



# Use of cast immobilisation versus removable brace in adults with an ankle fracture: multicentre randomised controlled trial

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Additional material is published online only. To view please visit the journal online.

Cite this as: *BMJ* 2021;374:n1506 <http://dx.doi.org/10.1136/bmj.n1506>

Accepted: 9 June 2021

## ABSTRACT

### OBJECTIVES

To assess function, quality of life, resource use, and complications in adults treated with plaster cast immobilisation versus a removable brace for ankle fracture.

### DESIGN

Multicentre randomised controlled trial.

### SETTING

20 trauma units in the UK National Health Service.

### PARTICIPANTS

669 adults aged 18 years and older with an acute ankle fracture suitable for cast immobilisation: 334 were randomised to a plaster cast and 335 to a removable brace.

### INTERVENTIONS

A below the knee cast was applied and ankle range of movement exercises started on cast removal. The removable brace was fitted, and ankle range of movement exercises were started immediately.

### MAIN OUTCOME MEASURES

Primary outcome was the Olerud Molander ankle score at 16 weeks, analysed by intention to treat. Secondary outcomes were Manchester-Oxford foot questionnaire, disability rating index, quality of life, and complications at 6, 10, and 16 weeks.

### RESULTS

The mean age of participants was 46 years (SD 17 years) and 381 (57%) were women. 502 (75%) participants completed the study. No statistically significant difference was found in the Olerud Molander ankle score between the cast and removable brace groups at 16 weeks (favourable brace: 1.8, 95% confidence interval -2.0 to 5.6). No clinically significant differences were found in the Olerud Molander ankle scores at other time points, in the secondary unadjusted, imputed, or per protocol analyses.

## CONCLUSIONS

Traditional plaster casting was not found to be superior to functional bracing in adults with an ankle fracture. No statistically difference was found in the Olerud Molander ankle score between the trial arms at 16 weeks.

## TRIAL REGISTRATION

ISRCTN registry ISRCTN15537280.

## Introduction

Each year more than 120 000 people in the United Kingdom experience an ankle fracture.<sup>1</sup> Such fractures represent a major trauma workload, and demand is increasing—because the number of older adults who remain active is increasing, by 2030 ankle fractures are expected to increase threefold.<sup>1 2</sup> The frequency of this injury places an increasing burden on the UK National Health Service.<sup>3</sup> Affected adults are unable to engage in usual physical activities for prolonged periods.<sup>1 2 4</sup> The qualitative impact on individuals is substantial, affecting family and social life, sleep, sense of independence, and psychological wellbeing.<sup>5</sup>

Conventionally, after fracture the ankle is immobilised in a rigid cast for several weeks, which allows the bones to heal but can result in joint stiffness and muscle weakness.<sup>6</sup> An alternative is a removable brace, which can be taken off to allow early movement. Using a removable brace could prevent the consequences of rigid immobilisation and help to accelerate recovery. Both methods are routinely used in the UK.

A Cochrane review concluded that functional bracing might reduce activity limitation and pain and improve ankle movement. These potential advantages, however, need to be balanced against the increased incidence of adverse events. High quality evidence is not available to support the effectiveness or safety of early movement after ankle fracture.<sup>6</sup>

In light of the increasing numbers of ankle fractures and large personal and societal costs, we compared removable bracing with casting on function, quality of life, and complications in adults with an ankle fracture.

## Methods

This pragmatic, multicentre, superiority randomised controlled trial was undertaken at 20 trauma units in the UK National Health Service. The trial protocol (see supplementary file 1) was accepted for publication on 31 October 2018 and first published online on 18 December 2018.<sup>7</sup> The independent trial steering committee and data and safety monitoring committee approved the statistical analysis plan. These

## WHAT IS ALREADY KNOWN ON THIS TOPIC

Management of a fractured ankle has traditionally included cast immobilisation, which provides maximum support to bones during healing

As rigid immobilisation in a cast can result in stiff joints and weakened muscles, removable bracing might help with these problems by allowing earlier movement  
It is not known which of these treatments is superior

## WHAT THIS STUDY ADDS

Plaster cast immobilisation was not found to be superior to functional bracing for ankle fractures in adults at 16 weeks

Other factors will need to be considered in deciding optimal management

independent committees were convened to oversee the study throughout the trial's duration.

### Participants

Trauma research teams at UK NHS trust sites screened adults aged 18 years and older with a closed ankle fracture. In this pragmatic study design, if the treating clinician would usually treat the fracture in a cast for a minimum of three weeks, whether treated non-operatively or operatively, then the patient was considered eligible. Therefore, patients did not meet the initial criteria for entry to the study if the clinician decided that no immobilisation (cast or brace) was required.

On further screening, people were excluded if they had a fracture secondary to known metastatic disease, complex intra-articular fracture (eg, Pilon fracture), wound complications contraindicating a removable bracing, pre-existing neuropathic joint disease, previous ankle fracture already randomised in the present trial, were unable to adhere to trial follow-up procedures, or required close contact casting.<sup>8</sup>

Indications for first line definitive management (operative or non-operative) were according to usual practice for each individual clinician, as were any adjunctive treatments (eg, antibiotic use). The trial population included patients managed both operatively and non-operatively.

Operatively managed participants had initially received standard local clinical care in the UK, typically consisting of a temporary partial backslab, and wound check about two weeks after surgery. At this point in the care pathway, randomisation processes were completed and a member of the clinical team applied the intervention.

Non-operatively managed participants completed the randomisation processes immediately at presentation to the trauma service, when a member of the clinical team then applied the cast or removable brace. As it is usual clinical practice in the UK to delay decisions about first line non-operative management (ie, to check if the fracture is stable) for some patients, our eligibility criteria allowed up to three weeks before a definitive decision was required.

### Randomisation and blinding

Baseline data were collected before randomisation. Participants were randomised on a 1:1 basis to the two study intervention arms sequentially as they presented. A secure web based system maintained by an independent randomisation team allocated participants using a minimisation algorithm with a random element and stratification by centre, operative or non-operative management, and age ( $\leq 49$  v  $\geq 50$  years).<sup>19</sup>

Blinding of participants and clinicians was not possible. All follow-up data were participant reported through postal questionnaires; no clinicians or researchers assessed outcome measures.

### Interventions

The interventions were worn for a minimum of three weeks in both groups.

Standard below knee cast immobilisation was applied according to local procedures. Participants in the cast group started active unloaded ankle range of movement exercises once the cast was removed.

Removable braces were of a fixed angle design, to replicate what is routinely used in UK practice, and were applied in accordance with local procedures. The specific brand of removable brace was not standardised across sites, and each site used its own brand. The treating clinician in the trauma service setting encouraged participants in verbal and written formats to take off the removable brace to complete active unloaded ankle range of movement exercises as often as pain allowed, with a recommendation for each movement to be performed 10 times, three times a day (see supplementary file 2).

In this pragmatic trial, any other rehabilitation input beyond rigid immobilisation in a cast compared with early active movement in a removable brace was at the discretion of the treating member of the clinical team, in accordance with current UK practice. This included choice of weightbearing for the participant, duration of immobilisation period (beyond the minimum of three weeks), and decision to onward refer participants to physiotherapy services. These details were collected for each participant as part of the trial dataset.

### Outcome measures

The primary outcome was the Olerud Molander ankle score at 16 weeks; a self-administered questionnaire that consists of nine different items (pain, stiffness, swelling, stair climbing, running, jumping, squatting, supports, and work or activities of daily living).<sup>10</sup> Scores range from 0 for totally impaired to 100 for completely unimpaired.

We chose the primary outcome time point of 16 weeks after consultation with academics, clinicians, and public and patient representatives. This time point was based on previous trials of ankle fracture, which found that the steepest recovery occurs in the first four months of injury.<sup>8</sup> Additional longer term secondary data are being collected at 6, 12, 18, and 24 months as part of a preplanned longer term follow up, to be reported separately to capture any later stage complications.

Secondary outcomes were complications (deep vein thrombosis, pulmonary embolism, pain, swelling, numbness around the foot, wound infection, and fracture healing), resource use, and self-administered health related quality of life measures (EQ-5D-5L) and leg specific functional scores (Manchester-Oxford foot questionnaire and disability rating index).<sup>11-13</sup> All data were collected at 6, 10, and 16 weeks, except for the Manchester-Oxford foot questionnaire, which was collected at 16 weeks only. All follow-up data were collected through postal questionnaires returned to the central trial team.

### Statistical analysis

The target between group difference for the primary Olerud Molander ankle score outcome was 10 points, consistent with other studies of ankle fracture management—this is the accepted minimally clinically important difference.<sup>8,14</sup> The standard deviation of the Olerud Molander ankle score from previous feasibility work was 28 points, so we used a conservative estimate of 30 points for the sample size calculation.<sup>15</sup> With significance set at the 5% level and at 90% power, we determined that we needed data on 382 participants. Allowing for 20% loss to follow up, 478 participants were required. As recruitment exceeded planned expectations, to improve precision of our effect size estimate we obtained relevant approvals to continue recruiting to the predefined end recruitment date. The study was not powered to detect differences in the secondary outcome measures.

The primary analysis was the Olerud Molander ankle score at 16 weeks. The planned main analysis, which was on an intention-to-treat basis, used adjusted mixed effects linear regression analysis to assess evidence for differences in the Olerud Molander ankle score between the intervention arms. We included study recruitment centre as a random effect and adjusted the analysis for the stratification variables (age and operative or non-operative management) as fixed effects. Participants who maintained their allocated intervention for at least three weeks were considered to have followed the protocol. A sensitivity analysis to investigate the effect of missingness and adherence was conducted using multiple imputation.<sup>16</sup> All analyses were implemented in R.<sup>17</sup>

Two prespecified subgroup analyses were undertaken to determine whether the intervention effect differed between participants who received operative or non-operative treatment before the study intervention and between those who were younger than 50 years or 50 years and older at randomisation; those older than 50 years being more likely to have experienced a fragility fracture related to osteoporosis. The original cut-off for 60 years was amended to 50 years following advice from the independent oversight committees but before publication of the final protocol<sup>7</sup> and approval of the statistical analysis plan. The subgroup analyses followed the methods described for the primary analysis, with additional interaction terms incorporated into the mixed effects model.

### Patient and public involvement

Public and patient representatives co-produced this study. After a single site feasibility trial funded by the National Institute for Health Research (ISRCTN17809322),<sup>15</sup> two public and patient representatives (RG and KK) continued their roles through the planning, development, and delivery of the current main randomised controlled trial.

### Results

Between 9 October 2017 and 30 September 2019, 20 NHS trusts screened 3144 adults with an ankle

fracture, of whom 1152 were not eligible. Of the remaining 1992 (35%) participants, 669 were randomised: 334 to a cast and 335 to a removable brace. Six hundred and twenty seven of the remaining 1323 patients (31%) did not want to take part in the trial (428 had preference for a specific treatment, 79 did not want to be part of a research study, and 90 had other reasons) and for the other 696 (35%) patients the treating clinician did not offer the option to take part (579 had preference for a specific treatment and 117 had other reasons).

Twenty seven participants withdrew before the primary outcome point of 16 weeks. Five hundred and two participants completed the primary outcome Olerud Molander ankle score score (75%) and were included in the final analysis (fig 1).

The mean age of participants was 46.3 years (SD 17 years) and more than half the participants were women (57%). All participants had a clear ankle fracture on a radiograph, with 624 (93%) showing lateral malleolar involvement, 194 (29%) medial malleolar involvement, and 120 (18%) posterior malleolar involvement. Ankle fracture in 428 (64%) participants was due to a low energy fall. Surgery was performed in 54% of the randomised participants. The groups were well balanced across all baseline characteristics (table 1).

Twenty three participants in the cast group (n=334) did not adhere to the treatment allocation and crossed over to the removable brace group (20 owing to participant preference). Seven participants in the removable brace group (n=335) did not adhere to the treatment allocation and crossed over to the cast group (four owing to participant preference; see supplementary file 3, table 4).

Other rehabilitation input beyond rigid immobilisation in a cast versus early active movement in a removable brace was at the discretion of the treating member of the clinical team. This input was balanced across the groups. The number of onward referrals to physiotherapy was similar between the groups: 182 in the cast group and 166 in the removable brace group (see supplementary file 3).

No statistically significant difference was found in the Olerud Molander ankle score at 16 weeks, using the primary adjusted intention-to-treat analysis (mean difference 1.8, 95% confidence interval -2.0 to 5.6, favours brace). Nor was a clinically relevant difference found at the six week and 10 week time points (table 2). No clinically relevant differences were found in the disability rating index, Manchester-Oxford foot questionnaire, or EQ-5D-5L secondary outcomes at any time point (table 3).

The results of secondary unadjusted and per protocol analyses were not materially different from those of the primary analysis. The study was not, however, powered to detect a difference in secondary outcome data. No evidence was found in predefined subgroup analyses that effects differed according to age or whether or not the participant had surgical treatment (see supplementary file 3, table 6).

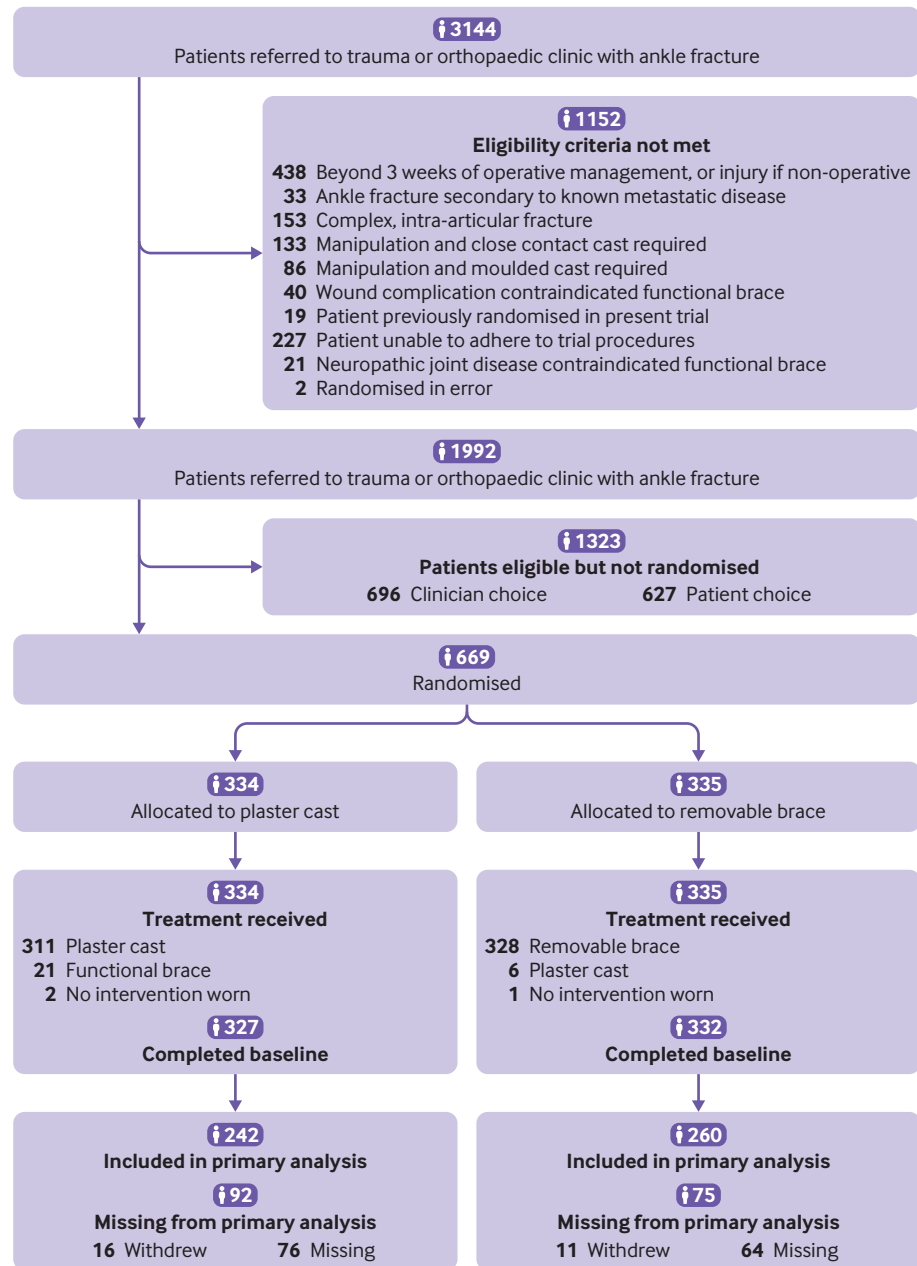


Fig 1 | Trial profile

As loss to follow-up was higher than the expected 20% at the primary analysis point, multiple imputation using chain equations was used to investigate the robustness of the results. Missingness of the primary outcome was not evenly distributed between the groups, with more data missing in the cast group (completeness: cast group 73%; removable brace 78%).

Twenty five imputed datasets were created for each model and the coefficients were pooled using Rubin's rules used to combine estimates. Missing data on the Olerud Molander ankle score were imputed using a predictive mean matching method. Variables were chosen from the baseline and randomisation set on the basis of association with missingness at 16 week follow-up. Predictor variables chosen were fractures

on medial and posterior malleolus, concurrent injuries on the same leg, body weight, smoking status, age group, sex, and fracture management.

Sensitivity analyses on the imputed dataset gave similar results to those of the primary analysis, suggesting that missingness did not impact on the interpretation of the primary analysis (see supplementary file 3, table 3).

Complications were similar across the two groups. Important complications in the cast group were deep vein thrombosis (n=3), pulmonary embolism (n=1), chronic regional pain syndromes (n=2), and further surgery (n=4)—revision surgery for failed primary fixation (n=1), elective removal of metal work (n=2), and removal of metal work secondary to infection (n=1). Important complications in the

**Table 1 | Baseline characteristics of adults with ankle fracture allocated to plaster cast or removable brace in intention-to-treat population\***

Characteristics	Cast (n=334)	Removable brace (n=335)	Overall (n=669)
Sex:			
Women	198 (59)	183 (55)	381 (57)
Men	136 (41)	152 (45)	288 (43)
Ethnicity:			
Asian	15 (5)	12 (4)	27 (4)
Black, African, and Caribbean	15 (5)	14 (4)	29 (4)
Mixed race	7 (2)	8 (2)	15 (2)
Other	47 (2)	6 (2)	13 (2)
White	289 (87)	289 (88)	581 (87)
Mean (SD) pre-injury OMAS score	93.4 (16)	93.4 (16)	93.4 (16)
Mean (SD) baseline (post-injury) OMAS score	20.8 (17)	21.2 (18)	21.0 (17)
Mean (SD) age (years)	46.7 (17)	45.9 (16)	46.3 (17)
Age category (years):			
≤49	185 (55)	186 (56)	371 (55)
≥50	149 (45)	149 (44)	298 (45)
Mean (SD) body mass index	28.2 (6)	28.6 (6)	28.4 (6)
Mechanism of injury†:			
Low energy fall	216 (64)	212 (63)	428 (64)
High energy fall	49 (15)	60 (18)	109 (16)
Road traffic incident	14 (4)	12 (4)	26 (4)
Crush injury	1 (<1)	1 (<1)	2 (<1)
Sports injury	26 (8)	23 (7)	49 (7)
Other	32 (10)	29 (8)	61 (9)
Side of injury:			
Right	158 (47)	170 (51)	328 (49)
Left	176 (52)	161 (48)	337 (50)
Malleolus involvement†:			
Lateral	310 (93)	314 (94)	624 (93)
Medial	110 (33)	84 (25)	194 (29)
Posterior	60 (18)	60 (18)	120 (18)
Fracture management:			
Operative	182 (55)	182 (54)	364 (54)
Non-operative	152 (45)	153 (46)	305 (46)
Advised weightbearing:			
Full	110 (33)	109 (33)	219 (33)
Partial	65 (20)	75 (22)	140 (21)
None	157 (47)	146 (44)	303 (45)
Concurrent injuries:			
No	307 (92)	317 (95)	624 (93)
Yes	27 (8)	18 (5)	45 (7)
Regular smoker:			
No	268 (80)	259 (77)	527 (79)
Yes	64 (19)	71 (21)	135 (20)
Alcohol/week (units):			
0-7	233 (70)	205 (61)	438 (65)
8-14	50 (15)	71 (21)	121 (18)
15-21	31 (9)	33 (10)	64 (10)
>21	20 (6)	24 (7)	44 (7)
Concurrent drugs:			
Steroids	14 (4)	10 (3)	24 (4)
Other	224 (67)	215 (64)	439 (66)
Diagnosis before injury:			
Diabetes	16 (5)	16 (5)	32 (5)
Leg fracture (past 12 months)	3 (1)	2 (1)	5 (1)
Injury to leg (past 12 months)	2 (1)	4 (1)	6 (1)

OMAS=Olerud Molander ankle score.

\*&lt;3% missing in any category.

†Multiple categories possible.

removable brace group were deep vein thrombosis (n=3), pulmonary embolism (n=1), chronic regional pain syndrome (n=1), problems with fracture healing (n=1), and further surgery (n=8)—revision surgery for failed primary fixation (n=1), elective removal of metal work (n=4), and removal of metal work secondary to infection (n=3; table 4).

## Discussion

This randomised controlled trial found no statically significant difference in ankle function between a plaster cast and a removable fixed angle brace at 16 weeks in adults with an ankle fracture. The upper limit of the 95% confidence interval effectively excluded any possibility that one intervention was superior to the other.

**Table 2 | Olerud Molander ankle score (OMAS) in adults with ankle fracture allocated to plaster cast or removable brace in intention-to-treat population\***

	Cast (n=334)		Removable brace (n=335)		Between group difference (95% CI)		P value
	No	Mean (SD) OMAS	No	Mean (SD) OMAS	Unadjusted	Adjusted†	
6 weeks	241	37.2 (22.1)	256	39.6 (20.6)	2.4 (-1.4 to 6.2)	2.2 (-1.4 to 5.8)	0.23
10 weeks	229	47.1 (21.7)	239	51.5 (23.0)	4.5 (0.4 to 8.5)	4.5 (0.6 to 8.3)	0.02
16 weeks	242	62.4 (23.4)	260	64.5 (22.4)	2.1 (-1.9 to 6.2)	1.8 (-2.0 to 5.6)	0.35

\*Positive values in favour of removable brace.

†Estimates are from linear regression model adjusted for patient sex, age group, and fracture management at baseline.

**Table 3 | Secondary outcomes in adults with ankle fracture allocated to plaster cast or removable brace in intention-to-treat population\***

	Cast (n=334)		Removable brace (n=335)		Between group difference (95% CI)		P value
	No	Mean (SD)	No	Mean (SD)	Unadjusted	Adjusted†	
DRI:							
6 weeks	222	57.7 (20.6)	247	51.7 (22.6)	-6.0 (-9.9 to -2.1)	-5.6 (-9.4 to -1.8)	0.004
10 weeks	218	43.8 (22.5)	229	38.8 (23.4)	-5.0 (-9.3 to -0.8)	-5.0 (-9.2 to -0.9)	0.01
16 weeks	213	32.8 (23.9)	235	31.4 (24.7)	-1.5 (-6.0 to 3.0)	-1.0 (-5.4 to 3.4)	0.65
EQ-5D-5L:							
6 weeks	241	0.497 (0.272)	258	0.534 (0.258)	0.037 (-0.010 to 0.084)	0.036 (-0.010 to 0.082)	0.12
10 weeks	228	0.647 (0.192)	239	0.66 (0.18)	0.013 (-0.021 to 0.047)	0.013 (-0.020 to 0.047)	0.43
16 weeks	241	0.702 (0.198)	259	0.73 (0.177)	0.028 (-0.005 to 0.061)	0.026 (-0.006 to 0.058)	0.11
MOXFQ:							
16 weeks	218	38.9 (24.7)	233	36.9 (23.6)	-2.0 (-6.5 to 2.5)	-1.32 (-5.6 to 3.0)	0.54

DRI=disability rating index; EQ-5D-5L=self-administered health related quality of life measures; MOXFQ=Manchester-Oxford foot questionnaire.

\*Positive values in favour of removable brace.

†Fixed effect model accounting for sex, age group, and fracture management only. Random effect model did not improve fit, hence omitted.

No clinically relevant differences were found in Olerud Molander ankle score at secondary time points or in the secondary outcome measures of Manchester-Oxford foot questionnaire, disability rating index, quality of life, and complications. We found no statistically significant differences in the safety profiles of serious complications across both interventions. A higher number of complications occurred in the removable brace group, particularly wound breakdown (7 v 15), wound infection (10 v 19), and need for further surgery (4 v 8). The study was not, however, powered to detect a difference in these secondary outcomes.

#### Comparison with other studies

A Cochrane review identified 10 randomised controlled trials that compared a removable type of immobilisation and early movement with a cast and no early movement (n=531).<sup>6</sup> In our updated

search, we identified four subsequent randomised controlled trials (n=451).<sup>14 15 18 19</sup> One trial (n=50) was the Ankle Injury Rehabilitation feasibility study to this current study and made no inferences to clinical effectiveness.<sup>15</sup> A further study (n=110) concluded that removable bracing was superior at six weeks, but the difference on the Olerud Molander ankle score diminished by 12 weeks.<sup>18</sup> These findings were supported by a further randomised controlled trial that used a visual analogue scale pain score as a primary measure (n=44).<sup>14</sup> The largest randomised controlled trial (n=247) indicated non-inferiority of removable bracing at 6, 12, and 52 weeks using the Olerud Molander ankle score.<sup>19</sup> No trials found a difference in safety profiles of removable bracing compared with cast.

This trial did not find any clinically relevant differences between traditional cast compared with

**Table 4 | Analysis of secondary outcome complications from baseline to 16 weeks in adults with ankle fracture allocated to plaster cast or removable brace in intention-to-treat population.\* Values are numbers (percentages) unless stated otherwise**

	Cast (n=334)	Removable brace (n=335)	Odds ratio (95% CI)	P value†
Wound infection requiring antibiotics‡	10 (5.5)	19 (10.4)	2.0 (0.9 to 5.0)	0.12
Wound breakdown or dehiscence‡	7 (3.8)	15 (8.2)	2.2 (0.8 to 6.7)	0.12
Further surgery for ankle fracture‡	4 (2.2)	8 (4.4)	1.8 (0.5 to 7.1)	0.41
Pressure sore or ulcer	10 (3.0)	6 (1.8)	0.6 (0.17 to 1.8)	0.32
Numbness at side of foot	51 (15.3)	42 (12.5)	0.8 (0.5 to 1.3)	0.31
Non-union of fracture	0	1 (0.3)	NA	1.00
Deep vein thrombosis	3 (0.9)	3 (0.9)	1 (0.1 to 7.5)	1.00
Pulmonary embolism	1 (0.3)	1 (0.3)	1 (0.0 to 78.4)	1.00
Chronic regional pain syndrome	2 (0.6)	2 (0.6)	1 (0.1 to 13.8)	1.00

NA=not applicable.

\*Numbers represent complications reported at least once by each participant.

†Fisher's exact test.

‡Numbers are only applicable to those who had operative management: cast (n=182) removable brace (n=182).

removable brace management at any time point, in keeping with previous trials.

### Strengths and limitations of this study

The current trial, a large scale pragmatic randomised controlled trial, was designed to evaluate the clinical effectiveness of a plaster cast versus removable bracing for the management of ankle fractures in adults. The main limitation of our study was the 25% loss to follow-up; however, the minimum sample size was exceeded by a large margin and our post hoc sensitivity analysis, accounting for missing data, produced similar results to the primary analysis, providing reassurance that the primary analysis was robust. Bias could potentially have been introduced because participants who were lost to follow-up might have been different from those included in the final analysis, although baseline characteristics of the randomised population compared with the analysed population were similar, providing further reassurance.

### Conclusions and policy implications

This trial provides strong evidence for no statistically significant difference between traditional cast immobilisation and removable bracing for ankle fractures in adults. Future research should consider the importance of later stage rehabilitation after the initial immobilisation phase.

We thank the patients and research support at each site, the patient and public involvement representatives (Richard Grant and Karen Keates), and data monitoring and ethics committee members (Mike Whitehouse, Elaine Nicholls, and Ed Roddy) and trial steering committee members (Dylan Morrissey, Joseph Alsousou and Ben Ollivere) for their contribution throughout the feasibility and main trial.

**The AIR trial collaborators are:** Jonathan Young and Eamon Ramahandany (University Hospitals Coventry and Warwickshire), Mike Kelly (North Bristol), Nima Heidari (The Royal London Hospital), Richard Jeavons and Rajesh Nanda (North Tees and Hartlepool), Carolyn Chadwick, Chris Blundell, Mark Davies and Howard Davies (Northern General Hospital), Raju Aluwahlia and Ines Reichert (Kings College Hospital), Sultan Qasim (Royal Victoria Infirmary), Atif Malik (Milton Keynes University Hospital), Jordi Ballester (St Helens and Knowsley Teach Hospital), Verity Currall and Simon Burt (Luton and Dunstable University Hospital), Sandeep Kapoor (The Rotherham NHS Foundation Trust), Fraser Harrold and Alasdair Macinnes (Ninewells Hospital and Medical School), Harish Karup, Holly Morris, Suranga Giurushihe, Melinda Hav, Abdul Moees, Hemanta Das and Vishal Rajput (United Lincolnshire Hospitals NHS Trust), Aamir Zubairy (East Lancashire Hospitals NHS), Andrew McAndrew (Royal Berkshire Hospital), Rupinderbir Deol (Lister Hospital), Syed Anjum, Togay Koc, Ahmed Abde Azaz, Zine Beech, Mike Dean, Zoe Lin, Jo Round (University Hospital Southampton NHS Foundation Trust) Craig White (South Tees Hospital NHS Foundation Trust), Yadu Shankarappa (Bedfordshire Hospitals NHS Foundation Trust), and Jit Mangwani (Leicester Royal Infirmary).

**Contributors:** RSK, MLC, MU, and ACR were conceived the study, designed the trial, obtaining grant funding, and managed the trial. RK acquired the data. NP, HP, and AH did the statistical analysis. JM and HN did the health economics analysis. All authors were responsible for the interpretation of the data and for drafting and approving the final submitted manuscript. RSK is the guarantor and accepts full responsibility for the work and the conduct of the study, had access to the data, and controlled the decision to publish. The corresponding author attests that all listed authors meet authorship criteria and that no others meeting the criteria have been omitted.

**Funding:** This trial was funded by the National Institute for Health Research (NIHR) commencing 1 January 2017, as part of a personal fellowship to RSK (NIHR: CDF-2016-09-009) and supported by

the NIHR Oxford Biomedical Research Centre. The views expressed are those of the authors and not necessarily those of the NIHR or the Department of Health and Social Care. The funders had no role in considering the study design or in the collection, analysis, interpretation of data, writing of the report, or decision to submit the article for publication.

**Competing interests:** All authors have completed the ICMJE uniform disclosure form at [www.icmje.org/coi\\_disclosure.pdf](http://www.icmje.org/coi_disclosure.pdf) and declare: all authors had financial support from the National Institute for Health Research (NIHR) for the submitted work; no financial relationships with any organisations that might have an interest in the submitted work in the previous three years. RSK is a member of the UK NIHR Health Technology Assessment (HTA) Cost Effectiveness Threshold (CET) board, NIHR Integrated Clinical Academic (ICA) doctoral panel, and chair of the NIHR Research for Patient Benefit (RfPB) board. MLC is a member of the UK NIHR HTA general board and holder of a NIHR senior investigator award. ACR is a member of the NIHR ICA clinical lectureship/senior clinical lectureship panel and holder of a NIHR senior investigator award. RSK, MLC, ACR, NP, HP, and PW have been awarded current and previous NIHR research grants. HP, MU, and RSK are co-investigators on two NIHR funded studies receiving additional support from Stryker. MU is chief investigator or co-investigator on multiple previous and current research grants from the UK NIHR and Arthritis Research UK and is a co-investigator on grants funded by the Australian National Health and Medical Research Council. He is an NIHR senior investigator. He has received travel expenses for speaking at conferences from the professional organisations hosting the conferences. He is a director and shareholder of Clinivo that provides electronic data collection for health services research. He is part of an academic partnership with Serco, funded by the European Social Fund, related to return to work initiatives. He has accepted honorariums for teaching and lecturing from consortium for advanced research training in Africa. Until March 2020 he was an editor of the NIHR journal series and a member of the NIHR Journal Editors Group, for which he received a fee.

**Ethical approval:** This study was approved by the National Research Ethics Committee on 4 July 2017 (17/WM/0239), with each trial site granting individual NHS trust approval before recruitment at each site. This study was prospectively registered on 24 July 2017.

**Data sharing:** Trial data are not publicly available but access to the anonymised dataset can be obtained from the corresponding author on reasonable request.

The manuscript's guarantor (RSK) affirms that the manuscript is an honest, accurate, and transparent account of the study being reported; that no important aspects of the study have been omitted; and that any discrepancies from the study as originally planned have been explained.

**Dissemination to participants and related patient and public communities:** A lay summary of the results of the study will be made available to research participants on the trial website.

**Provenance and peer review:** Not commissioned; externally peer reviewed.

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**Supplementary information:** file 1

**Supplementary information:** file 2

**Supplementary information:** file 3