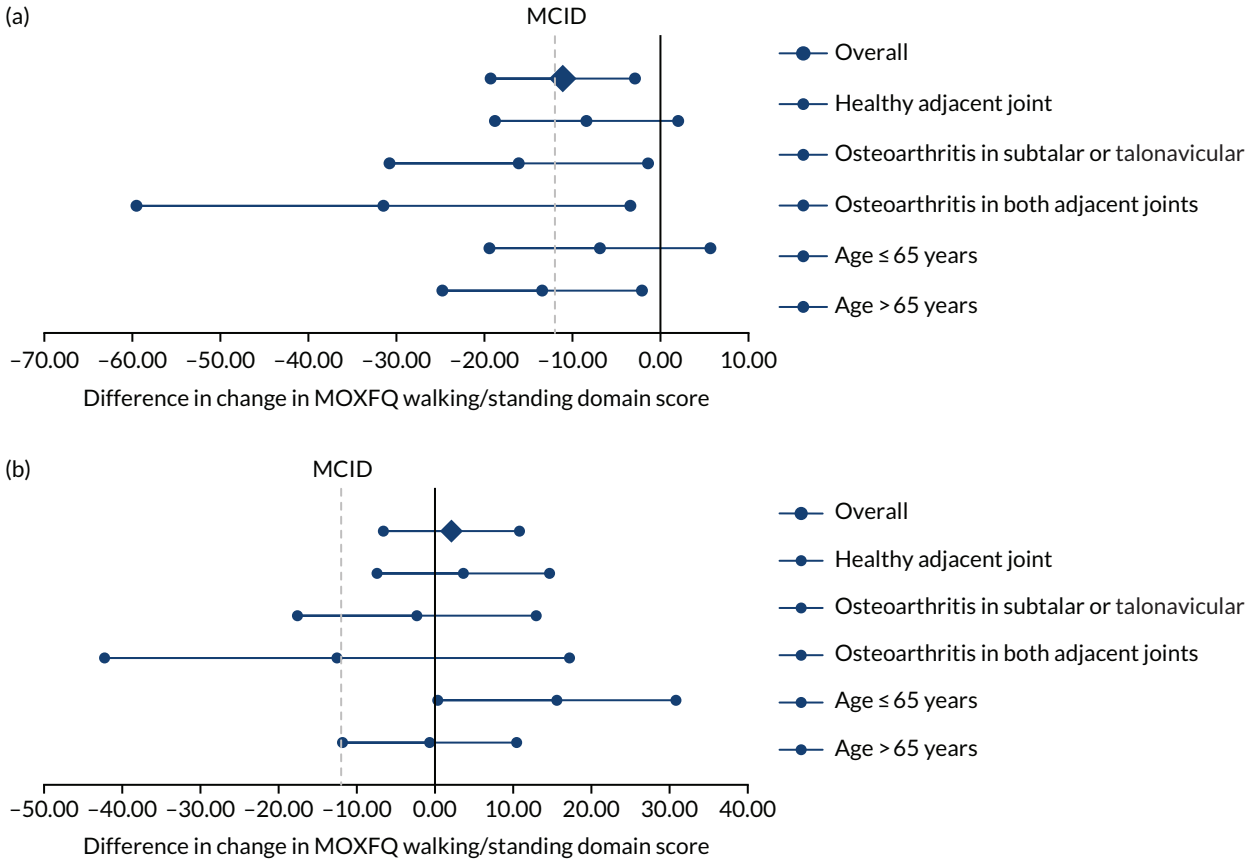

FIGURE 3 Forest plots showing subgroup analysis by treatment arm and TAR subtype. (a) Fixed-bearing TAR vs. ankle fusion; and (b) mobile-bearing TAR vs. ankle fusion.

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Chapter 4 Economic evaluation

Overview

The main objective of the economic evaluation was to assess the cost-effectiveness of TAR compared with ankle fusion for patients with end-stage osteoarthritis. We compared the costs and outcomes in the TAR and ankle fusion arms over a 52-week time horizon. The primary analysis was conducted in accordance with the ITT principle from the NHS and personal social services (PSS) perspective. Sensitivity analysis included per-protocol analysis and analysis from a societal perspective. The per-protocol analysis included only patients who received the surgery to which they were randomised. The societal perspective included out-of-pocket costs incurred by participants and productivity loss. The analytical approach took the form of cost–utility analysis. The main result of the analysis was the mean incremental cost per QALY gained. Costs and outcomes were not discounted because of the short time horizon (i.e. 52 weeks) of the within-trial economic evaluation.

We estimated a long-term cost-effectiveness of TAR compared with ankle fusion using decision-analytic modelling. The effect of TAR on participants' QoL is expected to last longer than the time horizon of the trial and is affected by the rate of future revisions. We constructed a simple Markov model that simulated patients' pathways after TAR and ankle fusion. The costs were taken from the trial data. The transition probabilities, cost of revision and EQ-5D-5L index values were obtained from published sources detailed in the subsequent section. The rate of revision was based on the clinicians' opinion.

Methods

Cost of surgery

The cost of surgery in both the TAR and ankle fusion arm is based on the surgery duration, grade of operating surgeon, cost of operating theatre, prices of devices, duration of hospital stay, duration of immobilisation and cost of materials for immobilisation (plaster or boot). The information was obtained from the trial CRF. The cost of each component was then calculated using the unit costs for each component (*Table 17*).

All costs are reported in Great British pounds and valued in 2018/19 prices. Where needed, costs were adjusted for inflation using the NHS cost inflation index.[51] Unit costs of operating theatre and operating surgeon's time were multiplied by the surgery duration to calculate the overall cost. The average duration of TAR operations was 121 (range 60–244) minutes; the average duration of ankle fusion operations was 103 (range 45–240) minutes. The cost of hospital stay is the unit cost per day multiplied by the duration of stay. The average hospital stay was 2.5 (range 0–12) days in the TAR arm and 2.1 (range 0–17) days in the ankle fusion arm. The unit cost was obtained from patient-level costing and information systems data[50] and were specifically for foot procedures.

If a walking boot was prescribed, use was assumed for the duration of immobilisation. Participants were wearing a boot for an average of 8.9 (range 0–46) weeks in the TAR arm and for an average of 13.8 (range 0–52) weeks in the ankle fusion arm. If plaster was prescribed, the unit cost was multiplied by the number of times it was applied. The plaster was assumed to be changed every 6 weeks. Participants were wearing plaster for an average of 3 (range 0–52) weeks in the TAR arm and for an average of 4.6 (range 0–26) weeks in the ankle fusion arm.

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TABLE 17 Unit costs associated with cost of surgery

Resource item	Unit cost (£)	Unit of analysis	Source of unit cost
Operating theatre	11.39	Per minute	Patient-level costing and information systems data 2014/15[50]
Operating surgeon			
Consultant	109.00	Per hour	*Unit Costs of Health and Social Care 2019*[51]
Specialty doctor	108.00	Per hour	*Unit Costs of Health and Social Care 2019*[51]
Specialty registrar, stage of training 3–8	47.00	Per hour	*Unit Costs of Health and Social Care 2019*[51]
Hospital stay	1380.84	Per day	Patient-level costing and information systems data 2014/15[50] (HRG group HN32A, HN32B, HN32C)
Walking boot	100.00	Per procedure	Estimated by clinician
Plaster	105.16	Per procedure	*NHS Reference Costs 2017/18*[52] (HRG VB09, service non-admitted)
Average cost of TAR implant	4055.98	Per implant	Manufacturer quotations
Average cost of devices for ankle fusion	2441.89	Per patient	Hospital quotation, including disposables (K-wires, drills, arthroscopic shavers)

HRG, Healthcare Resource Group.

Cost of health-care resource use

The data on health service resource use were collected using the CSRI. The CSRI was adapted to the trial's needs and was collected at baseline and at 12, 26 and 52 weeks post surgery. The components include inpatient care, outpatient care, community care and PSS. Community care includes GP surgery and home visits, GP phone calls, GP nurse practice visits and phone calls, district nurse visits and community physiotherapist visits. PSS includes social worker visits and phone calls, home help and using Meals on Wheels. Components were costed for each patient using unit costs from *NHS Reference Costs 2017/18*[52] and *Unit Costs of Health and Social Care*.[51,53,54] Unit costs are presented in *Appendix 2*, *Table 31*.

The CSRI questionnaire also collects data on costs borne by the patient, including transportation costs incurred in the receipt of care, equipment, mobility aids, home adaptations, patients' time off work and family and friends' time off work or usual activities because of care. The cost of lost productivity for TAR compared with ankle fusion was calculated using the human capital approach. The number of hours by which patients had to reduce their employment was multiplied by a unit cost. Unit costs were the average gross hourly earnings for men/women and full-time/part-time employees.[55] We also estimated the cost of family and friends' time using average gross hourly earnings multiplied by the number of hours.

Equipment costs were included in both the NHS and PSS perspective and the societal perspective, as we have information on whether these costs were paid by the PSS or out of pocket. Transportation unit costs include fuel costs for private car journeys only, as we have precise information on how much patients paid out of pocket for parking and taxi, bus and train journeys. We include the cost of replacing an employee for information only, as this unit cost comes from a private study conducted by Oxford Economics and income protection provider Unum, and has not been confirmed by any peer-reviewed publications.[56] All unit costs associated with out-of-pocket costs are presented in *Appendix 2*, *Table 32*.

We provided descriptive statistics for resource use variables by treatment arm and follow-up. Between-group differences were estimated using two-sample *t*-tests. Statistical significance was assessed at the 5% significance level.

Information on concomitant medications was collected in the trial CRF, including duration, dosage and frequency of prescriptions. Unit costs of medications were obtained from the *British National Formulary*.[57] When medication dosage was missing, we assumed that the participant received the same dosage as other participants who received the same medication.

Total costs from the NHS and PSS perspective include cost of surgery, health-care resource use, concomitant medications, and mobility aids and home adaptations paid for by the PSS. All costs were reported in 2018/19 Great British pounds. The overall mean cost per patient per arm was calculated. We adjusted for baseline values and minimisation factors. The factors are surgeon and presence of osteoarthritis in two adjacent joints (subtalar and talonavicular) as determined by preoperative MRI/CT. We used bias-corrected bootstrapping to calculate 95% CIs. Total costs from the societal perspective include all costs from the section above, and transportation costs, costs of equipment, mobility aids and adaptations paid out-of-pocket and cost of lost productivity. We calculated the total costs from the societal perspective in the same way.

Outcomes

The primary outcome was QALYs, which were calculated as the area under the curve using the EQ-5D-5L index values at baseline and at 12, 26 and 52 weeks post surgery. The EQ-5D-5L is a five-item, five-level questionnaire, scored 1 (no problem) to 5 (extreme problems). The EQ-5D-5L Crosswalk Index Value Calculator was used to estimate the index values.[38] It maps the EQ-5D-5L to the EQ-5D-3L value set and is recommended by NICE.[38] We estimated mean index values at each time point for TAR compared with ankle fusion, mean unadjusted QALYs from baseline to the end of the trial period and mean QALYs adjusted for baseline index values and minimisation factors using regression analysis.[58] We accounted for uncertainty by applying the bootstrapping technique and reporting 95% CIs. The EQ-5D-5L index values are shown in *Table 11*.

Cost–utility analysis methods

The cost and QALY data were combined to calculate an incremental cost-effectiveness ratio (ICER). Uncertainty in the point estimate of cost per QALY was quantified using bootstrapping methods to calculate CIs around the ICER.[59] Bootstrap ICERs were presented on the cost-effectiveness plane to determine in which quadrant TAR is located compared with ankle fusion and if a decision rule is required.

The bootstrapping results were used to construct the cost-effectiveness acceptability curve (CEAC):[58] the probability that TAR is cost-effective compared with ankle fusion at 52 weeks for a range of cost-effectiveness thresholds. The analysis was complete case as < 15% of participants were missing an ICER.

Sensitivity analysis involved a pre-protocol analysis, which included patients who received the surgery to which they were randomised only. We also adopted a societal perspective that included out-of-pocket costs incurred by participants, loss of earnings and productivity loss.

Long-term economic modelling

We used a modelling approach to extrapolate to a lifetime horizon. Our literature search identified two relevant cost-effectiveness studies comparing TAR with ankle fusion.[24,60] Based on these studies, we constructed a simple Markov model that simulated patients' pathways after TAR or ankle fusion. The structure of the model is shown in *Figure 4*.

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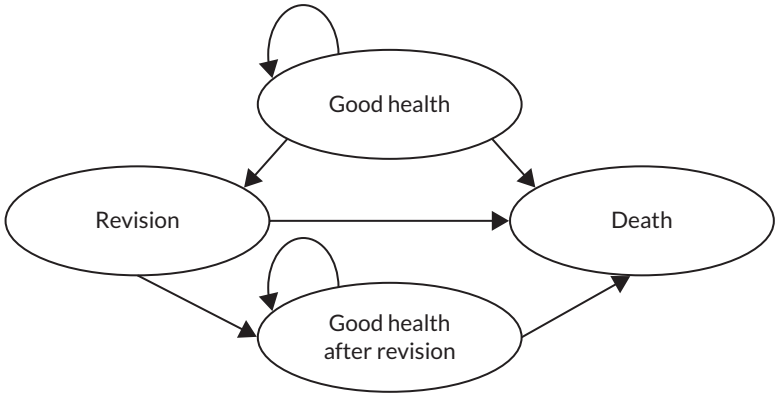

FIGURE 4 Model structure.

The Markov model, based on 1-year cycles, was used to simulate the impact of TAR and ankle fusion on patients' health for the lifetime horizon. There are 17 cycles in the model, as average life expectancy for a cohort aged 50–85 years is 17 years.[61] After surgery (TAR or ankle fusion) in year 1, patients stay in good health, move to revision or die. A patient can be in a revision state for 1 year only and then they can move to the good health or death state. We specify the 'good health after revision' state as we assume that revision reduces the QoL of a patient. Transition probabilities are reported in Tables 18 and 19.

Revision rates are based on clinicians' opinion. They are comparable to the previous cost-effectiveness model of TAR compared with ankle fusion.[60,62] The revision rate for ankle fusion was assumed to be 5% in the first 3 years (see *Table 19*) and 0% thereafter. The death rate is based on Public Health England's *Life Expectancy Calculator 2021*.[63] Each health state in the model was assigned a cost and a QALY outcome. These are reported in *Table 20*.

We assume that the resource use estimated at baseline is a good estimate of what patients would use in 'good health' and 'good health after revision' states. The cost of revision is based on the cost of ankle

TABLE 18 Transition probabilities for TAR

Transition probability (%)	Good health	Revision	Good health after revision	Death
Good health	95.8	1.2	0.000	3.00
Revision	0.00	0.00	97.00	3.00
Good health after revision	0.00	0.00	97.00	3.00
Death	0	0	0	100

TABLE 19 Transition probabilities for ankle fusion

Transition probability (%)	Good health	Revision	Good health after revision	Death
Good health	92.0	5.0	0.00	3.00
Revision	0.00	0	97	3.00
Good health after revision	0.00	0	97	3.00
Death	0	0	0	100

TABLE 20 State rewards

State reward	Good health	Revision	Good health after revision	Death
Cost £)				
TAR	275	7218	275	0
Ankle fusion	316	7218	316	0
EQ-5D-5L index value				
TAR	0.74	0.59	0.59	0
Ankle fusion	0.71	0.66	0.66	0

fusion. We assumed that patients continue to have the same EQ-5D-5L index values in the subsequent years after the surgery while they are in good health. Decrements in index values after revision are based on estimates in SooHoo and Kominski[62] as this is the only available source of these data.[62] The QoL decreases after revision surgery and patients have the same QoL for the rest of their life. We discount costs and QALYs at the rate of 3.5% recommended by NICE.[64]

A cost-per-QALY ratio was calculated using the data from the trial for year 1 and data from the Markov model for years 2–17. Probabilistic sensitivity analysis (PSA) was conducted to account for parameter uncertainty. We assigned probability distributions to parameters in the model and then used Monte Carlo simulations to obtain ICERs. We plotted the incremental costs and QALYs on a cost-effectiveness plane. We also estimated the probability of the intervention being cost-effective at a range of cost-effectiveness thresholds. The probabilities were plotted against the thresholds on a CEAC.

Results

This section presents the results of the health economic analysis of TAR compared with ankle fusion. We compare the cost of surgery, cost of health-care resource use, out-of-pocket costs, total costs, QALYs and cost–utility results of the base-case and sensitivity analyses.

Cost of surgery

Table 21 summarises the components of the cost of surgery: devices, operating theatre, orthopaedic surgeon's time, hospital stay and immobilisation. The total cost of surgery is a sum of the components, and 95% CIs are obtained using bootstrapping.

TABLE 21 Cost of surgery by treatment arm

	Cost (£), mean (SD)				
Cost component	TAR arm ($n = 138$)	Ankle fusion arm ($n = 144$)	Mean difference	p-value	Bootstrap 95% CI
Devices	4055.98 (387.47)	2441.89 (466.51)	1614.09	0.000	1511.60 to 1716.58
Operating theatre	1457.33 (363.80)	1227.98 (430.63)	229.34	0.000	142.36 to 328.22
Orthopaedic surgeon's time	221.78 (55.36)	184.38 (63.58)	37.39	0.000	23.81 to 51.20
Hospital stay	3562.17 (3133.79)	3164.43 (4879.62)	397.74	0.418	−595.96 to 1227.41
Immobilisation	193.80 (50.99)	209.58 (65.38)	−15.78	0.025	−29.94 to −1.59
Total cost of surgery	9491.06 (3166.44)	7218.45 (5129.87)	2272.61	0.000	1282.55 to 3262.67

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On average, TAR surgery took longer than ankle fusion surgery (121 minutes vs. 103 minutes, respectively). Therefore, the costs of using the operating theatre and surgeon's time are higher in the TAR arm than in the ankle fusion arm. TAR devices are also more expensive than ankle fusion devices (£4055.98 vs. £2441.89, respectively). The difference in the cost of devices, using the operating theatre and orthopaedic surgeon's time was statistically significant. The cost of hospital stay was higher in the TAR arm than in the ankle fusion arm (£3562.17 vs. £3164.43, respectively), as TAR patients stayed in hospital longer after the surgery. However, this difference was not statistically significant (p = 0.418). The duration of immobilisation was shorter in the TAR arm, so the cost was lower in the TAR arm than the ankle fusion arm (£193.80 vs. £209.58, respectively) and was statistically significant (p = 0.025). The difference in surgery costs was £2272.61 (95% CI £1282.55 to £3262.67) and was statistically significant.

Cost of health-care resource use

The response rate for the CSRI questionnaire was high and we have complete data collection on costs for 93.5% (n = 129) of TAR patients and 93.8% (n = 135) of ankle fusion patients. Components of health-care resource use by treatment arm and follow-up period are summarised in *Table 22*.

TABLE 22 Cost of health-care resource use by treatment arm and follow-up period

	Cost (£), mean (SD)			
Cost category by period	**TAR arm (n = 129)**	**Ankle fusion arm (n = 135)**	**Mean difference**	***p*-value**
Baseline				
Inpatient care	39 (285)	112 (527)	−73	0.16
Outpatient care	98 (158)	110 (179)	−12	0.57
Community care	121 (429)	77 (108)	44	0.24
PSS	0 (0)	3 (22)	−3	0.14
12 weeks				
Inpatient care	498 (2,201)	115 (326)	383	0.04
Outpatient care	199 (326)	134 (191)	65	0.04
Community care	183 (650)	86 (319)	96	0.12
PSS	6 (50)	7 (66)	−1	0.87
26 weeks				
Inpatient care	180 (1493)	61 (508)	118	0.39
Outpatient care	70 (180)	86 (165)	−15	0.45
Community care	177 (593)	135 (734)	−8	0.92
PSS	0 (0)	0 (0)	0	N/A
52 weeks				
Inpatient care	125 (516)	78 (386)	46	0.41
Outpatient care	106 (421)	80 (168)	26	0.50
Community care	138 (544)	191 (847)	−52	0.55
PSS	2 (18)	2 (17)	−0.1	0.97

N/A, not applicable.

The differences in resource use are due to chance and are not statistically significant. Nevertheless, we account for the difference in baseline values in the analysis of the total costs. Post surgery, TAR patients used more resources than ankle fusion patients, except for community care use at 52 weeks, which was higher in the ankle fusion arm. The only statistically significant differences were in inpatient care and outpatient care costs at 12 weeks: the costs were higher in the TAR arm than in the ankle fusion arm.

Societal costs

Societal costs include equipment, mobility aids and home adaptations that were paid out of pocket, loss of earnings due to time off work, family and friends' time and transportation costs. These are summarised in *Table 23*. The costs are shown for participants with complete cost data collection.

The differences at baseline are due to chance and are not statistically significant. We assumed that all patients who were employed part or full time at baseline had to take 6 weeks of leave because of the surgery. This assumption was based on the data collected on the duration of immobilisation. This resulted in lost earnings of £2807.07 in the TAR arm and £2946.77 in the ankle fusion arm. A total of 85 participants were employed, 40 in the TAR arm and 45 in the ankle fusion arm. The average loss of earnings over 52 weeks was £683.69 in the TAR arm and £1034.92 in the ankle fusion arm. This difference was not statistically significant (p = 0.27). Two patients in the TAR arm and three patients in the ankle fusion arm had to retire because of their ankle problem. The out-of-pocket spending on equipment, aids and adaptations, and the transportation costs were similar in both arms. Participants in the ankle fusion arm were using more help from their family or friends than those in the TAR arm, which resulted in a higher cost of family's and friends' time. On average, this cost £1716.22 in the TAR arm and £3707.92 in the ankle fusion arm. This difference is statistically significant (p = 0.00). Patients in the TAR arm used, on average, 9 hours of their friends' or family's time; patients in the ankle fusion arm used, on average, 20 hours.

TABLE 23 Societal costs by treatment arm and follow-up period

Cost category	Cost (£), mean (SD)		Mean difference	*p*-value
	TAR arm (N = 129)	Ankle fusion arm (N = 135)		
Baseline				
Equipment, mobility aids and home adaptations	30.29 (330.17)	24.55 (191.40)	5.74	0.86
Loss of earnings	233.33 (776.65)	228.32 (842.86)	5.01	0.96
Family and friends' time	535.00 (1625.31)	606.33 (1482.53)	−68.32	0.72
Transportation costs	4.29 (17.89)	7.10 (34.36)	−2.80	0.41
52 weeks post surgery				
Equipment, mobility aids and home adaptations	7.35 (48.54)	7.58 (34.81)	−0.23	0.96
Leave (TAR, n = 40; ankle fusion, n = 45)	2807.07 (1343.37)	2946.77 (1283.84)	−139.70	0.63
Loss of earnings (TAR, n = 40; ankle fusion, n = 45)	683.69 (2087.20)	1034.92 (2974.46)	−351.22	0.27
Family and friends' time	1716.22 (3340.69)	3707.916 (6403.59)	−1990.95	0.00
Transportation costs	8.69 (24.01)	11.04 (45.69)	−2.34	0.60

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Total costs

Table 24 summarises the cost components discussed above and presents the total costs by treatment arm from the NHS and PSS perspective.

The total costs are reported for participants with complete cost data collection; therefore, these values differ from those in *Table 21* as it reported costs for all patients. The total cost of TAR from the NHS and PSS perspective was £2638.45 higher than the total cost of ankle fusion. This is statistically significant (p = 0.00). When we adjusted for baseline values and minimisation factors, the difference was reduced slightly to £2576.21 and was statistically significant. The main driver for the cost difference was the cost of surgery, which was £2230.10 higher in the TAR arm than in the ankle fusion arm. Other differences in cost components were not statistically significant.

We conducted a subgroup analysis of total costs based on the type of TAR implant used (fixed bearing vs. mobile bearing) as there were differences noted in the statistical analysis. The results are presented in *Table 25*.

The total costs in the TAR arm were higher than those in the ankle fusion arm; however, the total cost in the mobile-bearing TAR group was higher than that of both the ankle fusion arm and the fixed-bearing TAR group.

Quality-adjusted life-years

Quality-adjusted life-years were the outcome in the cost–utility analysis. We present unadjusted and adjusted difference in QALYs by treatment arm in *Table 26*.

TABLE 24 Total cost per patient by treatment arm (NHS and PSS perspective)

	Cost (£), mean (SD)				
Cost component	TAR arm (n = 129)	Ankle fusion arm (n = 135)	Mean difference	p-value	Bootstrap 95% CI
Surgery	9488.61 (3107.47)	7258.51 (5281.82)	2230.10	0.00	1024.22 to 3102.77
Health-care resource use over 52 weeks	1689.82 (3620.35)	1047.59 (1591.92)	642.24	0.06	−18.21 to 1302.68
Concomitant medications	676.60 (839.68)	893.09 (1370.38)	−216.49	0.12	−512.23 to 38.97
Mobility aids and home adaptations provided by PSS	1.54 (6.84)	18.94 (207.07)	−17.39	0.34	−68.33 to 1.26
Total cost unadjusted	11,856.59 (5549.61)	9218.13 (5992.82)	2638.45	0.00	1191.20 to 3942.11
Total cost adjusted	11,824.76	9248.55	2576.21	0.00	1181.39 to 3988.13

TABLE 25 Total cost (£) per patient (NHS and PSS perspective): subgroup analysis

		TAR arm	
Measure	Ankle fusion arm (n = 131)	Fixed bearing (n = 72)	Mobile bearing (n = 61)
Total cost (unadjusted)	9222.44 (6071.35)	10,868.10 (3458.01)	12,841.07 (7088.72)
Total cost (adjusted)	9241.65	10,878.31	12,787.77
Mean difference	–	1636.66	3578.71
Bootstrap 95% CI	–	243.09 to 2824.29	1744.83 to 5889.34
p-value	–	0.014	0.000

TABLE 26 The QALYs at 52 weeks by treatment arm

Analysis	QALYs at 52 weeks		Mean difference	*p*-value	Bootstrap 95% CI
	TAR arm (*n* = 135)	Ankle fusion arm (*n* = 141)			
Unadjusted	0.68 (SD 0.15)	0.65 (SD 0.17)	0.03	0.09	−0.004 to 0.07
Adjusted for baseline values	0.68	0.66	0.02	0.14	−0.008 to 0.05

The QALY is an outcome measure that combines quantity and QoL; 1 year in perfect health is equal to 1 QALY. Patients in the TAR and ankle fusion arms had, on average, 0.68 and 0.65 QALYs, respectively. The difference between the arms was not statistically significant. Adding minimisation factors to the model did not change the result.

We conducted a subgroup analysis by TAR implant type. The results are presented in *Table 27*.

The mobile-bearing TAR group did not differ from the ankle fusion arm in terms of QALYs (p = 0.754). By contrast, there was some evidence that fixed-bearing TAR generated more QALYs than ankle fusion (0.69 vs. 0.66, respectively); however, it would not be considered statistically significant at the conventional significance level of 5% (p = 0.053).

Cost–utility analysis

Primary within-trial analysis

Although orthopaedic surgery lasts patients for many years, if we analyse the data over the 52 weeks of the study, the mean incremental cost per QALY gained was £127,931.50 from the NHS and PSS perspective. Using the bootstrapping technique, we generated an empirical distribution of ICERs and presented them on the cost-effectiveness plane (*Figure 5*).

Virtually all ICERs are above the *x*-axis; therefore, TAR is more expensive than ankle fusion. However, with respect to QALYs, most ICERs suggest that TAR generates more QALYs than ankle fusion. However, some ICERs are on the negative side of the *x*-axis, implying that TAR generates fewer QALYs than ankle fusion. Hence, there is a high degree of uncertainty in the data. In total, 95% of iterations fall between −£253,647.40 and £182,814.20, implying that TAR may be more expensive or cost-saving.

We also used the bootstrapping results to estimate the probability of TAR being cost-effective compared with ankle fusion at various cost-effectiveness thresholds. The probability is low: 1.3% at the threshold of £30,000 per QALY gained. The probability increases and reaches 37.6% at the threshold of £100,000 per QALY gained (*Figure 6*).

TABLE 27 The QALYs at 52 weeks: subgroup analysis

Measure	QALYs at 52 weeks		
		TAR arm	
	Ankle fusion arm (*n* = 137)	Fixed bearing (*n* = 76)	Mobile bearing (*n* = 64)
Unadjusted	0.65 (0.17)	0.69 (0.14)	0.67 (0.15)
Adjusted	0.66	0.69	0.66
Mean difference	–	0.04	0.006
Bootstrap 95% CI	–	−0.004 to 0.07	−0.03 to 0.04
p-value	–	0.053	0.754

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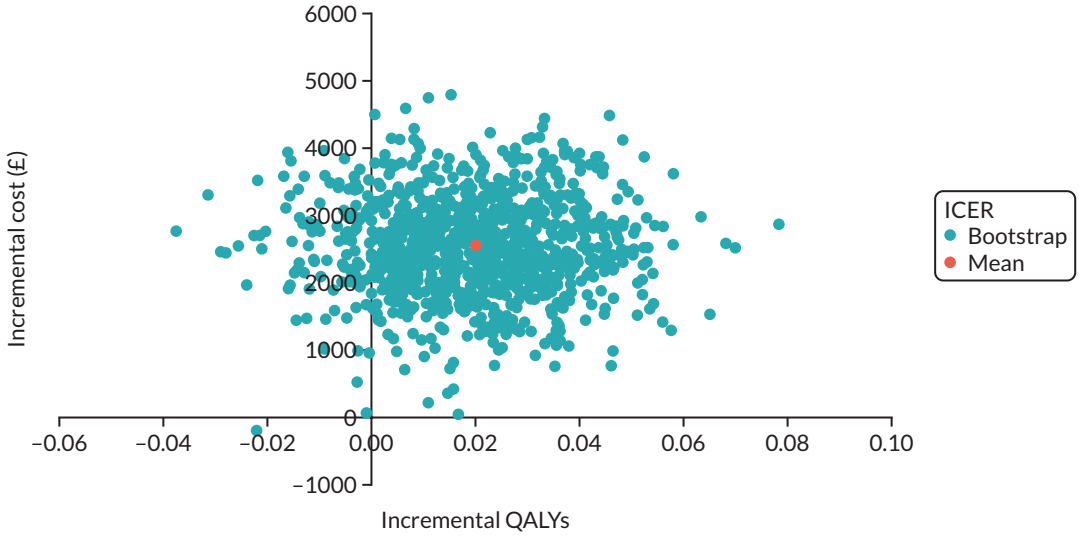

FIGURE 5 Cost-effectiveness plane: ITT, NHS and PSS perspective.

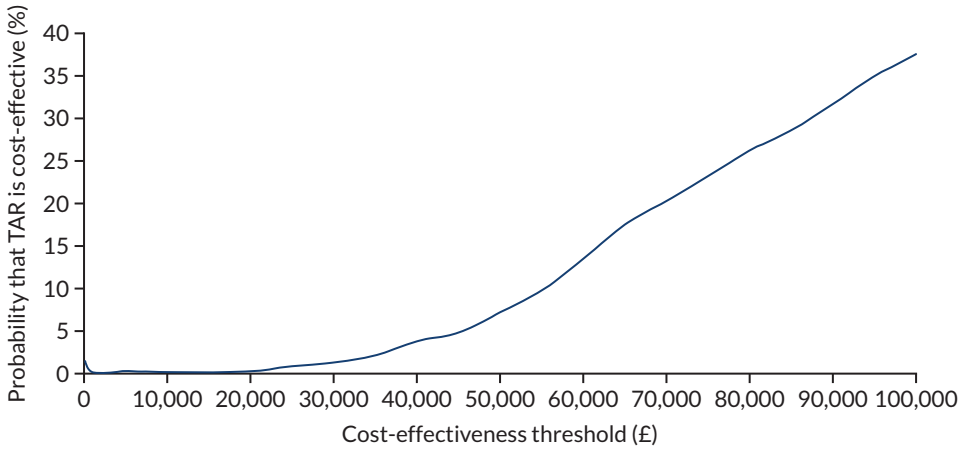

FIGURE 6 Cost-effectiveness acceptability curve: ITT, NHS and PSS perspective.

It is important to note that the benefits of the surgery begin after the 52-week window. Therefore, the results need to be interpreted with caution and we conducted long-term economic modelling to account for this.

Sensitivity analysis

The total societal costs were £15,142.95 (SD £7820.42) for TAR and £14,961.09 (SD £9978.75) for ankle fusion. The unadjusted mean difference was £181.86. This difference was not statistically significant. When we adjusted for baseline values and minimisation factors, the mean difference was £198.55. The difference in costs between the two arms was lower than that in the NHS and PSS perspective and it lost significance.

Over 52 weeks, the mean incremental cost per QALY gained was £9927.50 from the societal perspective. This ICER is considerably lower than the base-case result and would be recommended under NICE's threshold of £20,000–30,000 per QALY gained.[65] However, costs from the societal perspective introduced considerable uncertainty as they were difficult to estimate. Using the bootstrapping technique, 95% of iterations fall between −£41,024.23 and £184,899.90. The cost-effectiveness plane shows that the ICERs can be in any quadrant of the plane, which implies a high degree of uncertainty (*Figure 7*).

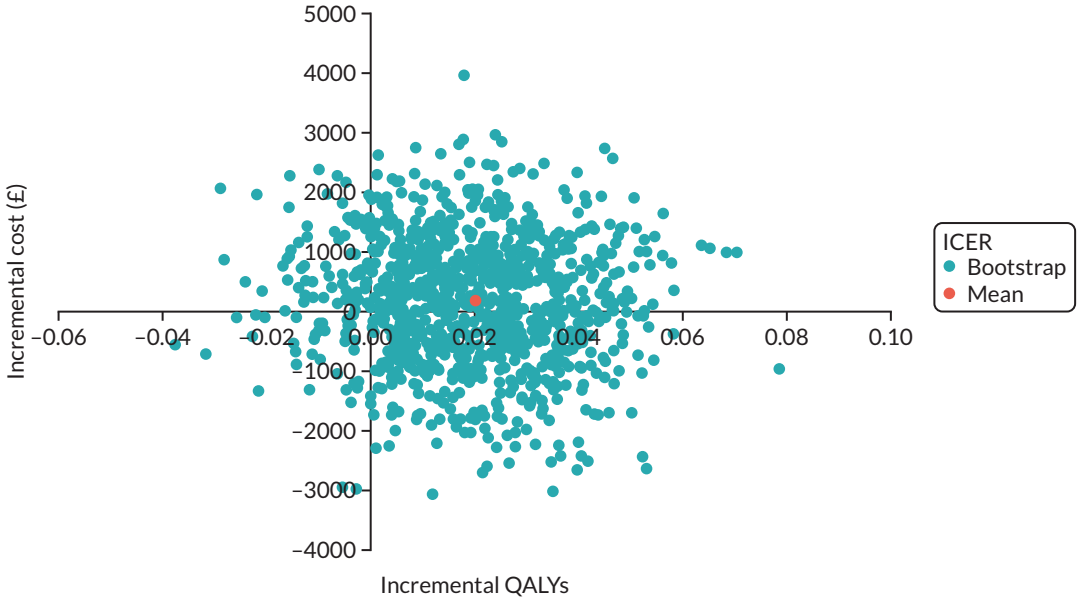

FIGURE 7 Cost-effectiveness plane: ITT, societal perspective.

The CEAC shows that the probability of TAR being cost-effective compared with ankle fusion at £30,000 per QALY gained is 61.6% and increases to 80.6% when the threshold increases to £100,000. The CEAC is shown in *Figure 8*.

The probability is equal to about 60% when the cost-effectiveness threshold is zero because 60% of ICERs on the cost-effectiveness plane suggest that TAR is cost-saving compared with ankle fusion.

When we included the cost of replacing an employee, total societal costs were £15,616.05 (SD £8854.13) for TAR and £15,622.46 (SD £11,071.48) for ankle fusion. The unadjusted difference between arms was small (£6.42) and not statistically significant (p-value 0.996). Adjusting for the baseline values and minimisation factors did not change the result. We applied this cost to patients who retired after the surgery and reported that they retired because of their ankle problem. There were two such patients in the TAR arm and three in the ankle fusion arm.

The per-protocol analysis resulted in very minor differences in total costs and QALYs. The ICER was £127,154.60 per QALY gained, which is a lot higher than the threshold used by NICE.[65] In total, 95% of bootstrap values fall between −£165,764.40 and £654,921.60. The cost-effectiveness plane shows that TAR is more expensive than ankle fusion, as all ICERs are on the positive side of the y-axis (*Figure 9*).

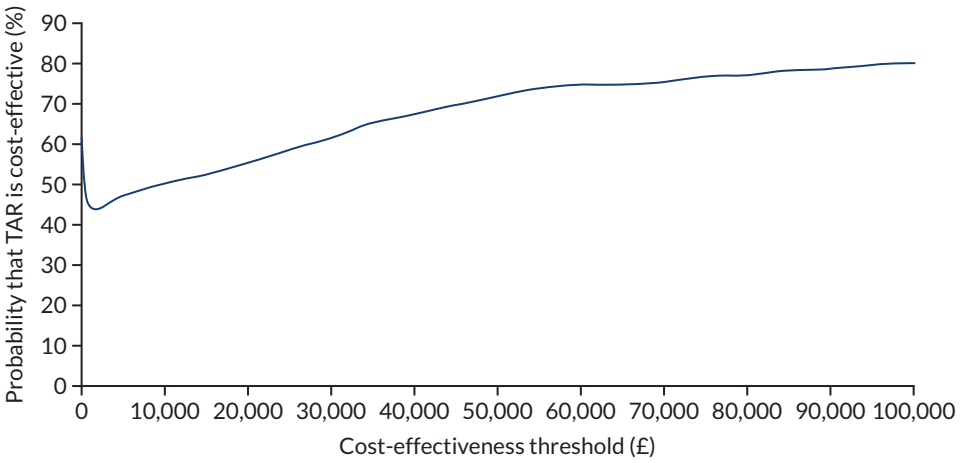

FIGURE 8 Cost-effectiveness acceptability curve: ITT, societal perspective.

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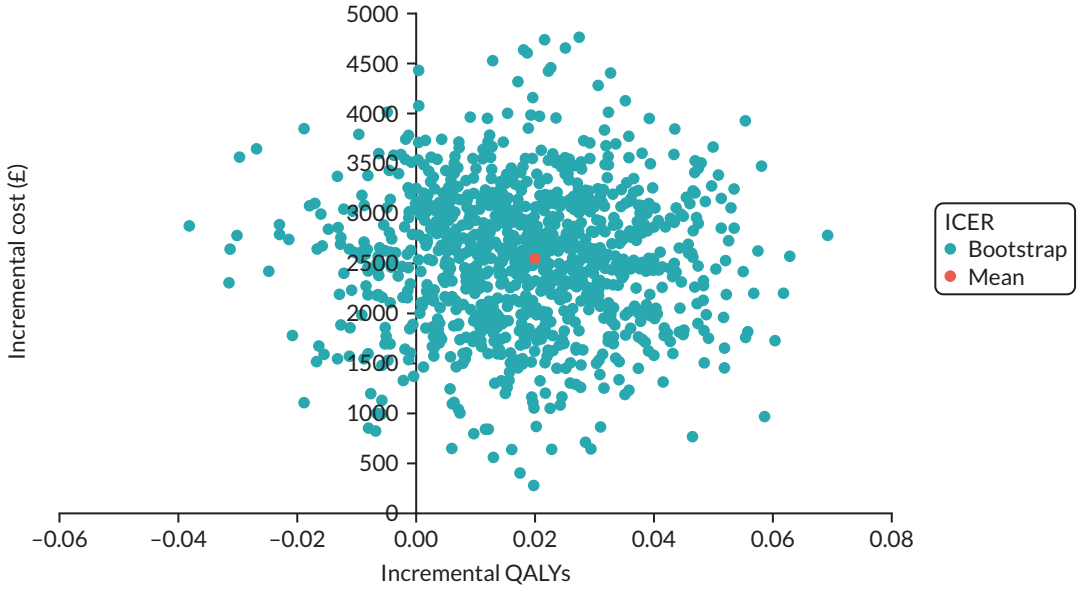

FIGURE 9 Cost-effectiveness plane: per-protocol, NHS and PSS perspective.

Therefore, the within-trial probability of TAR being cost-effective at 52 weeks was 1% at the cost-effectiveness threshold of £30,000 per QALY gained, increasing to 35.7% if the threshold increases to £100,000 per QALY gained. The CEAC is shown in *Figure 10*. The results suggest that it is important to account for societal costs when comparing TAR and ankle fusion, as these have a large impact on the ICER. However, societal costs also introduce a high degree of uncertainty. When considering implants and definitive surgery, 52-week data need to be interpreted with caution, as the benefits begin after the 52-week window; hence, the more important analysis relates to longer-term modelling.

Long-term economic modelling

The model-based analysis suggested that TAR is more expensive than ankle fusion, but generates more QALYs when extrapolated to a lifetime horizon. The ICER was estimated to be £4201.81. Cost and QALY differences are presented in *Table 28*.

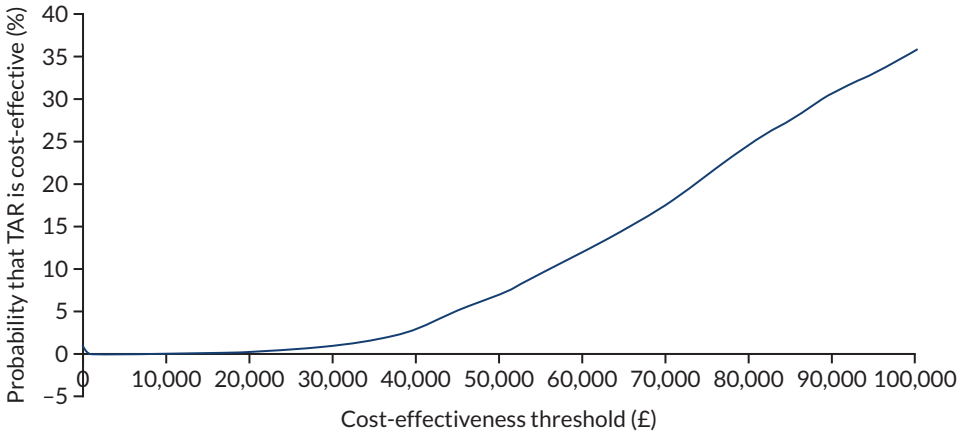

FIGURE 10 Cost-effectiveness acceptability curve: per-protocol, NHS and PSS perspective.

TABLE 28 Model-based total cost and QALYs per treatment arm

Measure	TAR arm (*n* = 129)	Ankle fusion arm (*n* = 134)	Difference
Total cost (£)	2,138,343	1,878,140	260,202
Total QALYs	1110	1048	61

The result of Monte Carlo simulation (n = 5000) is presented in the cost-effectiveness plane in *Figure 11*.

The mean ICER is in the north-east quadrant. This means that TAR is more expensive and also generates more QALYs than ankle fusion. When we varied cost and QoL parameters in the model, we observed that most points still lay in the north quadrant. Therefore, TAR is likely to be more expensive than ankle fusion over the lifetime horizon. However, there was uncertainty regarding the number of QALYs attained as some ICERs were in the north-west quadrant, implying that TAR may generate fewer QALYs and be more expensive than ankle fusion. Hence, there is considerable uncertainty around the lifetime ICER, and longer-term data are required to obtain a more robust result.

Although there is uncertainty, over the lifetime horizon there was a 69% probability that TAR is cost-effective compared with ankle fusion at the cost-effectiveness threshold of £20,000 per QALY gained (*Figure 12*).

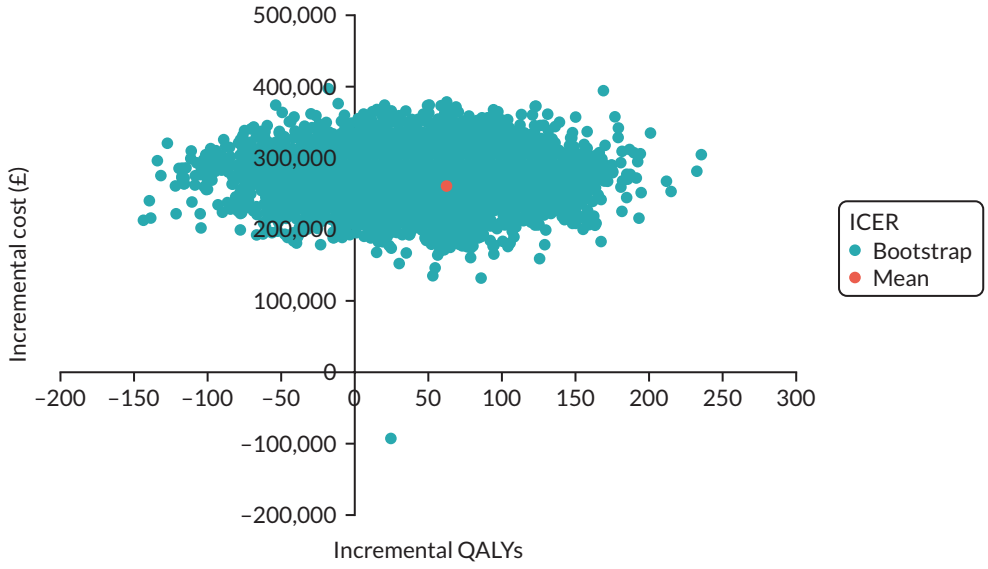

FIGURE 11 Cost-effectiveness plane: lifetime horizon.

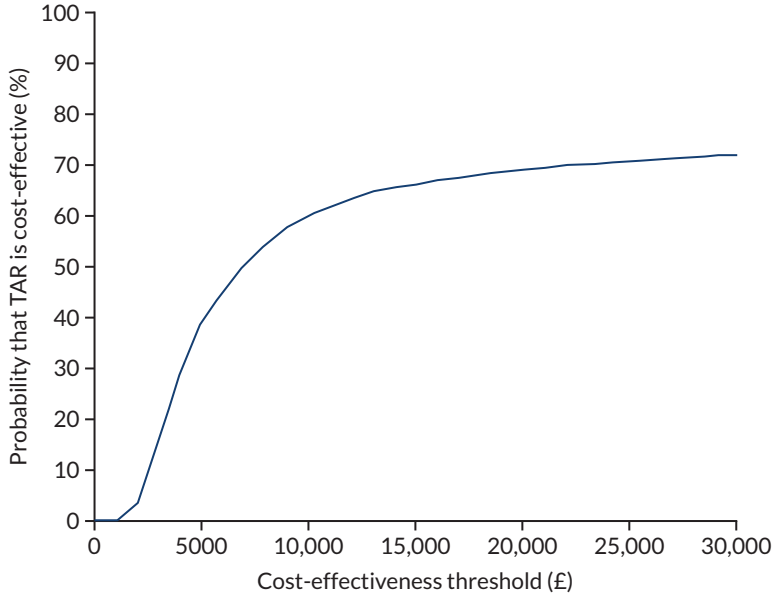

FIGURE 12 Cost-effectiveness acceptability curve: lifetime horizon.

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As seen in the statistical and economic analysis, the fixed-bearing TAR group performed better than the mobile-bearing TAR group and the ankle fusion arm. If we assume that all patients receive fixed-bearing TAR and assign their QoL to all TAR patients, the difference in QALYs between the two arms increases (*Table 29*).

Total ankle replacement is still more expensive and generates more QALYs than ankle fusion. The ICER was £2535.32. When we conducted a PSA for this result, the probability of TAR being cost-effective compared with ankle fusion was 72.2% at the cost-effectiveness threshold of £20,000 per QALY gained.

TABLE 29 Costs and QALYs: fixed-bearing TAR vs. ankle fusion

Measure	TAR arm: fixed-bearing group (*n* = 129)	Ankle fusion arm (*n* = 134)	Difference
Total cost (£)	2,138,343	1,878,140	260,202
Total QALYs	1150	1048	102

Chapter 5 Discussion

To the best of our knowledge, this is the first RCT to compare TAR with ankle fusion for patients with end-stage ankle osteoarthritis. This was a pragmatic, multicentre, parallel-group, non-blinded RCT that aimed to ensure that the outputs were generalisable and focused on the needs of patients and the public. Our aim was to determine the clinical effectiveness and cost-effectiveness of two recognised treatments for end-stage ankle arthritis in patients aged between 50 and 85 years.

There was a significant improvement in the primary outcome measure at 52 weeks after surgery in both the TAR and ankle fusion arms, with the TAR arm improving, on average, by 49.9 (30.7) points and the ankle fusion arm improving by 44.4 (31.9) points. Although the proportion of patients who met the MID of 12 points was higher in the TAR arm than in the ankle fusion arm (82% vs. 80%, respectively), the adjusted difference in MOXFQ walking/standing domain scores of −5.56 (95% CI −12.49 to 1.37) was not statistically significantly different (p = 0.12). Therefore, we have shown that there was no greater improvement in the TAR arm than in the ankle fusion arm at 52 weeks, whether analysed by ITT or per protocol. At 26 weeks, the adjusted difference in MOXFQ walking/standing domain score was −8.21 (−15.4 to −1.27), which was statistically significant (p = 0.02), but this difference had reduced by 52 weeks.

The difference between TAR and ankle fusion in the change in FAAM-ADL scores at 52 weeks was statistically significant (p = 0.01), with both arms showing substantial improvements from baseline and a difference of 6.16 (95% CI 1.54 to 10.78) between the arms. The changes in EQ-5D-5L index values between the two treatment arms were not significantly different at 26 weeks (p = 0.08) or 52 weeks (p = 0.32). The EQ-5D-5L VAS was statistically significant at 26 weeks (p = 0.03), but not at 52 weeks (p = 0.07).

The arms were similar at baseline in terms of age, sex, comorbidity and clinical scores. Owing to chance, some differences were noted, such as a slightly larger number of obese patients in the ankle fusion arm than in the TAR arm, and more patients who had deformity or previous internal fixation for trauma in the TAR arm than in the ankle fusion arm. We do not, however, believe these differences to be material. Participants appeared to be equally distributed between treatment arms with regard to the minimisation factors, that is the presence of osteoarthritis in the subtalar or talonavicular adjacent joints. The planned subgroup analysis did not identify a significant interaction between the treatment effect and the presence of arthritis in one or both adjacent joints at the 52-week time point, nor did we find a significant interaction with age.

Most studies that have compared TAR and ankle fusion to date have been observational. Daniels *et al.*[20] looked at 281 TARs and 107 ankle fusions and found comparable outcome scores between the two surgeries at a mean follow-up of 5.5 years. In their study, which was not randomised, patients treated with ankle fusion were younger, more likely to be diabetic, less likely to have inflammatory arthritis and more likely to be smokers than those treated with TAR.[20] Veljkovic *et al.*[21] analysed 88 TARs and 150 ankle fusions at a follow-up of 3.6 years and found that ankle fusion had comparable clinical outcomes to TAR for patients with non-deformed end-stage ankle arthritis.

Attempts have been made to run RCTs in this area. Norvell *et al.*[66] reported a prospective study in which 386 TARs were compared with 93 ankle fusions. Although it was designed at the outset as an RCT, patients were unwilling to agree to randomisation, which forced a change from a RCT to a cohort design. This led to an imbalance in the study arms, with differences in baseline characteristics. At 2 years, the study showed both treatments to be effective, with a difference in FAAM-ADL score between TAR and ankle fusion of 9 points.[66] This compares favourably with our study, which showed a difference in FAAM-ADL score of 6.16 (1.54 to 10.78) between TAR and ankle fusion at 52 weeks.

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In this trial, 54% of TAR and 53% of ankle fusion patients experienced at least one AE during the trial, although the vast majority were medical complications unrelated to the type of surgery. It is difficult to compare this finding with the literature, which reports only implant-specific complications.

We did not find a difference between the TAR and ankle fusion arms in terms of the risk of patients experiencing an AE overall, but we did find differences in the types of AEs. A total of 19 (13.4%) patients in the TAR arm and eight (5.7%) in the ankle fusion arm had wound-healing problems, although only one patient in the ankle fusion arm required a reoperation as a result. Six patients (4.2%) in the TAR arm and one (< 1%) in the ankle fusion arm had nerve injuries.

There were fewer patients with thromboembolic events in the TAR arm than in the ankle fusion arm [four (2.9%) vs. seven (4.9%), respectively], which might be explained by prolonged immobilisation. Two patients in the ankle fusion arm had multiple events (two events each). There were no fatal pulmonary embolism events. There are sparse comparative data on thromboembolism following ankle surgery. Although the incidence of thromboembolism has been reported as low,[67] Hospital Episode Statistics-based studies are confounded because deep-vein thrombosis invariably does not lead to admission,[68] meaning that data are not captured in national databases. In our study, 98% of patients received chemical or mechanical prophylaxis, so our data provide pragmatic figures of thromboembolic risk.

It is important to state, however, that, to the best of our knowledge, there are very few papers that report the complications of ankle fusion and none that have compared the complications of both treatments in a randomised cohort. Glazebrook *et al.*[69] classified complications following TAR in terms of risk to implant survival, referring to high-grade complications such as deep infection, medium-grade complications such as subsidence and low-grade complications such as intraoperative fractures and wound-healing issues. The higher the grade, the more likely the complication would result in implant failure. Gadd *et al.*[70] later suggested a simpler classification of high- and low-grade complications. We have adapted these classifications to enable the comparison with ankle fusion, which, to the best of our knowledge, has not been undertaken in a randomised trial before now.

There were five further unplanned reoperations other than revisions in the TAR arm and four in the ankle fusion arm. Although only one revision procedure took place within the 52-week window, we are aware of at least four patients who will require revision (TAR, $n = 1$; ankle fusion, $n = 3$).

Robust outcome studies on ankle fusion are sparse, but the risk of an ankle fusion going on to non-union has previously been estimated to be between 7.8%[71] and 10%.[13] In this study, there were 17 non-unions (12%), which were diagnosed by the presence of a lucent line on plain radiographs at the 52-week follow-up. Seven of these patients had no symptoms whatsoever; hence, 10 (7%) of the 140 patients who received ankle fusion went on to symptomatic non-union. Although none of the non-unions were revised in the first 52 weeks following surgery, it is likely that the 10 symptomatic patients may go on to have further investigation and revision surgery.

Haddad *et al.*'s[13] meta-analysis of the literature showed that TAR and ankle fusion have similar intermediate-term outcomes for clinical scores, patient satisfaction, complications and revision rate, although they did not include any studies that directly compared TAR with ankle fusion. A more recent systematic review and meta-analysis comparing TAR with ankle fusion showed no statistically significant difference between the groups, but commented on significant methodological flaws and the heterogeneity of outcome measures.[72]

In clinical practice in the UK, the most common implant type currently used is a fixed-bearing prosthesis, with a > 70% market share.[22] The shift from three-component mobile-bearing prostheses to two-component fixed-bearing prostheses has taken place over the last 5 years during the trial. As a result, it was important for us to perform a post hoc analysis of mobile-bearing and fixed-bearing TAR compared with ankle fusion.

In this trial, 54% of patients in the TAR arm received a fixed-bearing prosthesis and 46% received a mobile-bearing prosthesis. We found an adjusted difference in MOXFQ walking/standing score of 2.1 points (95% CI −6.6 to 10.8 points; $p = 0.64$) between mobile-bearing TAR and ankle fusion, which suggests that, on average, patients who received mobile-bearing TAR had MOXFQ walking/standing scores 2.1 points higher than those in the ankle fusion arm at 52 weeks post surgery.

In the assessment of fixed-bearing TAR, we found an adjusted difference in MOXFQ walking/standing score of −11.1 (95% CI −19.3 to −2.9; $p = 0.008$) between fixed-bearing TAR and ankle fusion, which suggests that, on average, patients who received fixed-bearing TAR had MOXFQ walking/standing scores 11.1 points lower than those in the ankle fusion arm at 52 weeks post surgery. This difference was statistically significant ($p = 0.008$) and we believe this to be clinically meaningful, especially as the FAAM-ADL score also showed a statistically significant improvement between baseline and 52 weeks.

It appears that, when fixed-bearing TAR is compared with ankle fusion, TAR outperforms ankle fusion based on our primary outcome measure, a finding that was not apparent when assessing mobile-bearing TAR as a separate group. In the ankle fusion arm, 60% of patients underwent an arthroscopic approach, but the results for the ankle fusion arm appeared to be similar whether or not an open or an arthroscopic technique was used.

Recruitment

Our aim was to recruit one patient per centre per month. Overall, the recruitment rate achieved was 0.46 patients per centre per month. The lead site achieved a recruitment rate of 1.7 patients per month and the other 16 sites achieved an average recruitment of 0.38 patients per month. There were several challenges to recruitment, which is not unusual for surgical trials. A qualitative study was conducted that identified four common obstacles: (1) patient preference for an intervention, (2) a complex recruitment pathway, (3) logistical issues and (4) lack of equipoise and role conflicts. Clinicians in the study felt that they could predict that specific patients may achieve better outcomes with either TAR or ankle fusion.

A total of 22 (7.3%) randomised patients were excluded from our ITT analysis, which was well within the anticipated 10% drop-out rate from our power calculation. Our trial attrition is similar to that of other reported orthopaedic trials, which had attrition rates of between 5.3% and 18.2%.[73–75] The original sample size calculation for the TARVA trial made a number of assumptions. Based on the data available now, loss to follow-up at 52 weeks was slightly lower than predicted: 9% rather than 10%. The number of recruiting surgeons was 34 rather than 17, so the average number of patients per surgeon was nine rather than 14. Therefore, the power achieved with our 276 patients who had data available at 52 weeks for the ITT analysis was > 88%, very close to our desired power of 90%. The slightly lower power achieved is unlikely to have influenced our conclusions.

Economic evaluation

Over the first 52 weeks following primary surgery, TAR was more expensive than ankle fusion, which was expected owing to the higher prices of the implants and longer duration of the surgery. However, after accounting for other costs associated with the surgery, including mobility aids and home adaptation, productivity loss and transportation cost, the difference between the two arms was no longer statistically significant and the ICER reduced considerably. This suggests that TAR is likely to have a wider impact on patients' lives that is not accounted for in the effectiveness and QoL measures.

To the best of our knowledge, there is sparse published health economic data regarding the cost-effectiveness of ankle surgery. Slobogean *et al.*[16] estimated index values in patients after TAR and ankle fusion using a prospective non-randomised cohort of TAR and ankle fusion patients. Their baseline

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values were higher than those of the TARVA trial for both TAR (0.67, 95% CI 0.64 to 0.69) and ankle fusion (0.66, 95% CI 0.63 to 0.68). At 52 weeks, their index values (TAR 0.73, 95% 0.71 to 0.76; ankle fusion 0.73, 95% 0.70 to 0.76) were comparable with those of the TARVA trial (TAR 0.74, 95% CI 0.70 to 0.77; ankle fusion 0.71, 95% CI 0.67 to 0.74). In their cohort, the authors were unable to account for medical comorbidities.[16]

Extrapolating the results further than 1 year after the surgery is common in the orthopaedic literature.[76–78] Two models have been used to explore the cost-effectiveness of TAR compared with ankle fusion.[60,62] SooHoo and Kominski[62] implemented a simple decision-tree model, which suggested that TAR had the potential to be cost-effective compared with ankle fusion if the implant survived more than 7 years, but these data were obtained when TAR surgery was in its infancy. Courville *et al.*[60] built a Markov model and, at the lifetime horizon, showed the cost-effectiveness of TAR compared with ankle fusion in a similar hypothetical cohort of patients aged 60 years with end-stage ankle osteoarthritis. The researchers highlighted the lack of data on the QoL of these patients and the requirement for more detailed estimates of both direct and indirect medical costs.

Our study provided the index values using the EQ-5D-5L at baseline, and at 26 and 52 weeks, which allowed us to estimate QALYs and detailed cost estimates from both health care and PSS, and societal perspectives. Therefore, the results of the model-based analysis are more robust than those of existing studies and we estimate a 69% probability of TAR being cost-effective compared with ankle fusion at the NICE cost-effectiveness threshold of £20,000 per QALY gained.[65] This increases to 72.2% probability when comparing fixed-bearing TAR implants with ankle fusion.

Patient and public involvement

This study had a significant impact on the patients and members of the public who were involved at all stages of the trial. Almost all patients asked to be kept informed, and high-quality newsletters were developed and sent out at regular intervals, summarising recruitment updates and featuring interviews with the research and oversight team and educational insights. More than 1350 people followed the TARVA trial's Twitter account (@TARVA_Trial, twitter.com; Twitter, Inc., San Francisco, CA, USA). One patient recorded a video log (vlog) for their own blog channel and many patients remain in communication with the trial team. Following publication, the authors intend to present the results of the study widely and work closely with relevant charities to relay the findings to their members.

Limitations

The limitations relate to the pragmatic nature of this study. There is always a conflict between pragmatic studies and perceived robustness. It could be argued that the arms were too heterogenous because surgeons were allowed to use any implant for TAR and any technique for ankle fusion. However, a design in which surgeons used only one implant and one ankle fusion technique would be logistically difficult, especially across sites, and far less generalisable.

A further limitation relates to the use of a patient-reported outcome as the primary outcome measure, which may be insensitive to a clinically meaningful outcome even if one were present. There are many methods used to assess patient-reported outcome measures. In anchor-based methodology, the outcome of interest is 'anchored' to someone's clinical judgement, typically that of a patient or clinician, to define the important difference. In a distribution-based methodology, two approaches are used. The first looks at measurement error and tries to find a consistent difference that patients would consider meaningful and that is also greater than the imprecision of the measurement. The second distribution approach uses a 'rule of thumb'; for example, a 10% change may be considered important.

The magnitude of the target difference on a standardised scale (standardised effect size) is commonly used to infer the value of detecting this difference in comparison with other possible standardised effects.[79,80] Cohen's *d* has been used as de facto justification for this, using a standardised effect size of 0.2, 0.5 and 0.8 for small, medium and large effects, respectively.[81]

For our primary outcome measure, the MOXFQ walking/standing domain, there had been no previous RCTs and, hence, the literature used pertained to studies published by the author of the tool. Dawson *et al.* evaluated the utility of the measure in several cohorts of patients with forefoot, midfoot and hindfoot disorders.[31,32,46,82–84] These studies looked at the change in score from baseline to post surgery. Two main approaches were used to estimate the smallest change on the measure that was likely to be meaningful or important. The first approach was distribution based, that is based on the statistical characteristics of the sample under study. Examples include the effect size, the standard error of measurement and the minimal detectable change. This approach aimed to identify the smallest change for an individual that is beyond the measurement of error of a given instrument and therefore likely to represent a true change. Although Dawson *et al.*'s 2007 paper[46] looked at hallux valgus, later papers[31,32,82–84] specifically studied surgical ankle procedures as a subgroup, estimating the MID to be 10.67 for the MOXFQ walking/standing domain.

Based on this information, we determined that it was important to detect a difference of 12 in the change in MOXFQ walking/standing domain score from baseline between the two treatment arms; it was on this premise that our power calculation was performed. Cohen's *d* for a small, medium and large effect size would be between 6 and 24 points based on the SD in our series, which is not too different from the MID determined by Dawson *et al.*[31,32,46,82–84] More than 80% of patients in our study achieved the MID when comparing their pre-surgery scores with their postsurgery scores. In fact, they exceeded their MID severalfold, with a mean (SD) improvement for TAR patients of 49.9 (30.7) and 44.3 (31.9) for the ankle fusion patients. However, the difference in the changes between the TAR and ankle fusion arms was 5.56 points, with TAR having, on average, an improvement of 5.56 points more than ankle fusion (because a negative score is better). Our CI for the difference in the improvement was −1.37 to 12.49, which included both the 10.67- and 12-point differences defined by Dawson *et al.*[31,32,46,82–84] Hence, we cannot rule out this being meaningful. It is important to be aware that the MID of 12 was an estimate only.

Another method for determining clinical importance involves opinion-seeking. A value, a range of plausible values or a prior distribution for the target difference is sought by asking one or more 'experts' to state their opinion on what would be an important and/or realistic value for a difference. It is possible that once patients' scores have improved by > 40 points from baseline to 52 weeks an additional 5.56 points may still be clinically relevant. However, on the basis of our estimated MID of 12, overall, the current study showed no significant difference between the groups in our primary outcome measure at 52 weeks post surgery.

Total ankle replacement is more expensive than ankle fusion at 52 weeks. Resource use for these costs were collected from patients during the trial and hence bias due to missing data and loss to follow-up is limited. We considered the societal perspective and the analysis showed that the difference in costs between TAR and ankle fusion may be lower and not statistically significant. Estimating costs from the societal perspective requires more assumptions, such as the length of time off work for those patients who were employed. Because it was considered that most patients would not be at work, patients were not asked this question directly; therefore, the value was estimated based on the average duration of immobilisation after surgery. The cost of lost productivity was calculated using national average gross hourly earnings,[55] accounting for sex. The cost of informal care, which is based on time spent taking care of the patient by family and friends, is difficult to estimate and different approaches are used in the literature.[85] We used national average gross hourly earnings as unit costs.

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As joint replacements last for several years, not just 52 weeks, we extrapolated our results to the patients' lifetime horizon. In this situation, TAR was still more expensive than ankle fusion, but the ICER was low, at £4401.81. The model structure was based on existing literature. However, it was simplified and did not account for, for example, possible below-knee amputation or developing ipsilateral arthritis. Important assumptions were made regarding the revision rate in the ankle fusion arm as data on this in the literature are scarce. Decrements in EQ-5D-5L index values after revision are based on estimates in SooHoo and Kominski,[62] as these estimates are the only available source of these data.[62] The model has parameter uncertainty, which we accounted for by conducting a PSA. We made the parameters probabilistic by randomly selecting them from appropriate distributions. The results of the PSA show that there is uncertainty in the QALY estimates, but there is a 69% probability of TAR being cost-effective at the NICE threshold of £20,000 per QALY gained.[65] The model is a simplification of reality and the results may change as new evidence becomes available. However, based on the sensitivity analysis, current results are fairly robust.

Generalisability

We designed the trial with the aim of ensuring that the decision-making streams reflected the usual standard of care as closely as possible. Our 17 centres were widely dispersed across the NHS, including district general hospitals, university teaching hospitals and specialist orthopaedic hospitals. Recruitment was performed by experienced surgeons who chose to use the specific technique that they also used in regular NHS practice. Other than MRI, which is invariably part of standard of care, there were no requirements for extra tests or hospital visits. The use of fixed-bearing TAR implants is now dominant in the NHS, with the NJR, which covers England, Wales, Northern Ireland, the Isle of Man and Guernsey, showing that these implants were used in over 70% of cases in 2019.[22] The results should therefore be generalisable to standard NHS care. Although one centre recruited 24% of the total patients, several other centres also recruited well, which enhances the generalisability of the results.

Interpretation

Both TAR and ankle fusion improve patients' QoL at 1 year, but we have not shown one group to be superior in terms of clinical scores at 52 weeks using either ITT or per-protocol analysis. The TARVA trial is inconclusive in terms of the superiority of TAR, as the 95% CI for the adjusted treatment effect includes both a difference of 0 and the MID of 12, but it can rule out superiority of ankle fusion. Both operations appear to be safe, but there were more wound-healing problems and nerve injuries in the TAR arm than in the ankle fusion arm. Seven per cent of patients in the ankle fusion arm went on to symptomatic non-union and are likely to require revision surgery in the future.

When we excluded mobile-bearing TAR and assessed the most common type of implant in the UK (fixed-bearing TAR, representing a 70% market share), we showed a statistically significant improvement of TAR over ankle fusion, suggesting that fixed-bearing TAR may outperform ankle fusion. However, it is important to point out that this is a post hoc analysis and may be inadequately powered. The reason for using post hoc analysis is that, at the time the study began, fixed-bearing TAR was not used in the UK. In 2014, the study onset was delayed owing to the withdrawal of the most commonly used implant in the UK (the Mobility mobile-bearing implant). Therefore, no Mobility implants were used in this study. Between 2014 and 2019, fixed-bearing implants became the dominant implant used and hence this post hoc analysis was considered essential by the investigators.

Using long-term economic modelling, we estimate that there is a 69% probability of TAR being cost-effective compared with ankle fusion at the NICE cost-effectiveness threshold of £20,000 per QALY gained over a patient's lifetime.[65] This increases to a 72% probability when analysing fixed-bearing implants against ankle fusion.

Recommendations for research

To the best of our knowledge, this is the first level 1 RCT in this area and we would recommend longer-term follow-up of this important cohort of patients with end-stage ankle arthritis. There is a strong case for continuing follow-up, in particular to study the radiological and clinical progress of these patients, and the need for revision surgery.

Although there is a focus on selecting outcome measures that matter to patients, it is clear that studies such as these have to select MIDs based on observations between baseline and a postsurgery time point. Researchers have assumed that the MIDs within groups are the same as the MIDs between groups when both groups have already improved significantly from their baseline scores. We would recommend that studies explore the sensitivity of clinically important differences to patients in this situation.

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Iva Hauptmannova (Director for R&D, Royal National Orthopaedic Hospital) contributed to the analysis and interpretation of results and draft manuscript preparation.

Paul Cooke (Consultant Orthopaedic Surgeon, Nuffield Orthopaedic Centre) contributed to the study conception and design.

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All authors reviewed the results and approved the final version of the manuscript.

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Data-sharing statement

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

Patient data

This work uses data provided by patients and collected by the NHS as part of their care and support. Using patient data is vital to improve health and care for everyone. There is huge potential to make better use of information from people's patient records, to understand more about disease, develop new treatments, monitor safety, and plan NHS services. Patient data should be kept safe and secure, to protect everyone's privacy, and it's important that there are safeguards to make sure that it is stored and used responsibly. Everyone should be able to find out about how patient data are used. #datasaveslives You can find out more about the background to this citation here: https://understandingpatientdata.org.uk/data-citation.

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Appendix 1 Changes to the protocol

TABLE 30 Changes to the protocol

Version and date	Reason for amendment	Amendment number	Substantial or non-substantial	REC approval date
V1.0, 9 April 2014	Original application	N/A	N/A	10 June 2014
V2.0, 23 June 2014	Responses to REC additional conditions	N/A	N/A	24 June 2014
V3.0, 19 August 2014	To account for review by TSC/IDMC; change to imaging procedures	1	Substantial	26 September 2014
V4.0, 20 November 2014	Response to review by investigators; clarification of AE reporting procedures and inclusion of reference to Safety Management Plan	2	Substantial	18 December 2014
V5.0, 23 June 2015	• Schedule of assessments: corrections made to table and test to ensure consistency • All concomitant medications to be captured on a log at baseline and reviewed at each follow-up visit, rather than related medications being captured on a patient-completed health economic questionnaire only • Statistical analysis: main analysis to be conducted following the modified ITT principle using data from all patients who undergo surgery, in accordance with randomised surgical procedure. Only those who do not undergo surgery of any kind will be excluded from the analysis • Data monitoring for harm: modified for clarification and consistency • Comprehensive list of expected events included	3	Substantial	29 July 2015
V6.0, 17 August 2016	• Oversight Committee members list updated • Trial diagram: screening section updated to clarify that members of the research team other than the principal investigator may be involved in identifying potentially eligible patients, and that referral letters/clinic lists may be screened so that potentially eligible patients can be sent an invitation letter and study information in advance of clinic attendance • Screening and consent procedures modified to allow study information materials to be sent by post and for consent to be carried out by post in exceptional cases, which must be fully documented	6	Substantial	14 November 2016

continued

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TABLE 30 Changes to the protocol (*continued*)

Version and date	Reason for amendment	Amendment number	Substantial or non-substantial	REC approval date
	• Imaging: clarified that full tibia anteroposterior radiographs should be weight bearing • Schedule of assessments: key corrected so that symbols in text and diagram correspond • Statistical analysis: main analysis to be conducted following the ITT principle in accordance with the randomised intervention (changed at request of trial funders) • AE severity grade 3 clarified to emphasise hospitalisations that are unplanned • Ancillary qualitative study protocol added			

N/A, not applicable.

Appendix 2 Health economics

TABLE 31 Unit costs associated with health-care resource use

Resource item	Unit cost (£)	Unit of analysis	Source of unit cost
GP			
Surgery visit	33	Per consultation (average length of contact 9.22 minutes)	*Unit Costs of Health and Social Care 2019*[51]
Home visit	184	Per hour (average visit 23.4 minutes)	*Unit Costs of Health and Social Care 2019*[51]
Telephone call	15.32	Per telephone call (average length of contact 6.56 minutes)	*Unit Costs of Health and Social Care 2019*[51]
Nurse practice visit	37	Per hour (average visit 15.5 minutes)	*Unit Costs of Health and Social Care 2019*[51]
Nurse telephone call	6	Per telephone call (average call 4 minutes)	*Unit Costs of Health and Social Care 2019*[51]
District nurse visit	41.73	Per consultation	*Unit Costs of Health and Social Care 2018*[54]
Occupational therapist			
Surgery visit	43	Per hour (average visit 30 minutes)	*Unit Costs of Health and Social Care 2019*[51]
Home visit	44	Per hour (average visit 60 minutes)	*Unit Costs of Health and Social Care 2019*[51]
Community physiotherapist			
Home visit	55	Per hour (average visit 60 minutes)	*Unit Costs of Health and Social Care 2019*[51]
Surgery visit	55	Per hour (average visit 30 minutes)	*Unit Costs of Health and Social Care 2019*[51]
Clinical nurse telephone call	102.50	Per hour (average call time assumed to be 4 minutes)	*Unit Costs of Health and Social Care 2019*[51]
Inpatient stay	631	Per day	*NHS Reference Costs 2017/18*[52] (based on NHS trust)
Outpatient visit	135	Per attendance	*Unit Costs of Health and Social Care 2019*[51]
Social worker			
Visit	45	Per hour (average length of contact is not possible to estimate)	*Unit Costs of Health and Social Care 2019*[51]
Telephone call	45	Per hour (average length of contact is not possible to estimate)	*Unit Costs of Health and Social Care 2019*[51]
Home help	28	Per hour, weekday	*Unit Costs of Health and Social Care 2019*[51]
Meals on Wheels	6	Per meal (£44 per week)	*Unit Costs of Health and Social Care 2013*[53]

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TABLE 32 Unit costs associated with out-of-pocket costs

Resource item	Unit cost (£)	Unit of analysis	Source of unit cost
Equipment			
Back support cushion	2.70	Per item	Mobility Smart Ltd (Preston, UK), URL: www.mobilitysmart.co.uk/back-support-cushion.html
Bath board	3.20	Per item	Mobility Smart Ltd, URL: www.mobilitysmart.co.uk/bathroom-aids/benches-seats-and-stools/bath-and-shower-boards.html?product_list_order = price_desc
Bath cushion	1.30	Per item	Mobility Smart Ltd, URL: www.mobilitysmart.co.uk/bathroom-aids/bath-pillows-and-cushions.html
Bathtub mat	0.83	Per item	Mobility Smart Ltd, URL: www.mobilitysmart.co.uk/non-slip-bathtub-mat.html
Commode	11.98	Per item	*Unit Costs of Health and Social Care 2013*[53]
Cushion	3.80	Per item	Mobility Smart Ltd, URL: www.mobilitysmart.co.uk/cushions-and-supports/lower-limb-support.html
Food trolley	4.80	Per item	*Unit Costs of Health and Social Care 2013*[53]
Foot stool	6.20	Per item	Mobility Smart Ltd, URL: www.mobilitysmart.co.uk/daily-living-aids/steps-and-stools/foot-stools.html
Leg guards	4.10	Per item	Mobility Smart Ltd, URL: www.mobilitysmart.co.uk/foldalite-pro-replacement-leg-guards-pair.html
Legs wedge	2.80	Per item	Mobility Smart Ltd, URL: www.mobilitysmart.co.uk/putnams-8-wedge-cushion-beige-14x14x3.html
Perching stool	3.14	Per item	*Unit Costs of Health and Social Care 2013*[53]
Porta Potti®	16.10	Per item	Mobility Smart Ltd, URL: www.mobilitysmart.co.uk/porta-potti-165-toilet-frame.html
Shoe raise	4.60	Per item	Physique Management Company Limited (Havant, UK), URL: www.physique.co.uk/Orthotics-Footcare/Orthotics-Insoles/Vasyli-Blue-Custom-34-Orthotics-Medium-Density?gclid = Cj0KCQiA48j9BRC-ARIsAMQu3WS2vTe4pRfEnXz0IWgXfipF7KBpNcULyq4-jG4I-Pjl8dr6khUKv5kaAn2kEALw_wcB#fo_c = 2689&fo_k = 1ab3590be76f6a4a5d67d57732e6378d&fo_s = gplauk&fo_oid = 9737
Shower chair	7.67	Per item	*Unit Costs of Health and Social Care 2013*[53]
Toilet frame	4.18	Per item	*Unit Costs of Health and Social Care 2013*[53]
Toilet seat	4.18	Per item	*Unit Costs of Health and Social Care 2013*[53]
Urine bottle	1.10	Per item	Mobility Smart Ltd, URL: www.mobilitysmart.co.uk/toileting-aids/bed-pans-urinals/male-female-urinals.html
Washing tray	2.60	Per item	Mobility Smart Ltd, URL: www.mobilitysmart.co.uk/hair-washing-tray-with-strap.html
Home adaptations			
Hand rail(s)			
Bathroom	2.50	Per item	*Unit Costs of Health and Social Care 2019*[51]
Inside	4	Per item	*Unit Costs of Health and Social Care 2019*[51]
Outside	5.70	Per item	*Unit Costs of Health and Social Care 2019*[51]
Moving bed	5.70	Per item	*Unit Costs of Health and Social Care 2019*[51]
New bedroom	3750	Per item	*Unit Costs of Health and Social Care 2019*[51]
New shower	15	Per item	*Unit Costs of Health and Social Care 2019*[51]

TABLE 32 Unit costs associated with out-of-pocket costs (*continued*)

Resource item	Unit cost (£)	Unit of analysis	Source of unit cost
New toilet	1383	Per item	*Unit Costs of Health and Social Care 2019*[51]
New wet room	2191	Per item	*Unit Costs of Health and Social Care 2010*[86]
New driveway	327.50	Per item	*Unit Costs of Health and Social Care 2019*[51]
Painting floors	80.60	Per item	Painter.co.uk, URL: www.painter.co.uk/prices/
Ramp	44	Per item	*Unit Costs of Health and Social Care 2019*[51]
Shower replacing bath	357	Per item	*Unit Costs of Health and Social Care 2010*[86]
Stair lift	263	Per item	*Unit Costs of Health and Social Care 2010*[86]
Stair rail	4	Per item	*Unit Costs of Health and Social Care 2010*[86]
Mobility aids			
Crutches	4.40	Per pair	Mobility Smart Ltd, URL: www.mobilitysmart.co.uk/walking-aids/crutches.html?p=3
Mobility scooter	172.10	Per item	Mobility World Ltd (Letchworth, UK), URL: www.mobilityworld.co.uk/pages/mobility-scooters-1
Knee scooter	22.10	Per item	YourCare (Croydon, UK), URL: www.yourcare.org.uk/category_schemes/97-product-category/categories/3891-rollators/products/663-knee-walker
Walking frame	11.60	Per item	Mobility Smart Ltd, URL: www.mobilitysmart.co.uk/walking-aids/zimmer-frames.html
Wheelchair	206	Per item	*Unit Costs of Health and Social Care 2019*[51]
Transportation costs			
Fuel cost	0.115	Per mile	*Guidance: Advisory Fuel Rates*[87]
Productivity loss			
Gross earnings: full time, men	17.41	Per hour	*EARN08: Distribution of Gross Hourly Earnings of Employees*[55]
Gross earnings: full time, women	14.75	Per hour	*EARN08: Distribution of Gross Hourly Earnings of Employees*[55]
Gross earnings: part time, men	11.65	Per hour	*EARN08: Distribution of Gross Hourly Earnings of Employees*[55]
Gross earnings: part time, women	12.09	Per hour	*EARN08: Distribution of Gross Hourly Earnings of Employees*[55]
Gross earnings: all employees, all people	15.26	Per hour	*EARN08: Distribution of Gross Hourly Earnings of Employees*[55]
Replacing an employee	30,614	Per person	Oxford Economics and income protection provider Unum (Surrey, UK)[56]

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Appendix 3 Baseline characteristics by subtype of total ankle replacement and ankle fusion

TABLE 33 Baseline characteristics by subtype of TAR and ankle fusion[a]

Baseline characteristic	Treatment arm			
	TAR		Ankle fusion	
	Fixed (*N* = 76)	Mobile (*N* = 66)	Arthroscopic (*N* = 85)	Open (*N* = 55)
Age (years), mean (SD)	66.4 (7.6)	70.0 (8.2)	67.8 (8.6)	67.4 (7.2)
Sex, *n* (%)				
Female	16 (21.1)	18 (27.3)	26 (30.6)	21 (38.2)
Male	60 (78.9)	48 (72.7)	59 (69.4)	34 (61.8)
Height (metres), mean (SD)	1.7 (0.1)	1.7 (0.1)	1.7 (0.1)	1.7 (0.1)
Weight (kilograms), mean (SD)	85.5 (13.3)	86.1 (13.6)	89.4 (15.9)	86.8 (19.4)
Smoking status				
Current smoker, *n* (%)	3 (3.9)	2 (3.0)	2 (2.4)	3 (5.5)
Cigarettes per day, mean (SD)	4.7 (0.6)	7.5 (3.5)	10.5 (13.4)	10.3 (4.5)
Ex-smoker, *n* (%)	24 (31.6)	29 (43.9)	40 (47.1)	17 (30.9)
Time since cessation (years), mean (SD)	26.0 (16.1)	25.1 (16.2)	24.6 (15.9)	29.4 (14.4)
Patients' treatment preference, *n* (%)				
No preference expressed	52 (68.4)	51 (77.3)	65 (76.5)	44 (80.0)
TAR	18 (23.7)	9 (13.6)	9 (10.6)	10 (18.2)
Ankle fusion	4 (5.3)	4 (6.1)	9 (10.6)	0 (0.0)
Aetiology of osteoarthritis, *n* (%)				
Post traumatic	51 (67.1)	34 (51.5)	39 (45.9)	32 (58.2)
Primary	17 (22.4)	30 (45.5)	37 (43.5)	18 (32.7)
Rheumatoid arthritis	5 (6.6)	2 (3.0)	3 (3.5)	3 (5.5)
Other inflammatory	2 (2.6)	0 (0.0)	5 (5.9)	0 (0.0)
Other	1 (1.3)	0 (0.0)	1 (1.2)	3 (5.5)
Subtalar joint osteoarthritis, *n* (%)				
Absent	51 (67.1)	41 (62.1)	48 (56.5)	36 (65.5)
Present	25 (32.9)	25 (37.9)	37 (43.5)	19 (34.5)
Talonavicular joint osteoarthritis, *n* (%)				
Absent	65 (85.5)	58 (87.9)	74 (87.1)	44 (80.0)
Present	11 (14.5)	8 (12.1)	11 (12.9)	11 (20.0)

continued

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TABLE 33 Baseline characteristics by subtype of TAR and ankle fusion (*continued*)

Baseline characteristic	Treatment arm			
	TAR		Ankle fusion	
	Fixed (*N* = 76)	Mobile (*N* = 66)	Arthroscopic (*N* = 85)	Open (*N* = 55)
Presence/absence of osteoarthritis, *n* (%)				
Healthy adjacent joint	46 (60.5)	39 (59.1)	45 (52.9)	30 (54.5)
Osteoarthritis in subtalar or talonavicular	24 (31.6)	21 (31.8)	32 (37.6)	20 (36.4)
Osteoarthritis in both adjacent joints	6 (7.9)	6 (9.1)	8 (9.4)	5 (9.1)
User of assistive device, *n* (%)				
No	43 (56.6)	39 (59.1)	44 (51.8)	33 (60.0)
Yes	33 (43.4)	27 (40.9)	41 (48.2)	22 (40.0)
Assistive device, *n* (%)				
Crutches	10 (13.2)	2 (3.0)	10 (11.8)	4 (7.3)
Ankle brace	11 (14.5)	5 (7.6)	5 (5.9)	2 (3.6)
Frame	1 (1.3)	1 (1.5)	0 (0.0)	1 (1.8)
Wheelchair	1 (1.3)	2 (3.0)	3 (3.5)	0 (0.0)
Stick/cane	15 (19.7)	20 (30.3)	30 (35.3)	14 (25.5)
Wheeled walker	0 (0.0)	1 (1.5)	3 (3.5)	1 (1.8)
Knee scooter	1 (1.3)	0 (0.0)	0 (0.0)	1 (1.8)
Other	5 (6.6)	3 (4.5)	3 (3.5)	1 (1.8)
Medical history, *n* (%)				
Anticoagulants	11 (14.5)	14 (21.2)	18 (21.2)	5 (9.1)
History of cancer	10 (13.2)	4 (6.1)	13 (15.3)	6 (10.9)
Chronic pain	16 (21.1)	24 (36.4)	28 (32.9)	18 (32.7)
Connective tissue disorder	0 (0.0)	1 (1.5)	3 (3.5)	1 (1.8)
Diabetes	6 (7.9)	4 (6.1)	7 (8.2)	8 (14.5)
Gastrointestinal disease	8 (10.5)	9 (13.6)	13 (15.3)	9 (16.4)
Hypertension/hypercholesterolaemia	36 (47.4)	27 (40.9)	38 (44.7)	22 (40.0)
Inflammatory disorder	3 (3.9)	5 (7.6)	8 (9.4)	4 (7.3)
Metabolic disorder	3 (3.9)	2 (3.0)	3 (3.5)	0 (0.0)
Neurological disorder	0 (0.0)	2 (3.0)	4 (4.7)	2 (3.6)
Obesity	2 (2.6)	6 (9.1)	11 (12.9)	4 (7.3)
Peripheral nervous system disorder	0 (0.0)	0 (0.0)	2 (2.4)	3 (5.5)
Peripheral vascular disease	0 (0.0)	2 (3.0)	0 (0.0)	3 (5.5)
Renal pathology	2 (2.6)	5 (7.6)	3 (3.5)	0 (0.0)
Respiratory pathology	4 (5.3)	8 (12.1)	15 (17.6)	5 (9.1)
Thromboembolic disease	2 (2.6)	5 (7.6)	6 (7.1)	1 (1.8)
Other condition affecting mobility	20 (26.3)	20 (30.3)	21 (24.7)	21 (38.2)

TABLE 33 Baseline characteristics by subtype of TAR and ankle fusion (*continued*)

Baseline characteristic	Treatment arm			
	TAR		Ankle fusion	
	Fixed (*N* = 76)	Mobile (*N* = 66)	Arthroscopic (*N* = 85)	Open (*N* = 55)
Degree of deformity, *n* (%)				
16–30b0 varus	9 (11.8)	4 (6.1)	3 (3.5)	4 (7.3)
5–15b0 varus	18 (23.7)	19 (28.8)	26 (30.6)	16 (29.1)
Physiological neutral	28 (36.8)	21 (31.8)	35 (41.2)	14 (25.5)
5–15b0 valgus	10 (13.2)	11 (16.7)	11 (12.9)	6 (10.9)
16–30b0 valgus	5 (6.6)	5 (7.6)	3 (3.5)	3 (5.5)
Not available	5 (6.6)	6 (9.1)	7 (8.2)	12 (21.8)
Fixed flexion deformity of knee, *n* (%)	2 (2.6)	1 (1.5)	2 (2.4)	0 (0.0)
Fixed equinus, *n* (%)	4 (5.3)	3 (4.5)	4 (4.7)	1 (1.8)
ROM dorsiflexion (degrees)	14.2 (10.5)	14.6 (7.9)	14.8 (10.2)	13.0 (7.9)
ROM plantarflexion (degrees)	25.2 (7.8)	25.9 (8.7)	27.1 (11.4)	24.7 (9.1)
Outcome measures at baseline, mean (SD)				
MOXFQ walking/standing	81.8 (14.4)	81.0 (19.0)	82.6 (15.4)	80.4 (18.8)
MOXFQ pain	67.1 (16.8)	66.1 (17.2)	68.4 (16.2)	66.6 (18.9)
MOXFQ social interaction	53.8 (26.0)	55.2 (25.8)	55.5 (20.9)	57.5 (23.6)
FAAM-ADL	47.7 (15.0)	46.3 (18.4)	43.0 (15.9)	45.5 (17.9)
FAAM sport subscale	26.2 (16.4)	30.1 (25.7)	26.2 (24.6)	28.3 (13.9)
EQ-5D-5L index value	0.5 (0.2)	0.5 (0.2)	0.5 (0.2)	0.5 (0.2)
EQ-5D-5L VAS	71.6 (20.4)	74.1 (19.6)	65.3 (22.1)	70.2 (20.7)

a Table based on surgery that patients received not surgery that patients were randomised to (four participants crossed over from ankle fusion to TAR after randomisation).

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Appendix 4 Manchester–Oxford Foot Questionnaire walking/standing score at 52 weeks post surgery, by ankle fusion subtype

TABLE 34 The MOXFQ walking/standing score at 52 weeks post surgery, by ankle fusion subtype

	Ankle fusion subtype							
	Arthroscopic			Open				
Outcome	*n*	Value at follow-up, mean (SD)	Change from baseline, mean (SD)	*n*	Value at follow-up, mean (SD)	Change from baseline, mean (SD)	Difference in change from baseline (95% CI)	*p*-value
MOXFQ walking/standing	83	36.3 (30.4)	−46.0 (33.2)	53	37.3 (31.5)	−42.5 (30.8)	−1.15 (−11.44 to 9.15)	0.83

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Appendix 5 Manchester–Oxford Foot Questionnaire

Anybody wanting to use the MOXFQ must contact the copyright owners Oxford University Innovation at healthoutcomes@innovation.ox.ac.uk or via the online licence request portal at https://process.innovation.ox.ac.uk/.

UCL Comprehensive Clinical Trials Unit

TARVA RANDOMISED CLINICAL TRIAL

PATIENT ID: ☐☐☐☐☐

TVA7: MOXFQ

Site: ☐☐ Patient Initials: ☐☐ Date of birth: d d m m m y y y y

MANCHESTER-OXFORD FOOT QUESTIONNAIRE: *To be completed by patient*

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Prior to completing the questionnaire please complete the following:

1) Today's date: d d m m m y y y y

2) On which side of your body is the affected joint, for which you are receiving/have received treatment?

Left ☐ Right ☐

Please tick (✓) one box for each statement

	None of the time	Rarely	Some of the time	Most of the time	All of the time
3) During the past 4 weeks this has applied to me: I have pain in my foot/ankle	☐	☐	☐	☐	☐
4) During the past 4 weeks this has applied to me: I avoid walking long distances because of pain in my foot/ankle	☐	☐	☐	☐	☐
5) During the past 4 weeks this has applied to me: I change the way I walk due to pain in my foot/ankle	☐	☐	☐	☐	☐
6) During the past 4 weeks this has applied to me: I walk slowly because of pain in my foot/ankle	☐	☐	☐	☐	☐

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UCL Comprehensive Clinical Trials Unit

TARVA RANDOMISED CLINICAL TRIAL

PATIENT ID: | | | | | | |

TVA7: MOXFQ

7) During the past 4 weeks this has applied to me:

I have to stop and rest my foot/ankle because of pain

None of the time	Rarely	Some of the time	Most of the time	All of the time
☐	☐	☐	☐	☐

8) During the past 4 weeks this has applied to me:

I avoid some hard or rough surfaces because of pain in my foot/ankle

None of the time	Rarely	Some of the time	Most of the time	All of the time
☐	☐	☐	☐	☐

9) During the past 4 weeks this has applied to me:

I avoid standing for a long time because of pain in my foot/ankle

None of the time	Rarely	Some of the time	Most of the time	All of the time
☐	☐	☐	☐	☐

10) During the past 4 weeks this has applied to me:

I catch the bus or use the car instead of walking, because of pain in my foot/ankle

None of the time	Rarely	Some of the time	Most of the time	All of the time
☐	☐	☐	☐	☐

11) During the past 4 weeks this has applied to me:

I feel self-conscious about my foot/ankle

None of the time	Rarely	Some of the time	Most of the time	All of the time
☐	☐	☐	☐	☐

UCL Comprehensive Clinical Trials Unit

TARVA RANDOMISED CLINICAL TRIAL

PATIENT ID: | | | | | | |

TVA7: MOXFQ

	None of the time	Rarely	Some of the time	Most of the time	All of the time
12) During the past 4 weeks this has applied to me: I feel self-conscious about the shoes I have to wear	☐	☐	☐	☐	☐
13) During the past 4 weeks this has applied to me: The pain in my foot/ankle is more painful in the evening	☐	☐	☐	☐	☐
14) During the past 4 weeks this has applied to me: I get shooting pains in my foot/ankle	☐	☐	☐	☐	☐
15) During the past 4 weeks this has applied to me: The pain in my foot/ankle prevents me from carrying out my work/everyday activities	☐	☐	☐	☐	☐
16) During the past 4 weeks this has applied to me: I am unable to do all my social/recreational activities because of pain in my foot/ankle	☐	☐	☐	☐	☐

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UCL Comprehensive Clinical Trials Unit

TARVA RANDOMISED CLINICAL TRIAL

PATIENT ID: | | | | | | |

TVA7: MOXFQ

17) During the past 4 weeks :

How would you describe the pain you usually have in your foot/ankle?

None	Very mild	Mild	Moderate	Severe
☐	☐	☐	☐	☐

18) During the past 4 weeks :

Have you been troubled by pain in your foot/ankle in bed at night?

No nights	Only 1 or 2 nights	Some nights	Most nights	Every night
☐	☐	☐	☐	☐

Finally please check that you have answered every question.

Thank you very much.

FOR OFFICE USE ONLY:

19) Entered into MACRO database by: | | |

20) Date entered: | d | d | m | m | m | y | y | y | y |

21) Entered at site or CCTU: Site / CCTU

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