Early versus delayed weight-bearing following operatively treated ankle fracture (WAX): a non-inferiority, multicentre, randomised controlled trial

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Summary

Background After surgery for a broken ankle, patients are usually instructed to avoid walking for 6 weeks (delayed weight-bearing). Walking 2 weeks after surgery (early weight-bearing) might be a safe and preferable rehabilitation strategy. This study aimed to determine the clinical and cost effectiveness of an early weight-bearing strategy compared with a delayed weight-bearing strategy.

Methods This was a pragmatic, multicentre, randomised, non-inferiority trial including 561 participants (aged ≥18 years) who received acute surgery for an unstable ankle fracture in 23 UK National Health Service (NHS) hospitals who were assigned to either a delayed weight-bearing (n=280) or an early weight-bearing rehabilitation strategy (n=281). Patients treated with a hindfoot nail, those who did not have protective ankle sensation (eg, peripheral neuropathy), did not have the capacity to consent, or did not have the ability to adhere to trial procedures were excluded. Neither participants nor clinicians were masked to the treatment. The primary outcome was ankle function measured using the Olerud and Molander Ankle Score (OMAS) at 4 months after randomisation, in the per-protocol population. The pre-specified non-inferiority OMAS margin was –6 points and superiority testing was included in the intention-to-treat population in the event of non-inferiority. The trial was prospectively registered with ISRCTN Registry, ISRCTN12883981, and the trial is closed to new participants.

Findings Primary outcome data were collected from 480 (86%) of 561 participants. Recruitment was conducted between Jan 13, 2020, and Oct 29, 2021. At 4 months after randomisation, the mean OMAS score was 65·9 in the early weight-bearing and 61·2 in the delayed weight-bearing group and adjusted mean difference was 4·47 (95% CI 0·58 to 8·37, p=0·024; superiority testing adjusted difference 4·42, 95% CI 0·53 to 8·32, p=0·026) in favour of early weight-bearing. 46 (16%) participants in the early weight-bearing group and 39 (14%) in the delayed weight-bearing group had one or more complications (adjusted odds ratio 1·18, 95% CI 0·80 to 1·75, p=0·40). The mean costs from the perspective of the NHS and personal social services in the early and delayed weight-bearing groups were £725 and £785, respectively (mean difference –£60 [95% CI –342 to 232]). The probability that early weight-bearing is cost-effective exceeded 80%.

Interpretation An early weight-bearing strategy was found to be clinically non-inferior and highly likely to be cost-effective compared with the current standard of care (delayed weight-bearing).

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See Online for appendix

Introduction

Each day, approximately 190 people sustain an ankle fracture in the UK.[1] Many fractures can be treated in a cast or removable boot, but often surgery is used to realign the ankle bones and hold them stably in place while they heal. The surgical procedure is well established and follows consistent principles. However, postoperative weight-bearing strategies are variable.

Surgeons have historically restricted patients' normal walking (weight-bearing), fearing that excessive loading of the bone and metal implants could result in early misalignment, damage to soft tissue, unfavourable functional outcomes, and the need for further surgery.[2] This weight-bearing restriction, however, significantly affects both patients and health-care services. Patients encounter inconveniences because they are required to use crutches or other assistive devices, potentially leading to increased reliance on social care services and longer hospital stays.[3,4] Patients also report a later return to work with the consequent personal and societal financial implications.[3,5] If there were minimal risk of harm, many patients would prefer to walk without weight-bearing restrictions following their surgery.

A Cochrane review and the National Institute for Health and Care Excellence (NICE) concluded that current evidence to support either weight-bearing strategy is at

Research in context

Evidence before this study

There is disparity in the rehabilitation strategy used following ankle fracture surgery. Some patients are permitted to walk on their injured ankle 2 weeks after surgery whereas others are instructed to keep weight off their ankles for 6 weeks by using devices such as crutches. This discrepancy arises from a scarcity of evidence and differing opinions among surgeons regarding the optimal approach. Some argue that weight-bearing soon after surgery might result in loss of bony alignment, healing problems, and the need for further operations. Others suggest that an early weight-bearing strategy reduces the risk of venous thromboembolism, muscle wasting, and might improve functional outcomes. In 2012, a Cochrane review reported that the available evidence was insufficient to guide weight-bearing advice for people after operatively managed ankle fractures. To update this literature review, MEDLINE, Embase, and the Cochrane Central Register of Controlled Trials were searched for studies published between Jan 1, 2011, and March 23, 2023. We used the terms "ankle fracture", "weight-bearing" and "surgery", without language restrictions. We found four additional trials that favoured early weight-bearing, but their small size and limited generalisability were insufficient to change clinical practice. In 2017, a prospective UK multicentre evaluation of current practice found that 21% of patients were recommended an early weight-bearing strategy after ankle fracture surgery.

Added value of this study

In the WAX trial, 561 adults from 23 hospitals in the UK were randomly assigned to either an early (2 weeks postoperatively) or delayed (6 weeks postoperatively) weight-bearing strategy after their ankle fracture was treated with an operation. The study found an early weight-bearing strategy was not inferior in terms of ankle function to a delayed weight-bearing strategy as measured by the Olerud and Molander Ankle Score. The study also showed similar complication rates between the two approaches. A health economic evaluation indicated that an early weight-bearing strategy is highly likely to be cost-effective.

Implications of all the available evidence

Ankle fractures are a common injury that can significantly affect people's wellbeing and quality of life. The findings from the WAX trial can now serve as a valuable reference for patients and health-care professionals to determine the most suitable rehabilitation strategy. Policy makers should also take note of the health economic evaluation, which suggests that an early weight-bearing strategy is not only clinically effective but is also highly likely to be cost-effective.

very high risk of bias and insufficient to guide clinical decision making.[6,7] The aim of the Weight-bearing in Ankle Fracture (WAX) trial was to determine the clinical and cost-effectiveness of an early weight-bearing strategy (at 2 weeks postoperatively) compared with a delayed weight-bearing strategy (at 6 weeks postoperatively) for adults after ankle fracture surgery.

Methods

Study design

WAX was a pragmatic, non-inferiority, multicentre, randomised controlled trial done at 23 National Health Service (NHS) hospitals in the UK. The study protocol was previously published.[8] The study was given a favourable research ethics opinion by the Oxford A Research Ethics Committee on Nov 22, 2019 (reference 19/SC/0566). Each recruitment centre was granted site-specific approval from its NHS Trust Research and Development department before trial commencement. The trial was coordinated by the Oxford Clinical Trials Research Unit (OCTRU) at the University of Oxford, Oxford, UK. A trial steering committee and data and safety monitoring committee oversaw the conduct and progress throughout the trial. The trial was prospectively registered with ISRCTN Registry, ISRCTN12883981.

Participants

Patients aged 18 years or older who were treated with an operation for an ankle fracture within 14 days of their injury were eligible to enter the study. Patients were excluded if they had been treated with a hindfoot nail, did not have protective ankle sensation (eg, peripheral neuropathy), did not have the capacity to consent, did not have the ability to adhere to trial procedures, or had received explicit non-weight-bearing instructions from their treating surgeon. In contrast to previous studies, patients were not excluded for factors such as open fracture, syndesmotic injuries, or poor bone quality.[9–12] Eligible patients were approached by a member of the local research team within 2 weeks of their surgery and provided with verbal and written trial information. At their 2-week postoperative clinical visit, informed written consent was obtained from participants by a trained member of the research team. Baseline details, including a brief medical history, self-reported gender (male, female, or prefer to self-describe), and surgical details were collected. To provide baseline data, participants were asked to recall retrospective preinjury scores for the Olerud and Molander Ankle Score (OMAS)[13] and health-related quality of life measured with the EuroQol 5-dimensions-5-levels (EQ-5D-5L).[14]

Randomisation and masking

Participants were randomly allocated (1:1) to either an early (2 weeks postoperatively) or delayed (6 weeks postoperatively) weight-bearing strategy using a secure remote computer randomisation service. A minimisation algorithm, seeded using simple randomisation and

using a probabilistic random twist element, was used to randomly allocate participants, stratified by age (dichotomised at age 60 years) and treatment centre. A member of the local research team informed the participant and treating clinician of the treatment allocation. As the treating clinical team had to provide participants with weight-bearing instructions and the participant had to carry them out, neither clinicians nor patients could be masked.

Procedures

All participants were advised to not bear weight on their injured limb for the first 2 weeks after surgery, as is standard practice in the UK. At the 2-week postoperative clinic visit, the clinical team confirmed eligibility and decided on the type of ankle immobilisation (cast or boot) on the basis of their usual practice. The immobilisation method was decided before randomisation, as joint loading can occur with mobilisation and muscle contractions, potentially altering participant outcomes. Participants allocated to early weight-bearing were instructed to put as much weight through their affected leg as they felt comfortable and without causing pain. Participants allocated to delayed weight-bearing were instructed to continue non-weight-bearing and avoid putting weight through their operated leg for a further 4 weeks. Local research teams were trained in providing rehabilitation instructions by a member of the WAX research team. Copies of the rehabilitation booklets provided to the participants are available in the appendix (pp 28–93). The adherence to the provision of instructions by clinical teams was recorded on a rehabilitation case report form for each participant, based on the Template for Intervention Description and Replication checklist for the description and replication of rehabilitation interventions.[15] To monitor fidelity, sites were sent an encrypted voice recorder to record the delivery of the weight-bearing instructions, which was assessed against the training materials (appendix p 27). Participant adherence to their weight-bearing instructions was self-reported, with participants in both groups receiving weekly emails or text messages asking them to confirm if they had started weight-bearing. Subsequent rehabilitation or adjunctive therapies were left to the discretion of the treating clinician and participant.

Outcomes

Outcome data were collected with REDCap electronic data capture tools.[16] Participants were prompted by email or text messages to complete all follow-up questionnaires at 6 weeks, 4 months, and 12 months after randomisation. If there was no response to the initial and reminder messages, attempts were made to contact participants by telephone or post. The primary outcome measure was the OMAS at 4 months after randomisation.[13] OMAS is a reliable and valid ankle-specific patient-reported outcome measure that has three domains related to ankle symptoms, lower limb-related activities, and overall function. It has nine items that combine to give a score of 0 (worst) to 100 (best). 4 months was selected for the primary outcome assessment as ankle function typically improves significantly in the first 3 months after surgery, shows slight improvements between the third and sixth months, and then tends to stabilise.[17]

The secondary outcomes were health-related quality of life measured with the EQ-5D-5L utility and visual analogue scores,[14] return to work measured with the Work Productivity and Activity Impairment: Specific Health Problem (WPAI),[18] complications, and health care and broader resource use, which included information on related health-care costs and out-of-pocket expenses. All outcomes were patient-reported and assessed centrally with an electronic reporting system. In addition, complications including reoperation were reported by the local clinical or research team. Where a complication was reported by a participant, this was reviewed and confirmed by the local research team against hospital records within 12 months of randomisation. Where there was doubt, this was assessed by a masked member of the trial management group. Radiological outcomes will be assessed and reported in a future publication.

Statistical analysis

Previous studies have shown a minimal clinically important difference of 10 points for the primary outcome (OMAS).[19,20] A difference of 10 points would represent the difference between someone who can walk without any support compared with someone who would require a crutch to support their walking. Based on the largest published randomised controlled trial reporting OMAS data within 6 months for operatively treated ankle fractures,[19] an SD of 21·1 and a non-inferiority margin of –6 points were selected. With these assumptions, the study required 392 participants to provide primary outcome data at 4 months after randomisation, to declare non-inferiority with 80% power and 2·5 % (one-sided) significance. Allowing for a 10% loss to follow-up, we required an overall minimum target of 436 participants (218 per group). The trial recruited ahead of schedule and so, with the approval of the research ethics committee, recruitment was continued for the planned period rather than according to the prespecified minimum sample size to increase the precision of the trial and account for any unanticipated loss to follow-up.

Baseline characteristics, outcomes, and treatment adherence were reported with standard statistical summaries. Effect estimates were presented with 95% CIs and p values. Significance was declared at 5%. Analyses were done with SAS version 9.4, Stata version 17.0, and R version 4.2.1.

The primary analysis was an adjusted one-sided test of non-inferiority in the 4-months post-randomisation OMAS score in the per-protocol populations. The per-protocol population was defined as participants who

received the intervention as specified. Participants were excluded from the per-protocol population if they withdrew before treatment, they did not satisfy the eligibility criteria for the study, or they were involved in major protocol deviations. The OMAS score was compared between treatment groups as the dependent variable in a mixed-effects linear regression model with adjustments for the fixed effects of age, gender, and preinjury OMAS score. Since fixed effects do not capture the variability of treatment effect across centres and participants, random effects were included in the model to account for heterogeneity due to recruitment centre and within-subject correlation. A treatment-by-time interaction was also included in the model. The analysis was repeated on the intention-to-treat (ITT) population and a complier average causal effect (CACE) analysis was performed accounting for participant compliance with the weight-bearing instruction. The ITT population was defined as participants analysed according to the group to which they were randomised regardless of the treatment received. For the CACE analysis, participant compliance to treatment was defined as those following the delayed weight-bearing instructions at least 75% of the time (equivalent to at least 3 of the 4 weeks after randomisation). All participants allocated to early weight-bearing were by definition compliers. A test of superiority on the ITT population was planned at 2·5% (one-sided) significance if the early weight-bearing strategy was found to be non-inferior. Additional sensitivity analyses of the primary outcome included an unadjusted analysis using analysis of covariance, adjusting for baseline scores only. Analysis of prespecified subgroups, including age group, sex, and whether the participant had syndesmosis fixation, was done for the primary outcome under the ITT and per-protocol populations.

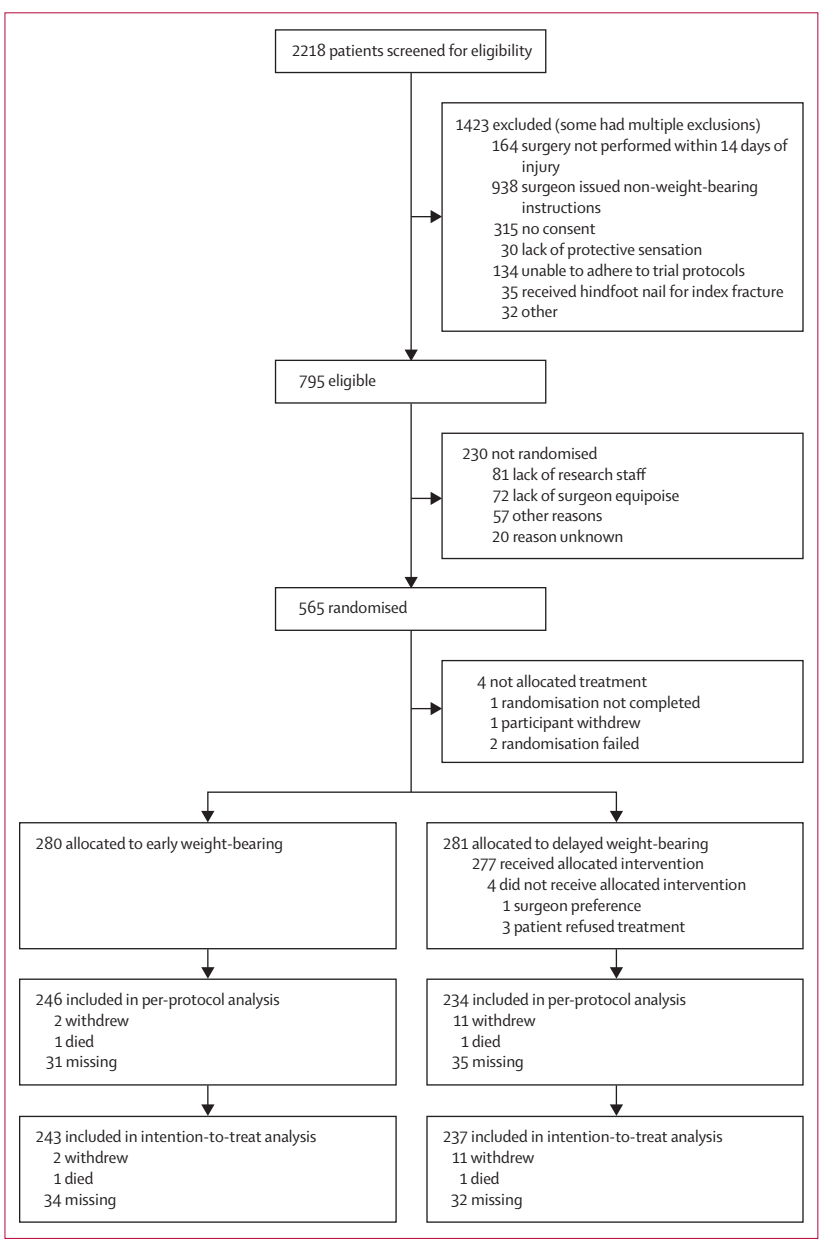

Figure 1: **Trial profile**

EQ-5D-5L responses were converted into multi-attribute utility scores using the algorithm by van Hout and colleagues[21] for cross-walking 5-level responses to 3-level utility norms for the UK.[22] EQ-5D-5L utility scores and EQ-5D-5L visual analogue scores were analysed using repeated-measures mixed-effects multilevel linear regression models similar to the one used for OMAS scores to detect superiority. Between-group risk differences and odd ratios were reported for the binary outcome of whether a participant had any complications or further unplanned surgery resulting from a complication, adjusting for age and sex. Safety was analysed by summarising complications related to the ankle fracture. Scores at each timepoint were summarised by treatment group using median and IQRs, means, and SDs, as well as adjusted differences, associated 95% CIs, and p values. Significance was declared at 5%.

A prospective health economic evaluation was done from an NHS and personal social services (PSS) perspective, using a time horizon of 12 months after randomisation. Economic costs were calculated using estimates of resource inputs associated with the broader use of hospital and community-based health and social care services, and for the purposes of a sensitivity analysis that adopted a societal perspective, also encompassed estimates of out-of-pocket medical expenses, and broader societal costs such as values of work losses and additional care costs associated with ankle fracture surgery. The unit costs of hospital and community health and social services were obtained from the latest Unit Costs of Health and Social Care 2021 report published by the Personal Social Services Research Unit,[23] and the national reference costs 2021 schedules.[24] The costs of prescribed medication were based on the prescription cost analysis

	Early weight-bearing group (n=280)	Delayed weight-bearing group (n=281)	Total (n=561)
Age, years	48·5 (16·4); 49·5 (36·0–61·0)	48·1 (16·6); 50·0 (34·0–62·0)	48·3 (16·4); 50·0 (35·0–62·0)
BMI, kg/m²	29·1 (5·8); 28·3 (24·9–31·9)	28·9 (6·4); 27·6 (24·8–31·7)	29·0 (6·1); 28·0 (24·8–31·9)
Days after surgery at randomisation	14·5 (3·2); 14·0 (13·0–17·0)	14·5 (3·1); 15·0 (13·0–16·0)	14·5 (3·1); 14·0 (13·0–17·0)
Sex			
Female	179 (64%)	180 (64%)	359 (64%)
Male	101 (36%)	101 (36%)	202 (36%)
Mechanism of injury			
Low energy	205 (73%)	216 (77%)	421 (75%)
High energy	75 (27%)	65 (23%)	140 (25%)
Malleolus involvement			
None	10 (4%)	9 (3%)	19 (3%)
Unimalleolar	106 (38%)	101 (36%)	207 (37%)
Bimalleolar	97 (35%)	100 (36%)	197 (35%)
Trimalleolar	67 (24%)	71 (25%)	138 (25%)
Syndesmosis fixation			
Yes	86 (31%)	81 (29%)	167 (30%)
Prerandomisation immobilisation			
Cast	103 (37%)	96 (34%)	199 (36%)
Removable orthosis (eg, boot)	171 (61%)	178 (63%)	349 (62%)
Other	6 (2%)	7 (3%)	13 (2%)
Preinjury walking aids			
No	273 (98%)	271 (96%)	544 (97%)
Yes, one stick	6 (2%)	10 (4%)	16 (3%)
Yes, frame or rollator	1 (0%)	0 (0%)	1 (0%)
Medical history			
Diabetes	9 (3%)	11 (4%)	20 (4%)
Rheumatoid arthritis	7 (3%)	5 (2%)	12 (2%)
Osteoporosis	7 (3%)	12 (4%)	19 (3%)
Alcohol, units per week			
0–7	220 (79%)	204 (73%)	424 (76%)
8–14	42 (15%)	49 (17%)	91 (16%)
15–21	10 (4%)	16 (6%)	26 (5%)
>21	8 (3%)	12 (4%)	20 (4%)
Regular smoker, cigarettes per day			
No	224 (80%)	225 (80%)	449 (80%)
Yes, 0–10	35 (13%)	32 (11%)	67 (12%)
Yes, 11–20	18 (6%)	22 (8%)	40 (7%)
Yes, >20	3 (1%)	2 (1%)	5 (1%)
Years smoked*			
0–10	19 (34%)	17 (30%)	36 (32%)
11–20	17 (30%)	13 (23%)	30 (27%)
>20	20 (36%)	26 (46%)	46 (41%)
Employment status			
Full time	101 (36%)	117 (42%)	218 (39%)
Part time	37 (13%)	42 (15%)	79 (14%)
Self-employed	38 (14%)	35 (13%)	73 (13%)
Unemployed	33 (12%)	26 (9%)	59 (11%)
Voluntary work	1 (0%)	1 (0%)	2 (0%)
Full-time student	7 (3%)	5 (2%)	12 (2%)
Retired or looking after home	63 (23%)	55 (20%)	118 (21%)
Job description†			
Labour	56 (32%)	69 (36%)	125 (34%)
Intermediate	56 (32%)	69 (36%)	125 (34%)
Sedentary	65 (37%)	57 (29%)	122 (33%)

Data are mean (SD), median (IQR), or n (%). *As a percentage of those who smoked regularly. †As a percentage of those who were working full time, part-time, or were self-employed.

Table 1: **Baseline factors by treatment group**

2021 tables,[24] and the online version of the British National Formulary 2021 edition.[25] Out-of-pocket medical expenditures were self-reported by trial participants. The median national wage obtained from the Office for National Statistics was used for the valuation of participants' work losses.[26] Participant-level costs for each resource variable were calculated by multiplying resource quantities with their respective unit costs, weighted by length of stay or duration of contact, where applicable. The two-sample *t* test was used to compare the between-group differences for mean resource use and mean costs at each assessment point. The main health outcome measured in this within-trial economic evaluation was the quality-adjusted life-year (QALY), which is recommended in the NICE reference case.[27]

Multiple imputation by chained equations, implemented through the R package MICE,[28] was used to predict values for any missing items within the economic dataset, assuming that the data were missing at random. Bivariate regression using seemingly unrelated regression was used to estimate incremental NHS and PSS costs and incremental QALYs between early and delayed weight-bearing, controlling for baseline covariates (eg, age, sex, and either baseline EQ-5D-3L utility scores [for incremental QALYs] or baseline NHS and PSS costs [for incremental costs]). The cost-effectiveness outcomes generated included the incremental cost-effectiveness ratio, net monetary benefit statistics, and the probability that a strategy of early weight-bearing is cost-effective at the prespecified cost-effectiveness threshold of £20 000. Decision uncertainty was assessed by varying the cost-effectiveness threshold to £15 000 and £30 000 for an additional QALY. All analyses were done with the statistical package R version 4.2.1. Further details of the health economic evaluation, including the sensitivity

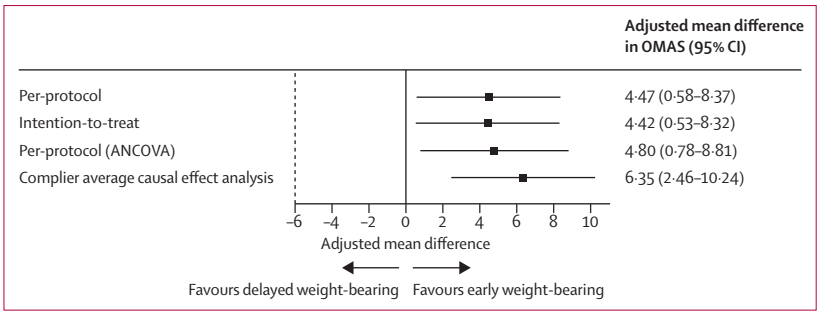

Figure 2: **Primary analysis forest plot**
A non-inferiority margin of –6 points was considered. OMAS=Olerud Molander Ankle Score.

analyses and subgroup analyses, are provided in the appendix (pp 19–20).

Role of the funding source

The funders of the study had no role in study design, data collection, data analysis, data interpretation, and writing of the report.

Results

Between Jan 13, 2020, and Oct 29, 2021, 2218 patients were screened, 795 of whom were deemed eligible and 561 were randomly allocated to an early weight-bearing (n=280) or delayed weight-bearing (n=281) strategy. A summary of patients screened, randomly assigned, and included in the primary outcome analysis, including reasons for exclusion and dropout, is included in figure 1 (appendix p 5). Participants had a median age of 50 years (IQR 16·4), 359 (64%) of 561 were female, and baseline characteristics were well balanced between treatment groups (table 1).

Four participants allocated to delayed weight-bearing did not receive their allocated treatment due to their refusal or surgeon preference. One participant in each group received verbal weight-bearing instructions only, due to local unavailability of a rehabilitation booklet. The remaining participants all received both verbal and written weight-bearing instructions. Of the 23 sites, nine returned a fidelity recording, of which six sites returned two recordings and three sites returned one recording. All recorded episodes successfully delivered the key instructions for their respective weight-bearing strategy (appendix p 10). In the delayed weight-bearing group, 175 (62%) of 281 complied, 91 (32%) were non-compliers, and 15 (5%) were unknown. The median time to self-reported weight-bearing after randomisation was 4 days (IQR 1–7) for the early weight-bearing group and 28 days (IQR 14–29) for the delayed weight-bearing group. The median time participants used walking aids from randomisation was 31 days (IQR 23–48) in the early weight-bearing group and 41 days (29–69) in the delayed weight-bearing group. Follow-up data were available for 480 (86%) of 561 participants 4 months after randomisation, with data available for 243 (87%) participants in the early weight-bearing group and 237 (84%) participants in the delayed weight-bearing group (appendix p 7).

In the primary analysis of OMAS scores 4 months after randomisation, a strategy of early weight-bearing was found to be non-inferior (adjusted mean difference 4·47; 95% CI 0·58–8·37) to a strategy of delayed weight-bearing (figure 2). Early weight-bearing was hence tested for superiority in the ITT population, which showed that early weight-bearing was superior to delayed weight-bearing (adjusted difference 4·42; 95% CI 0·53–8·32) at 4 months with a p value of 0·026. Sensitivity analyses found similar differences (table 2). The CACE analysis mirrored the primary analysis findings with an adjusted mean difference in OMAS 4 months after randomisation of 6·35 (95% CI 2·46–10·24) in favour of an early weight-bearing strategy. OMAS and EQ-5D-5L scores were statistically superior at 6 weeks after randomisation in favour of early weight-bearing strategy but this difference tapered off by 12 months after randomisation (figure 3; appendix p 11). No significant interactions were found from prespecified subgroup analyses of age group, gender, or syndesmotic fixation (appendix pp 14–15). Complication profiles were similar in both groups over the 12-follow-up period (table 3), with 46 (16%) of 280 participants in the early weight-bearing group and 39 (14%) of 281 in the delayed weight-bearing group experiencing one or more complications (adjusted odds ratio 1·18; 95% CI 0·80–1·75). In the early weight-bearing group, 21 (8%) participants had a complication requiring further, unplanned surgery, compared with 16 (6%) participants in the delayed weight-bearing group (adjusted odds ratio 1·33; 95% CI 0·71–2·49). In patients with syndesmosis screws, 11 (13%) of 86 in the early weight-bearing group and 7 (9%) of 81 in the delayed weight-bearing group had further unplanned surgery. Analysis of the WPAI found no statistically significant differences in the mean number of work hours lost at 6 weeks, 4 months, or 12 months between the groups. A full report of the WPAI responses is in the appendix (pp 12–14). Over the 12 months from randomisation, the median number of physiotherapy sessions attended was 4·5 in the early and delayed weight-bearing group and 8 sessions in the delayed weight-bearing group (appendix p 14).

The mean costs from the NHS and PSS perspective in the early and delayed weight-bearing groups over a 12-month horizon were £725 and £785, respectively (mean difference –£60 [95% CI –342 to 232]). Additionally, the early weight-bearing strategy was associated with a reduction in work losses (valued in economic terms) compared with delayed weight-bearing. Hence, from the societal perspective, the mean cost was £2175 for the early weight-bearing group and £2897 in the delayed weight-bearing group, resulting in a mean cost difference of –£722 (95% CI –1921 to 227).

Results from the base-case analysis indicated that early weight-bearing following ankle fracture surgery resulted in QALY gains (mean adjusted QALY difference 0·031

	Early weight-bearing group	Delayed weight-bearing group	Mixed-effects model		ANCOVA	
			Adjusted mean difference (95% CI)*	p value	Adjusted mean difference (95% CI)†	p value
Per-protocol						
Baseline	96·2 (11·0), 100·0 (100·0 to 100·0), n=284	97·2 (9·3), 100·0 (100·0 to 100·0), n=277	..	..	..	..
6 weeks	47·3 (21·3), 45·0 (35·0 to 65·0), n=239	38·7 (22·1), 35·0 (20·0 to 50·0), n=231	8·51 (4·72 to 12·30)	<0·0001	8·73 (4·80 to 12·66)	<0·0001
4 months	65·9 (22·2), 70·0 (50·0 to 85·0), n=246	61·2 (22·8), 62·5 (45·0 to 80·0), n=234	4·47 (0·58 to 8·37)	0·024	4·80 (0·78 to 8·81)	0·019
12 months	76·5 (21·3), 80·0 (65·0 to 95·0), n=233	72·4 (23·5), 75·0 (60·0 to 90·0), n=228	3·73 (–0·18 to 7·64)	0·062	4·15 (0·15 to 8·15)	0·042
Intention-to-treat						
Baseline	96·2 (11·1), 100·0 (100·0 to 100·0), n=280	97·2 (9·2), 100·0 (100·0 to 100·0), n=281	..	..	..	..
6 weeks	47·0 (21·3), 45·0 (35·0 to 65·0), n=236	39·1 (22·2), 40·0 (20·0 to 55·0), n=234	7·82 (4·02 to 11·62)	<0·0001	8·01 (4·06 to 11·95)	<0·0001
4 months	65·9 (22·1), 70·0 (50·0 to 85·0), n=243	61·2 (22·9), 65·0 (45·0 to 80·0), n=237	4·42 (0·53 to 8·32)	0·026	4·78 (0·76 to 8·79)	0·020
12 months	76·5 (21·3), 0·0 (65·0 to 95·0), n=230	72·5 (23·5), 75·0 (60·0 to 90·0), n=231	3·64 (–0·26 to 7·55)	0·068	4·09 (0·09 to 8·09)	0·045
Complier average causal effect analysis						
Baseline	96·4 (10·6), 100·0 (100·0 to 100·0), n=386	97·5 (9·2), 100·0 (100·0 to 100·0), n=175	..	..	..	..
6 weeks	47·6 (21·9), 45·0 (35·0 to 65·0), n=304	34·8 (20·1), 35·0 (20·0 to 50·0), n=166	11·23 (6·90 to 15·55)	<0·0001	11·50 (4·99 to 18·01)	0·0004
4 months	65·8 (21·9), 70·0 (50·0 to 85·0), n=317	59·3 (23·3), 60·0 (45·0 to 80·0),n=163	6·35 (2·46 to 10·24)	0·0014	6·86 (1·01 to 12·71)	0·018
12 months	75·7 (22·4), 80·0 (65·0 to 95·0), n=301	72·2 (22·6), 75·0 (55·0 to 90·0), n=160	5·23 (0·85 to 9·61)	0·019	5·88 (–0·56 to 12·31)	0·066

Data are mean (SD) or median (IQR), unless otherwise stated. OMAS=Olerud and Molander Ankle Score. *Mixed-effects linear regression model adjusting for age as continuous, gender, and baseline OMAS as fixed effects with random effects for site. †Analysis of covariance, adjusting for baseline OMAS scores only.

Table 2: **Comparison of OMAS between treatment groups (primary outcome at 4 months)**

[95% CI –0·005 to 0·063]) compared with delayed weight-bearing over a 12-month period (table 4). The incremental cost-effectiveness ratio for the base-case analysis showed that early weight-bearing was the dominant rehabilitation strategy, generating both lower costs and higher QALYs, on average, over the follow-up period (figure 4).

The probability of cost-effectiveness of early weight-bearing was 84%, at a cost-effectiveness threshold of £20 000 per QALY gained. The results remained robust in sensitivity analyses, including analyses restricted to complete cases and analyses that considered costs from a societal perspective. A breakdown of costs and health-related quality-of-life outcomes and results of additional analyses, including subgroup analyses, are in the appendix (pp 19–20).

Discussion

This multicentre randomised controlled trial found that a rehabilitation strategy of giving early weight-bearing instructions to adults was non-inferior to delayed weight-bearing after ankle fracture surgery. There was a statistically significant difference in the OMAS at 6 weeks and 4 months after randomisation favouring the early weight-bearing strategy, although this was below the minimal clinically important difference for the OMAS. Health-related quality of life followed a similar trajectory, initially favouring the early weight-bearing strategy but attenuating at 12 months. Complications, including those requiring an unplanned surgery, were similar between groups. Additionally, early weight-bearing instructions following ankle fracture surgery is highly likely to be cost-effective compared with delayed weight-bearing instructions. Early weight-bearing dominated delayed weight-bearing, reducing NHS and PSS costs by £60 per person on average in the first year after randomisation and yielding improved health-related quality-of-life outcomes. This difference widened to £722 in favour of early weight-bearing when considering productivity losses from a societal perspective, supporting the significance of indirect costs highlighted by Noback and colleagues.[29]

Our results are concordant with the findings from a 2012 Cochrane review, which suggested that early weight-bearing appeared to be a safe strategy after ankle fracture surgery, although with low certainty, due to the quality of included studies.[7] Randomised controlled trials published since the Cochrane review suggested that early weight-bearing is associated with improved functional outcomes in the early postoperative phase, albeit with low precision and certainty.[9–12] Despite this, delayed weight-bearing has remained the standard of care, with a 2014 survey finding that USA surgeons recommend an average of 5–8 weeks of non-weight-bearing postoperatively.[30] Furthermore, a 2017[31] and 2019–21[32] UK prospective service evaluation found that only 21% and 11% of patients, respectively, were prescribed an early weight-bearing strategy. This contrasts with other lower limb fractures in which an early-weight-bearing strategy is more common, with 96% of patients permitted to weight-bearing immediately postoperatively after surgery for a hip fracture.[32] The reluctance among surgeons to adopt early weight-bearing might be attributed to the limitations of the Cochrane review, which included studies from restricted populations at high risk of bias and pooled data from trials of disparate immobilisation

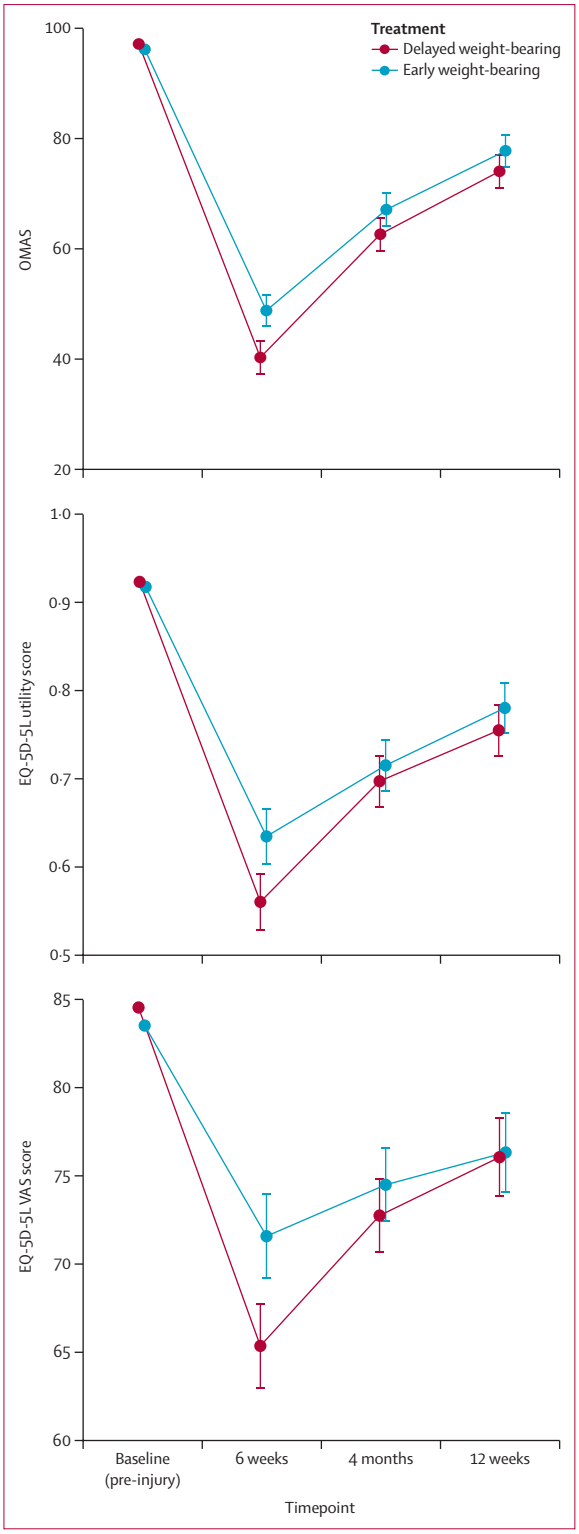

***Figure 3*: OMAS, EQ-5D-5L utility, and VAS scores, with 95% CIs from baseline to 12 months after randomisation**
EQ-5D-5L=EuroQol 5-dimensions-5-levels. VAS=Visual Analogue Scale. OMAS= Olerud and Molander Ankle Score.

	Early weight-bearing group (n=280)	Delayed weight-bearing group (n=281)	Total (n=561)
Prominent implant or metal work irritation	15	13	28
Surgical site infection	15	12	27
Wound dehiscence	7	5	12
Nerve palsy	3	4	7
Failed fixation	4	1	5
Complex regional pain syndrome	0	4	4
Refracture of same ankle	2	1	3
Deep vein thrombosis	1	1	2
Wound infection	2	0	2
Ankle metal work or implant breakage	1	0	1
Fall	0	1	1
Malunion	1	0	1
Non-union	0	1	1
Symptomatic pulmonary embolus	1	0	1
Vascular injury	1	0	1
All complications	53	43	96

Participants could have more than one complication.

***Table 3*: Summary of complications from baseline to 12 months by treatment group**

and weight-bearing protocols.[7] This is in addition to the historically high complication risks and the minor increase in superficial infections and wound healing issues reported in the studies.[2,33,34]

The WAX trial reported on more than double the number of participants than any other previous trial. Additionally, previous trials focused on younger, fitter patients with simpler fractures, excluding patients with open fractures, syndesmotic injuries, patients with poor bone quality, or those over the age of 65 years, making their results hard to generalise.[9–12] The comparative strengths of the WAX trial include the pragmatic multicentre nature of the trial, with broad inclusion criteria reflecting the patients treated in UK hospitals. Additionally, the standardisation of rehabilitation advice and documented adherence assessment were absent from other recent studies.

Despite the broad inclusion criteria, of the 2218 patients screened, 1423 (64%) were considered ineligible, of which 938 (66%) were due to a lack of surgeon equipoise, with the surgeon prescribing delayed weight-bearing instructions. The reason for exclusion was most commonly due to concerns regarding fixation stability, which could affect generalisability of the results, but is reflective of the pragmatic nature of the study. Nevertheless, of the 561 patients randomly assigned, 159 (28%) were aged 60 years or older, 138 (25%) had sustained trimalleolar fractures, and 167 (30%) underwent syndesmotic fixation, reflecting typical operatively treated

	Cost difference (95% CI)	QALY difference (95% CI)	Incremental cost-effectiveness ratio	Mean and 95% CI net monetary benefit at			Probability of cost-effectiveness at		
				£15 000 per QALY threshold	£20 000 per QALY threshold	£30 000 per QALY threshold	£15 000 per QALY threshold	£20 000 per QALY threshold	£30 000 per QALY threshold
Base case multiple imputation	–£90 (–535 to 355)	0·0293 (–0·0259 to 0·0846)	Dominant	543 (–490 to 1576)	687 (–603 to 1977)	975 (–847 to 2798)	0·840	0·843	0·856
Complete case analysis	–£88 (–326 to 150)	0·0227 (–0·0058 to 0·0513)	Dominant	444 (–89 to 977)	556 (–109 to 1221)	781 (–157 to 1719)	0·948	0·950	0·948
Societal perspective	–£742 (–2986 to 1502)	0·0293 (–0·0283 to 0·0868)	Dominant	1194 (–1526 to 3913)	1337 (–1573 to 4248)	1625 (–1709 to 4959)	0·800	0·810	0·834

Dominant refers to a treatment strategy that is both less costly and more effective than its comparator. QALY=quality-adjusted life-year.

Table 4: **Cost-effectiveness results**

populations, albeit with a slightly lower median age of 50 years compared with those aged 50–52 years in epidemiological studies.[31,35] Other limitations include the 14% attrition in the primary outcome and the incomplete fidelity recording responses, although this is similar to recent multicentre trials in the same population[11,36] and is reflective of challenges in trials involving trauma patients.[37] Furthermore, the 1-year follow-up period in this study might not capture the long-term development of ankle arthritis. However, the presence of radiographic ankle arthritis has been shown to have little correlation with symptoms, with functional levels continuing to improve a decade after surgery when compared with those observed 1 year after.[38] Another limitation is that 91 (32%) of 281 patients in the delayed weight-bearing group did not adhere to instructions for the duration of their treatment and self-reported commencing weight-bearing within 3 weeks of allocation. However, it should be noted that this study compared rehabilitation instructions, rather than patient behaviour, as the giving of the instructions is the only intervention the clinician can alter. Notably, the results from the CACE analysis supported the primary analysis, reinforcing the recommendation for early weight-bearing.

The underlying mechanism for the advantage gained from early weight-bearing is most likely tied to the recognised issues associated with immobility, encompassing stiffness and muscle atrophy, which tends to recover more slowly than it is lost.[39] Taken alongside other contemporary studies, the outcomes of the WAX trial imply that early weight-bearing and ankle movement expedite the restoration of baseline function following ankle fracture surgery.[7,36] Nevertheless, the risk of complications and the need for further surgery in the ankle fracture population is not insignificant and future research should focus on the prediction and early identification of those at risk of complications.

In conclusion, this trial finds that an early weight-bearing strategy is non-inferior to delayed weight-bearing after ankle fracture surgery and is highly likely to be cost-effective. This should provide clinicians around the world the confidence to recommend early weight-bearing to their patients after ankle fracture surgery.

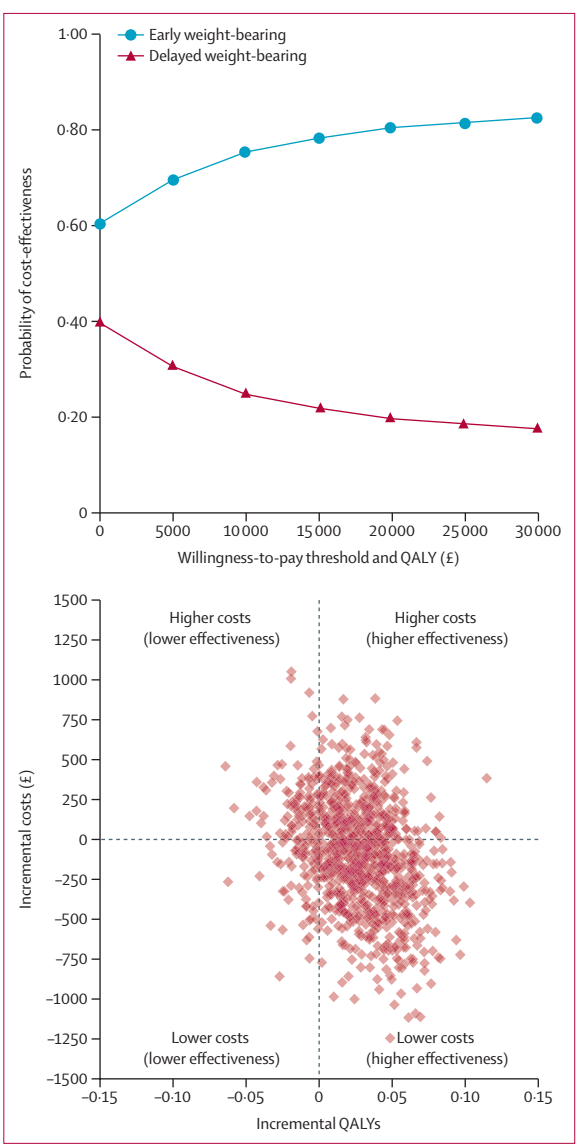

Figure 4: **Cost-effectiveness plane and cost-effectiveness acceptability curve**
QALY=quality-adjusted life-year.

Contributors

CPB: conceptualisation, data curation, formal analysis, funding acquisition, investigation, methodology, project administration, validation, visualisation, writing, original draft, and review and editing. JA: conceptualisation, data curation, funding acquisition, investigation, methodology, project administration, writing, and review and editing. VJ: data curation, formal analysis, validation, visualisation, writing, and review and editing. SP: conceptualisation, data curation, formal analysis, funding acquisition, investigation, methodology, validation, visualisation, writing, and review and editing. NP: data curation, formal analysis, investigation, methodology, validation, visualisation, and review and editing. FA: data curation, formal analysis, investigation, validation, visualisation, writing, and review and editing. DA: data curation, funding acquisition, investigation, methodology, project administration, and review and editing. RK: conceptualisation, funding acquisition, methodology, and review and editing. HC: funding acquisition, writing, and review and editing. PB: conceptualisation, funding acquisition, methodology, and review and editing. XLG: conceptualisation, data curation, funding acquisition, investigation, methodology, project administration, resources, supervision, writing, and review and editing. NP and VJ were responsible for the statistical analysis. SP and FA were responsible for the health economic evaluation. All authors contributed to the design and delivery of the WAX trial. CPB wrote the first draft of the trial report. All authors revised the draft report and approved the final version as submitted. All authors had access to the data and NP, VJ, and CPB accessed and validated the data.

Declaration of interests

CPB, JA, SP, DA, RK, HC, and XLG report receiving grants from the National Institute for Health and Care Research, paid to their host institution. All other authors declare no competing interests.

Data sharing

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

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References

1 NHS England. Hospital admitted patient care activity, 2021–22. Sept 22, 2022. https://digital.nhs.uk/data-and-information/publications/statistical/hospital-admitted-patient-care-activity/2021-22 (accessed Aug 25, 2023).
2 Ahl T, Dalén N, Holmberg S, Selvik G. Early weight bearing of displaced ankle fractures. *Acta Orthop Scand* 1987; **58:** 535–38.
3 McPhail SM, Dunstan J, Canning J, Haines TP. Life impact of ankle fractures: qualitative analysis of patient and clinician experiences. *BMC Musculoskelet Disord* 2012; **13:** 224.
4 McDonald MR, Sathiyakumar V, Apfeld JC, et al. Predictive factors of hospital length of stay in patients with operatively treated ankle fractures. *J Orthop Traumatol* 2014; **15:** 255–58.
5 Gul A, Batra S, Mehmood S, Gillham N. Immediate unprotected weight-bearing of operatively treated ankle fractures. *Acta Orthop Belg* 2007; **73:** 360–65.
6 NICE. Fractures (non-complex): assessment and management. London: National Institute of Health and Care Excellence, 2016.
7 Lin C-WC, Donkers NAJ, Refshauge KM, Beckenkamp PR, Khera K, Moseley AM. Rehabilitation for ankle fractures in adults. *Cochrane Database Syst Rev* 2012; **11:** CD005595.
8 Bretherton CP, Claireaux HA, Achten J, et al. Protocol for the weight-bearing in ankle fractures (WAX) trial: a multicentre prospective non-inferiority trial of early versus delayed weight-bearing after operatively managed ankle fracture. *BMC Musculoskelet Disord* 2021; **22:** 672.
9 Smeeing DPJ, Houwert RM, Briet JP, et al. Weight-bearing or non-weight-bearing after surgical treatment of ankle fractures: a multicenter randomized controlled trial. *Eur J Trauma Emerg Surg* 2020; **46:** 121–30.
10 Dehghan N, McKee MD, Jenkinson RJ, et al. Early weightbearing and range of motion versus non-weightbearing and immobilization after open reduction and internal fixation of unstable ankle fractures: a randomized controlled trial. *J Orthop Trauma* 2016; **30:** 345–52.
11 Park JY, Kim BS, Kim YM, Cho JH, Choi YR, Kim HN. Early weightbearing versus nonweightbearing after operative treatment of an ankle fracture: a multicenter, noninferiority, randomized controlled trial. *Am J Sports Med* 2021; **49:** 2689–96.
12 Schubert J, Lambers KTA, Kimber C, et al. Effect on overall health status with weightbearing at 2 weeks vs 6 weeks after open reduction and internal fixation of ankle fractures. *Foot Ankle Int* 2020; **41:** 658–65.
13 Nilsson GM, Eneroth M, Ekdahl CS. The Swedish version of OMAS is a reliable and valid outcome measure for patients with ankle fractures. *BMC Musculoskelet Disord* 2013; **14:** 109.
14 Herdman M, Gudex C, Lloyd A, et al. Development and preliminary testing of the new five-level version of EQ-5D (EQ-5D-5L). *Qual Life Res* 2011; **20:** 1727–36.
15 Hoffmann TC, Glasziou PP, Boutron I, et al. Better reporting of interventions: template for intervention description and replication (TIDieR) checklist and guide. *BMJ* 2014; **348:** g1687.
16 Harris PA, Taylor R, Thielke R, Payne J, Gonzalez N, Conde JG. Research electronic data capture (REDCap)—a metadata-driven methodology and workflow process for providing translational research informatics support. *J Biomed Inform* 2009; **42:** 377–81.
17 Beckenkamp PR, Lin C-WC, Chagpar S, Herbert RD, van der Ploeg HP, Moseley AM. Prognosis of physical function following ankle fracture: a systematic review with meta-analysis. *J Orthop Sports Phys Ther* 2014; **44:** 841–51.
18 Reilly MC, Zbrozek AS, Dukes EM. The validity and reproducibility of a work productivity and activity impairment instrument. *PharmacoEconomics* 1993; **4:** 353–65.
19 Keene DJ, Mistry D, Nam J, et al. The ankle injury management (AIM) trial: a pragmatic, multicentre, equivalence randomised controlled trial and economic evaluation comparing close contact casting with open surgical reduction and internal fixation in the treatment of unstable ankle fractures in patients aged over 60 years. *Health Technol Assess* 2016; **20:** 1–158.
20 Penning D, Kleipool S, van Dieren S, Dingemans SM, RODEO Collaborator Group, Schepers T. The minimal clinically important difference (MCID) of the Olerud Molander Ankle Score (OMAS) in patients with unstable ankle fracture. *Arch Orthop Trauma Surg* 2023; **143:** 3103–10.
21 van Hout B, Janssen MF, Feng Y-S, et al. Interim scoring for the EQ-5D-5L: mapping the EQ-5D-5L to EQ-5D-3L value sets. *Value Health* 2012; **15:** 708–15.
22 Kind P, Dolan P, Gudex C, Williams A. Variations in population health status: results from a United Kingdom national questionnaire survey. *BMJ* 1998; **316:** 736–41.
23 Jones KC, Burns A. Unit costs of health and social care. Kent: Personal Social Services Research Unit, 2021.
24 NHS England. National cost collection for the NHS. https://www.england.nhs.uk/costing-in-the-nhs/national-cost-collection/ (accessed July 21, 2023).
25 Joint Formulary Committee. British national formulary. 2021. https://www.medicinescomplete.com/#/browse/bnf (accessed May 4, 2023).
26 Office for National Statistics. New Earnings Survey (NES) and Annual Survey of Hours and Earnings (ASHE) public and private gross weekly time series. Oct 27, 2021. https://www.ons.gov.uk/employmentandlabourmarket/peopleinwork/earningsandworkinghours/adhocs/13882newearningssurveynesandannualsurveyofhoursandearningsashepublicandprivategrossweeklytimeseries (accessed July 21, 2023).

27 NICE. Guide to the methods of technology appraisal 2013. London: National Institute of Health and Care Excellence, 2013.

28 van Buuren S, Groothuis-Oudshoorn K. MICE: multivariate imputation by chained equations in R. *J Stat Softw* 2011; **45:** 1–67.

29 Noback PC, Freibott CE, Dougherty T, Swart EF, Rosenwasser MP, Vosseller JT. Estimates of direct and indirect costs of ankle fractures: a prospective analysis. *J Bone Joint Surg Am* 2020; **102:** 2166–73.

30 Swart E, Bezhani H, Greisberg J, Vosseller JT. How long should patients be kept non-weight bearing after ankle fracture fixation? A survey of OTA and AOFAS members. *Injury* 2015; **46:** 1127–30.

31 BONE Collaborative. Weight-bearing in ankle fractures: an audit of UK practice. *Foot (Edinb)* 2019; **39:** 28–36.

32 Richardson C, Bretherton CP, Raza M, Zargaran A, Eardley WGP, Trompeter AJ. The fragility fracture postoperative mobilisation multicentre audit: the reality of weightbearing practices following operations for lower limb fragility fractures. *Bone Joint J* 2022; **104-B:** 972–79.

33 Beauchamp CG, Clay NR, Thexton PW. Displaced ankle fractures in patients over 50 years of age. *J Bone Joint Surg Br* 1983; **65:** 329–32.

34 Finsen V, Saetermo R, Kibsgaard L, et al. Early postoperative weight-bearing and muscle activity in patients who have a fracture of the ankle. *J Bone Joint Surg Am* 1989; **71:** 23–27.

35 Scott LJ, Jones T, Whitehouse MR, Robinson PW, Hollingworth W. Exploring trends in admissions and treatment for ankle fractures: a longitudinal cohort study of routinely collected hospital data in England. *BMC Health Serv Res* 2020; **20:** 811.

36 Kearney R, McKeown R, Parsons H, et al. Use of cast immobilisation versus removable brace in adults with an ankle fracture: multicentre randomised controlled trial. *BMJ* 2021; **374:** n1506.

37 Madden K, Scott T, McKay P, et al. Predicting and preventing loss to follow-up of adult trauma patients in randomized controlled trials: an example from the FLOW trial. *J Bone Joint Surg Am* 2017; **99:** 1086–92.

38 Regan DK, Gould S, Manoli A 3rd, Egol KA. Outcomes over a decade after surgery for unstable ankle fracture: functional recovery seen 1 year postoperatively does not decay with time. *J Orthop Trauma* 2016; **30:** e236–41.

39 Dittmer DK, Teasell R. Complications of immobilization and bed rest. Part 1: musculoskeletal and cardiovascular complications. *Can Fam Physician* 1993; **39:** 1428–32, 1435–37.