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The research reported in this issue of the journal was commissioned by the HTA Programme as project number 01/14/10. The contractual start date was in November 2002. The draft report began editorial review in July 2006 and was accepted for publication in July 2007. As the funder, by devising a commissioning brief, the HTA Programme specified the research question and study design. The authors have been wholly responsible for all data collection, analysis and interpretation, and for writing up their work. The HTA editors and publisher have tried to ensure the accuracy of the authors' report and would like to thank the referees for their constructive comments on the draft document. However, they do not accept liability for damages or losses arising from material published in this report.

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Abstract

Treatment of severe ankle sprain: a pragmatic randomised controlled trial comparing the clinical effectiveness and cost-effectiveness of three types of mechanical ankle support with tubular bandage. The CAST trial

MW Cooke,[1*] JL Marsh,[2] M Clark,[1] R Nakash,[1] RM Jarvis,[1] JL Hutton,[2] A Szczepura,[1] S Wilson[3] and SE Lamb,[1] on behalf of the CAST trial group

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Objective: To estimate the clinical effectiveness and cost-effectiveness of three methods of ankle support compared with double layer tubular compression bandage.
Design: A randomised controlled trial, designed to reflect practice in UK hospital emergency departments.
Setting: Eight emergency departments in England.
Participants: Aged 16 or over with acute severe ankle sprain, unable to weight bear, no fracture.
Interventions: 584 participants were randomised to one of four treatment arms: tubular bandage, below knee cast, Aircast® ankle brace or Bledsoe® boot, all applied 2–3 days after presentation to allow swelling to resolve.
Main outcome measures: Response to treatment was assessed using the Foot and Ankle Outcome Score and generic measures (Functional Limitations Profile, SF-12 and EQ-5D).
Results: When adjusted for age, sex and baseline scores, the below knee cast offered a small but statistically significant benefit at 4 weeks in terms of pain (FAOS pain difference 5.1; 95% CI 0.4–9.8), foot- and ankle-related quality of life (QoL) (FAOS QoL difference 5.9; 95% CI 0.1–11.8) and the physical component of the SF-12 (SF-12 score difference 2.2; 95% CI 0.0–4.4). Neither the Aircast brace nor the Bledsoe boot was statistically or clinically better. At 12 weeks the below knee cast was significantly better than tubular bandage in terms of pain (FAOS pain difference 5.1; 95% CI 0.3–10.0), activities of daily living (FAOS ADL difference 3.5; 95% CI 0.4–6.6), sports (FAOS sports difference 8.7; 95% CI 1.6–15.7) and QoL (FAOS QoL difference 8.7; 95% CI 2.4–15.0), and the Aircast brace was better only in terms of ankle-related QoL and mental health. The Bledsoe boot conferred no significant advantage over tubular bandage. By 9 months there were no significant differences. Based on mean direct health-care costs per participant, the Bledsoe boot was the most expensive (£215) and tubular bandage the least so (£1.44). Inclusion of indirect costs (sick leave) raised overall costs substantially and removed any significant differences between the therapies. Cost–utility analysis demonstrated that the Aircast brace [£301 per quality-adjusted life-year (QALY)] and below knee cast (£339 per QALY) were more cost-effective than the Bledsoe boot (£2116 per QALY). However, inclusion of indirect costs produced different rank orders, depending on the assumptions made, and results should be treated with caution.
Conclusions: The below knee cast and the Aircast brace offered cost-effective alternatives to tubular bandage for acute severe ankle sprain, the former having the advantage in terms of overall recovery at 3 months. As there were no differences in long-term outcome, practitioners should consider likely compliance and acceptability to patients when choosing a brace.
Trial registration: Current Controlled Trials ISRCTN37807450.

Contents

List of abbreviations

ADL	activities of daily living
ANCOVA	analysis of covariance
APS	Ankle Performance Scale
BMI	body mass index
BNF	*British National Formulary*
CAST	Collaborative Ankle Support Trial
CEAC	cost-effectiveness acceptability curve
CI	confidence interval
CT	computerised tomography
DMEC	Data Monitoring And Ethics Committee
DVT	deep vein thrombosis
EQ-5D	EuroQol 5 dimensions
FAOS	Foot and Ankle Outcome Score
FLP	Functional Limitations Profile
GCSE	General Certificate of Secondary Education
HRQoL	health-related quality of life
ICER	incremental cost-effectiveness ratio
MRI	magnetic resonance imaging
NICE	National Institute for Health and Clinical Excellence
QALY	quality-adjusted life-year
QoL	quality of life
RCT	randomised controlled trial
RR	relative risk
SF-12	short form questionnaire with 12 items
SF-36	short form questionnaire with 36 items
TSC	Trial Steering Committee
VAS	visual analogue scale

All abbreviations that have been used in this report are listed here unless the abbreviation is well known (e.g. NHS), or it has been used only once, or it is a non-standard abbreviation used only in figures/tables/appendices, in which case the abbreviation is defined in the figure legend or in the notes at the end of the table.

Executive summary

Background

The optimal treatment for severe ankle sprains is unclear. Potential treatments include no intervention, physiotherapy, different types of supports, immobilisation and surgical repair of the ligaments. Recent systematic reviews highlight a lack of good-quality evidence to aid clinical decision-making. There is a need for well-conducted and adequately powered randomised controlled trials of the effectiveness of different clinical approaches.

Objectives

Objectives were, first, to estimate the clinical effectiveness of three different methods of ankle support [below knee cast, Aircast® ankle brace (DJO Incorporated, Vista, CA) and Bledsoe® boot (Bledsoe Boot Systems, Grand Prairie, TX)] in comparison with double layer tubular compression bandage in terms of recovery of function (primary outcome), recovery of normal occupation (secondary outcome) and avoidance of residual symptoms including recurrent instability, lasting limitation of physical activity and need for further medical, rehabilitation or surgical treatment (secondary outcomes); and, second, to measure the cost-effectiveness of each strategy, including treatment and subsequent health-care costs.

Design

A pragmatic randomised controlled trial was designed to reflect a model of practice used in the majority of UK hospital emergency departments. It included an integral evaluation of the cost-effectiveness of the different therapies. A total of 584 participants were recruited and randomised to one of four treatment arms: tubular bandage, below knee cast (10 days), Aircast brace or Bledsoe boot. Follow-up was by postal questionnaire at 4 weeks, 12 weeks and 9 months, with response rates of 83%, 82% and 76% respectively.

Participants

Participants aged 16 or over with acute severe ankle sprain, unable to weight bear, with no fracture, were recruited from eight emergency departments across the UK.

Intervention

Treatments were applied 2–3 days after presentation to allow time for swelling to resolve. Participants were given written and verbal instructions regarding the use of supports. Instructions were standardised across all centres and derived from a combination of the manufacturer's recommendations, results of a national survey carried out to inform the design of the trial, and current clinical guidelines.

Main outcome measures

A disease-specific measure [Foot and Ankle Outcome Score (FAOS)] and generic measures [Functional Limitations Profile (FLP), short form questionnaire with 12 items (SF-12) and EuroQol 5 dimensions (EQ-5D)] were used to assess the response to treatment, and information was gathered to assess resource use.

Results

After adjustment for age, sex and baseline score, the below knee cast offered a small but statistically significant benefit at 4 weeks in terms of pain, foot- and ankle-related quality of life (QoL), and the physical component score of the SF-12. Neither the Aircast brace nor the Bledsoe boot was statistically significantly or clinically different from tubular bandage.

At 12 weeks, and in comparison with tubular bandage, the below knee cast was statistically significantly better in terms of pain, activities of daily living, return to sports and QoL. Calculation

of effect sizes suggests that these benefits were small to moderate, depending on the domain of outcome. The Aircast brace was associated with clinically and statistically significant changes in ankle-related QoL and mental health but not in other domains. The Bledsoe boot conferred no significant advantage over tubular bandage.

By 9 months there were no significant differences between the three comparator supports and tubular bandage for any outcome measure.

Economic evaluation results

Mean direct health-care costs per participant indicated that the Bledsoe boot was the most expensive support (£215 including fitting), with tubular bandage the least expensive (£1.44); Aircast (£39.23) was more expensive than the below knee cast (£16.46). Inclusion of indirect costs (sick leave) raised overall costs substantially, resulting in no significant difference between the groups.

Cost–utility analysis, comparing incremental costs with the differential impact on health-related quality of life over 9 months, demonstrated that the Aircast brace [£301 per quality-adjusted life-year (QALY)] and below knee cast (£339 per QALY) were more cost-effective than the Bledsoe boot (£2116 per QALY). Cost-effectiveness acceptability curves confirmed that the Bledsoe boot was least cost-effective and that the Aircast brace and below knee cast differences were broadly similar.

Inclusion of indirect costs produced different rank orders depending on the assumptions made; results should be treated with some caution.

Conclusions

Ankle sprains with an inability to weight bear have a prolonged recovery. The prognosis should be cautious, explaining that the injury, independent of treatment, has a significant risk of some disability in the form of symptoms, limitations of mobility or activities at 9 months.

Such patients, initially treated with 2–3 days of elevation, ice and non-weight-bearing exercise, had a more rapid resolution of symptoms and return to normal activities in the first 3 months when treated with a below knee cast for 10 days than when treated with tubular bandage.

By 9 months all treatments were equally effective. Mental health deteriorated in the early stages of recovery but returned to normal by 12 weeks. The study suggests that choice of treatment may affect speed of recovery but not long-term outcome.

Implications for health care

Two devices appeared to offer cost-effective alternatives to tubular bandage: the below knee cast and the Aircast brace. The below knee cast resulted in the fastest recovery and higher levels of sporting function and overall quality of recovery by 3 months. There were no differences in long-term outcome and the decision about which brace to apply should incorporate an assessment of likely compliance and acceptability to patients.

Recommendations for research

1. The role of physiotherapy is not known in these injuries. In view of the poor prognosis in relatively active people, the effects of a regime of physiotherapy during and after the period of functional support or as an alternative to immobilisation should be investigated.
2. There are still no adequately powered studies of less severe ankle sprains.
3. In the UK, anticoagulants are not routinely used in lower limb injury, whereas this is standard practice in most of mainland Europe. More research is needed to determine the risk–benefit of such strategies.

Trial registration

This trial is registered as ISRCTN37807450.

Chapter 1
Introduction

Background

Acute ankle sprain is one of the most common conditions seen in UK emergency departments, accounting for between 3% and 5% of all UK emergency department attendances[1] and approximately 5600 injuries each day.[2] The majority of ankle sprains involve the lateral ligament complex[3] (*Figure 1*), accounting for one-quarter of all sports injuries.[4] The injury is painful and incapacitating and, unless the injury is minor, weight bearing is difficult to tolerate. Lateral ligament sprains are widely viewed as being uncomplicated and self-limiting. However, several studies have shown that, although the acute symptoms resolve, residual symptoms can persist for months or even years after the initial injury.[5] One long-term follow-up study[6] showed that, 7 years post injury, 32% of subjects experienced chronic complaints of pain, swelling or recurrent sprains. Early effective treatment is not only crucial to promote a speedy resolution of acute symptoms but also an important feature in limiting the chronicity of the injury.[5]

Classification of ankle sprains

Sprains of the lateral ligament complex of the ankle vary in severity. The anterior talofibular ligament (ATFL) is always first to be injured, and in severe sprains the calcaneofibular ligament (CFL) is also disrupted (see *Figure 1*). A classification of the severity of ankle sprains has been developed by Crichton *et al.*[7] (*Table 1*).

Diagnosis of the grade of sprain in the emergency department is usually guided by the presenting clinical features. Previous trials have described diagnosing the grade of injury using stress radiography,[8–10] arthrography[11,12] or both.[13,14] Such diagnostic methods are rarely used clinically, making their results difficult to generalise into the clinical setting. Other studies have used talar tilt and anterior drawer tests to indicate the severity of the injury.[15–17] These tests are more easily incorporated into an elective orthopaedic examination, but are difficult to perform accurately in the first few hours following a sprain, when there is gross swelling and the tests themselves induce pain. Evidence shows that it is difficult to gauge the severity of sprain accurately in the acute situation,[18] and so the degree of severity is usually assessed based on the ability to weight bear and the extent of the pain, swelling and bruising.

Treatment of grade I and minor grade II injuries is generally conservative. Traditional teaching advocates ice, compression and elevation of the affected limb together with anti-inflammatory medication in the early phase,[19] although there is less consensus on the value of initial rest or early mobilisation. Optimal treatment for severe sprains (grade III), however, remains unclear. Treatments described include no intervention, physiotherapy, different types of brace and supports, immobilisation and surgical repair of the ligaments. Recent systematic reviews highlight a lack of good-quality evidence to aid clinical decision-making in managing these injuries.[2,7]

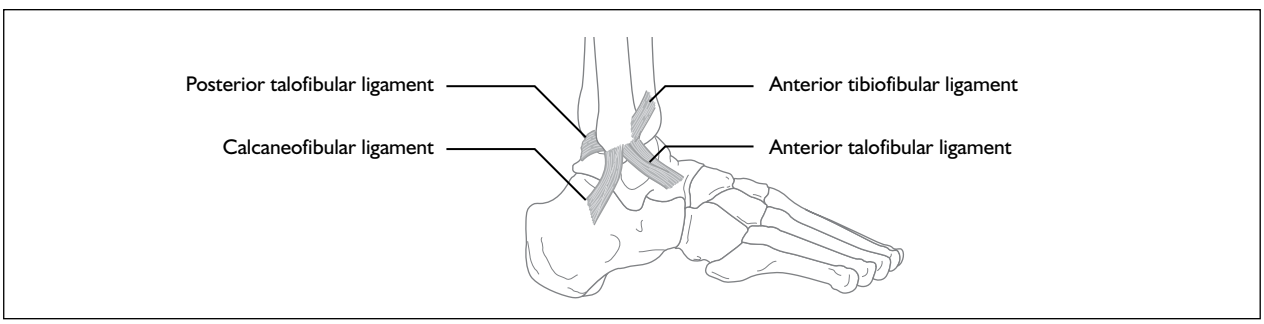

FIGURE 1 *Lateral ligaments of the ankle.*

TABLE I *Classification of ankle sprains*

Grade	Ligament	Joint stability	Anterior draw test	Symptoms
Grade I	Stretched but not torn	Stable	Negative	Minimal swelling and pain and mechanical function is hardly affected; can weight bear
Grade II	Partially torn	Some laxity	Some laxity	Moderate swelling and pain; partial or non-weight bearing
Grade III	Ligament complex is completely ruptured	Unstable	Positive	Severe pain, swelling, bruising and loss of function; unable to weight bear

Review of treatment of ankle sprains

Current practice

A recent survey of the management of severe (grades II and III) ankle sprains in UK emergency departments demonstrated the variation in treatment across the country.[20] The questionnaire was sent to all UK emergency departments seeing more than 50,000 new patients per year and received a 70% response rate (83 out of 118). The most popular treatments reported were ice, elevation, tubular bandage and exercise. Each of these was reported to be used in most cases by over 70% of respondents. Crutches, early weight bearing and non-steroidal anti-inflammatory drugs were each reported as used in most cases at over half of responding departments. Physiotherapy was usually used only in selected cases. Rest was usually advised for 1–3 days (35%). Follow-up was only recommended for selected patients.[20]

Current treatment alternatives

The three main treatments for severe ankle sprain are:

1. surgery
2. immobilisation
3. functional treatment.

Surgery

A recent Cochrane review[21] compared immobilisation in a plaster cast for up to 6 weeks with surgical repair. Significantly better results were found in the surgical group in the outcomes of return to sports and objective instability (although the authors questioned the clinical relevance of this). For the majority of outcomes, however, the pooled data failed to demonstrate a clearly superior treatment approach, and there was also some evidence of stiffness and restriction in ankle mobility after surgery. The authors stressed that, because of the heterogeneity in the results for the primary outcomes (pain, subjective instability and recurrence), the evidence should be interpreted with caution. All of the trials were considered to have methodological flaws and all but one of the trials were conducted more than 15 years ago, reflecting past practice, including more invasive surgical techniques. Recent studies of ankle ligament reconstruction have tended to focus on repair of the ligaments in patients with chronic instability[22–24] rather than primary repair of an acute injury.

It is widely documented that secondary surgical repair months or even years after the injury can be performed with comparable results to primary repair.[25–27] The current recommendation for treatment for acute lateral ligament injury is, therefore, conservative treatment.[21]

Immobilisation

Immobilisation is defined as any therapy that prevents movement of the ankle joint in both flexion/extension and inversion/eversion.

Studies of immobilisation have often used a period of several weeks in a cast.[10,14,15] A recent Cochrane review[28,29] showed that functional treatment (see next section) appeared to be better than immobilisation for several outcomes including a quicker return to sport and work and increased patient satisfaction. However, only 52% of included studies fit the criteria for high-quality studies, and most of the differences were found not to be significant after exclusion of the low-quality trials; many trials were poorly reported and there was heterogeneity amongst the functional treatments and duration of treatment evaluated. The current trend in lateral ankle ligament injury treatment is away from immobilisation[8,30,31] in favour of active mobilisation.[32]

Functional treatment

Functional treatment consists of a programme of early mobilisation that may include some initial external support to the ankle. The support may be in the form of an elasticated bandage, strapping, lace-up boots or an external orthosis, and the use of crutches has also been described as part of a functional treatment strategy.[8,33] The orthosis may prevent inversion/eversion but will allow some degree of flexion/extension. Immobilisation and functional treatment are not mutually exclusive methods as some regimes have an initial short period of immobilisation followed by functional treatment.

A recent meta-analysis of treatments for ruptures of the lateral ankle ligaments[2] found that operative treatment leads to better results than functional treatment, and functional treatment leads to better results than cast immobilisation for 6 weeks. However, most of the studies included were of poor quality and the meta-analysis classed all forms of functional treatment together, meaning that it was not possible to draw distinctions between the different methods.

A Cochrane review of different types of functional treatments[29] concluded that use of an elastic bandage had fewer complications than use of strapping but was associated with a slower return to work and sport and more reported instability than with use of a semi-rigid ankle support. Lace-up supports were effective in reducing swelling in the early phase compared with semi-rigid ankle support, elastic bandage and strapping. However, because of the variety of treatments used and the inconsistency of follow-up and outcome measures in the existing evidence, the most effective functional treatment is still unclear.

A recent trial comparing the use of elastic support bandage and the Aircast® (DJO Incorporated, Vista, CA) brace concluded that the Aircast brace produced significant improvement in ankle joint function at 10 days and 1 month compared with standard management with an elastic support bandage.[34] However, the trial reported results on only 35 patients and was not of high methodological quality.

Current clinical evidence suggests that functional treatment is more beneficial than immobilisation and leads to improved symptoms and functional outcomes at short (< 6 weeks), intermediate (6 weeks to 1 year) or long term (> 1 year) follow-up, although effects are less marked at long-term follow-up.[35]

Additional treatments

These treatments are usually additional to one of the methods outlined above and include:

1. Ice (cryotherapy) – one randomised controlled trial (RCT) found no significant difference in symptoms between cold pack placement and placebo (simulated treatment); one RCT found less oedema with cold pack placement compared with heat or a contrast bath at 3–5 days after injury.[36]
2. Elevation – elevation of the injured limb lowers the pressure in local blood vessels, helping to limit bleeding and improving the drainage of inflammatory exudate through the lymph vessels, reducing oedema. Studies have shown that elevation above the subject's heart level can help to reduce swelling and to increase drainage of the extravascular fluid away from the injured area.[35,37]
3. Physiotherapy:
   i. exercise therapy – there is limited evidence that the addition of supervised exercises to a conventional treatment approach results in greater reduction in swelling and a faster return to work[38]
   ii. diathermy – one systematic review found insufficient evidence on the effects of diathermy compared with placebo on walking ability and reduction in swelling[39]
   iii. ultrasound – a Cochrane review has recently concluded that the extent and quality of the available evidence for the effects of ultrasound therapy for acute ankle sprains is limited; the results of four placebo-controlled trials do not support the use of ultrasound in the treatment of ankle sprains and the magnitude of most reported treatment effects appeared to be small and they may be of limited clinical importance; as yet, only a few trials are available and no conclusions can be made regarding an optimal and adequate dosage schedule for ultrasound therapy and whether such a schedule would improve on the reported effectiveness of ultrasound for ankle sprains[40]
   iv. laser therapy – an RCT has shown that neither high- nor low-dose laser therapy is effective in the treatment of lateral ankle sprains.[41]

Context of the CAST trial

Three Cochrane reviews of different treatments for lateral ankle ligament injuries have been

conducted,[21,28,29] but none has been updated since 2002. To provide a context for the CAST trial, and to identify any new research since 2002, the search strategies of the Cochrane reviews of immobilisation versus functional treatment[28] and of different functional treatments[29] were rerun. Any new studies found were added to the results of the Cochrane review and the meta-analysis was repeated. The search strategy is detailed in Appendix 1.

Update of Cochrane reviews relevant to the CAST trial

Study selection

Types of studies

Randomised and quasi-randomised controlled trials comparing either immobilisation with functional treatment or different methods of functional treatment for injuries to the lateral ligament complex of the ankle were considered.

Types of participants

Studies recruiting adults who had sustained an acute injury to the lateral ligament complex of the ankle were eligible for inclusion. Studies involving children, patients with congenital deformities and patients with degenerative conditions were excluded. Trials that focused on the treatment of chronic instability or post-surgical rehabilitation were also excluded.

Types of intervention

The first Cochrane review under consideration (immobilisation versus functional treatment)[28] compared immobilisation (either by plaster cast or special boots) with three other interventions:

1. physiotherapy
2. functional treatment
3. non-intervention.

The relevant comparison for the CAST trial is immobilisation with functional treatment. Studies looking at physiotherapy or no intervention were therefore not included in this rerun of the review.

The second Cochrane review under consideration (different functional treatments)[29] included trials that compared one type of functional treatment with another but excluded those that compared different types of the same category of functional treatment. Four categories were used:

1. elastic bandage
2. strapping
3. lace-up ankle support
4. semi-rigid ankle support.

Types of outcome measures

The outcome measures used in the Cochrane reviews that are relevant to the CAST study are:

1. return to pre-injury level of work (yes/no; time to achieve)
2. return to pre-injury level of sport (yes/no; time to achieve)
3. pain (yes/no)
4. subjective instability (e.g. 'giving way') (yes/no)
5. recurrent injury (yes/no).

Follow-up times were grouped according to the Cochrane review:

(a) short term – within 6 weeks of randomisation
(b) intermediate term – 6 weeks to 1 year of follow-up
(c) long term – 1–2 years after treatment.

The literature searches were reviewed by two reviewers (RN and MWC) to identify any new potentially relevant trials from the title and abstract. From the full text two reviewers independently selected trials for inclusion in the review. Any disagreement was resolved by consensus.

Quality assessment

The method used in the Cochrane reviews to assess study quality was replicated in this review. Studies were assessed for quality without masking.[42] The quality assessment tool used was a modification of the generic evaluation tool used by the Cochrane Musculoskeletal Injuries Group. The tool covers 11 aspects of internal and external validity and is shown in *Table 2*. In the Cochrane review the cut-off point for high- and low-quality trials was set at 50% of the maximum score.

Data extraction

Data were independently extracted by two reviewers [RN and Simon Gates (SG)]. Extracted data included country of research, treatment interventions, number of participants randomised to treatment and control groups, outcome measures used and method of diagnosis.

Data synthesis

The data were analysed using the Cochrane review manager software (RevMan version 4.2; Oxford, UK). The analyses carried out in the Cochrane review[28,29] were repeated, if appropriate,

TABLE 2 *Quality assessment tool*

A. Was the assigned treatment adequately concealed prior to allocation?	2 = method did not allow disclosure of assignment 1 = small but possible chance of disclosure of assignment or unclear 0 = quasi-randomised or open list/tables Cochrane code: clearly yes = A, not sure = B, clearly no = C
B. Were the outcomes of patients who withdrew described and included in the analysis (intention to treat)?	2 = intention to treat analysis based on all cases randomised possible or carried out 1 = states number and reasons for withdrawal but intention to treat analysis not possible 0 = not mentioned or states number of withdrawals only
C. Were the outcome assessors blinded to treatment status?	2 = effective action taken to blind assessors 1 = small or moderate chance of unblinding of assessors 0 = not mentioned or not possible
D. Were the treatment and control groups comparable at entry?	2 = good comparability of groups, or confounding adjusted for in the analysis 1 = confounding small; mentioned but not adjusted for 0 = large potential for confounding or not discussed
E. Were the subjects blind to assignment status after allocation?	2 = effective action taken to blind subjects 1 = small or moderate chance of unblinding subjects 0 = not possible or not mentioned (unless double blind), or possible but not done
F. Were the treatment providers blind to assignment status after allocation?	2 = effective action taken to blind treatment providers 1 = small or moderate chance of unblinding treatment providers 0 = not possible or not mentioned (unless double blind), or possible but not done
G. Were care programmes, other than the trial options, identical?	2 = care programmes clearly identical 1 = clear but trivial differences 0 = not mentioned or clear and important differences in care programmes
H. Were the inclusion and exclusion criteria clearly defined?	2 = clearly defined 1 = inadequately defined 0 = not defined

including any new studies found as a result of the up-to-date search. In fact, only one new study was added to the comparison of immobilisation versus functional treatment[31] (see next section), and the only new study comparing different functional treatments[34] was not deemed of sufficient quality to be included and this analysis was not repeated. Results of similar studies were pooled using fixed-effects models. Individual and pooled statistics were reported as relative risks (RRs) with 95% confidence intervals (CIs) for dichotomous outcomes and weighted or standardised mean differences and 95% CI for continuous outcomes. A standard chi-squared test was used to test statistical heterogeneity between trials.

Results of the literature review

Trial flow

A flow chart summarising the study selection process is shown in *Figure 2*.

Study characteristics

The Cochrane review[28] of immobilisation versus functional treatment identified 20 trials[10,15,16,31,43–49,51–57] enrolling 2120 participants. Of these, seven trials compared immobilisation

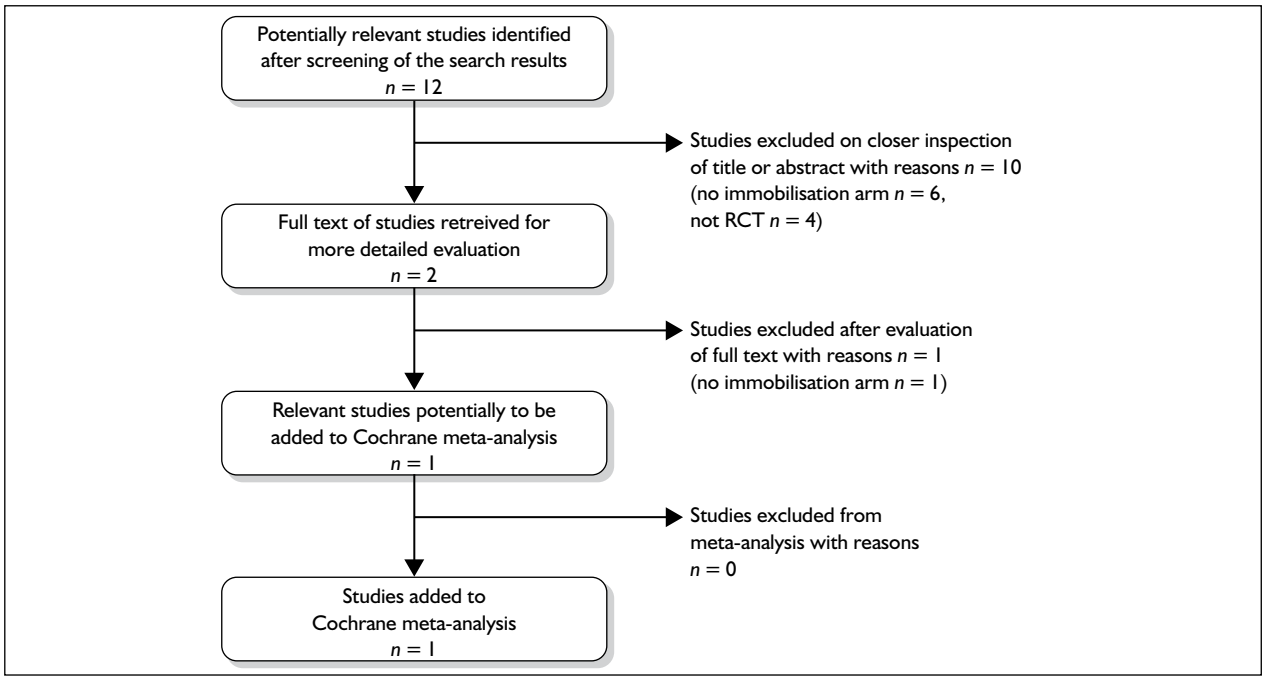

FIGURE 2 *Study selection process. RCT, randomised controlled trial.*

with the use of an ankle brace,[15,16,47–51] five trials compared immobilisation with an elastic bandage,[43–45,52,53] four trials compared immobilisation with strapping[14,51,54,55] and five trials compared cast immobilisation with treatment using a softcast or wrap.[8,10,46,56,57] The rerun of the search strategy identified only one new trial fulfilling the inclusion criteria,[31] comparing immobilisation with strapping. The trial enrolled 121 participants and used outcomes of pain, subjective instability and recurrent injury.

In the trials reported, participants were likely to be young (< 50 years) and trials tended to include a higher percentage of males. Seven of the Cochrane trials were initially deemed to be of high quality (i.e. scoring higher than 50% on the quality assessment tool).[8,10,44,46,48,52,54] After additional information was retrieved from the authors, three further trials were categorised as high quality.[45,50,56] The new study[31] was assessed for quality using the same tool by two independent reviewers (RN and SG) and was deemed to be of high quality.

The Cochrane review of different functional treatments[29] identified nine trials[33,47,51,58–63] enrolling 892 participants; however, none of the trials used the same intervention comparisons. Of these nine trials, four compared elastic bandage and strapping,[59,60,62,63] four compared elastic bandage with a semi-rigid ankle support,[33,47,61,63] one compared elastic bandage with strapping,[63] two compared strapping with semi-rigid ankle support,[51,63] two compared strapping and lace-up ankle support[58,63] and one compared semi-rigid with lace-up ankle support.[63] The new study[34] compared semi-rigid ankle support with elastic bandage, with a primary outcome of ankle joint function.

The mean validity score of the nine trials reported was 10.8 points (range 5–15 points, maximum attainable 22 points); following retrieval of additional information from authors the mean validity increased to 10.9 (SD 2.9). An additional study,[34] which enrolled only 50 participants and reported results for only 35 patients, was deemed to be of insufficient quality for inclusion; it was also assessed for quality using the same tool by two independent reviewers (RJ and SG) (validity 10.5 points). The existing Cochrane review results, therefore, have not been amended.

Quantitative data synthesis

For the review of immobilisation versus functional treatment, data were extracted for the outcomes of return to pre-injury level of work and sports activities, pain, subjective instability and recurrent injury. The new study identified from the rerun of the Cochrane literature search was added to the studies in the Cochrane review[28] and the meta-analysis was repeated.

Meta-analysis: pain

The new study[31] was added to the nine studies of the Cochrane review that reported whether the patient was experiencing pain after treatment. This is the only parameter for which the results of the original Cochrane analysis were changed by the addition of the new study (*Figure 3*). Four studies reported short-term results (6 weeks),[8,15,31,47] six reported intermediate results (6 weeks to 12 months)[8,15,31,47,53,56] and six reported long-term results (> 12 months).[8,10,31,46,55] The original Cochrane analysis showed no significant differences at any follow-up time point; addition of the new study altered these results showing that significantly fewer patients reported pain in the functionally treated group at both the short time point (3 months) (RR 1.6, 95% CI 1.20–2.08) and intermediate time point (12 months) (RR 1.6, 95% CI 1.08–2.40) compared with the immobilisation group. It is however possible that such change in updated meta-analyses can have occurred by chance.

Rationale for the CAST trial

The updating of these two Cochrane reviews shows clearly that there is a lack of high-quality

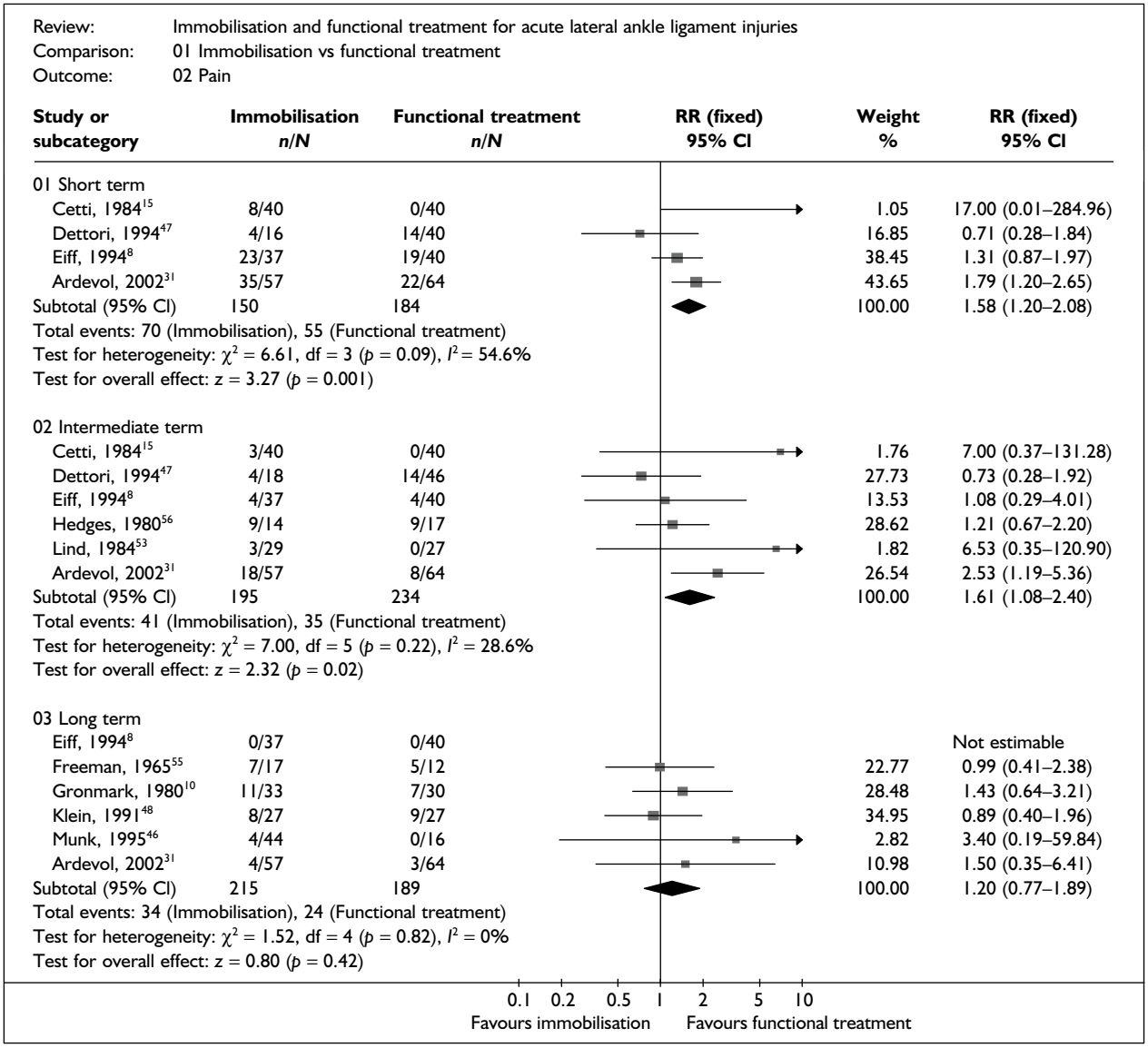

FIGURE 3 *Meta-analysis of effects of immobilisation vs functional treatment on pain, including the new study.*[31]

evidence to support clinical decisions about which type of treatment is best in the management of severe ankle sprains. Present evidence suggests that functional treatment is better than either immobilisation (for longer than 3 weeks) or no treatment. There remains a need for a well-conducted and adequately powered RCT of the clinical effectiveness and cost-effectiveness of different clinical approaches. Our survey of current practice[20] was used to inform decisions about the design of this trial. We selected three treatments to compare with tubular bandage, which between them represented one method of functional treatment (Aircast brace), one immobilisation method (below knee cast) and one intermediate method [Bledsoe® boot (Bledsoe Boot Systems, Grand Prairie, TX)]. The different methods also allowed varying degrees of ankle movement: full immobilisation (below knee cast), flexion/extension only (Aircast brace) and full range of movement (tubular bandage). In addition, three of the devices allowed the patient to exercise their ankle (tubular bandage, Bledsoe boot, Aircast brace) whereas one allowed no exercise regime (below knee cast).

The trial was designed to be pragmatic in nature and to reflect a model of practice used in the majority of UK hospital emergency departments. It included an analysis of the cost-effectiveness of the different therapies.

Chapter 2
Methods

Trial design

The Collaborative Ankle Support Trial (CAST) was a pragmatic multicentred RCT with blinded assessment of outcome. It was designed to estimate the clinical effectiveness and cost-effectiveness of three different types of mechanical support in the treatment of severe ankle sprains compared with tubular bandage [Tubigrip® (AliMed, Dedham, MA) was used in this study].

People attending selected emergency departments in England who had sustained a sprain of the ankle (ligamentous injury) and were unable to weight bear were identified at the time of presentation. The inability to weight bear was used as a proxy for a diagnosis of a grade II or III ankle sprain as classification is not possible in the acute stage. Potential participants were invited to join the trial and to attend a follow-up clinic 2–3 days following injury where they were randomised to one of four treatment arms: (1) tubular bandage, (2) Bledsoe boot, (3) Aircast ankle brace or (4) below knee cast.

Tubular bandage was chosen as the reference treatment following results of the national survey undertaken immediately before this study showing it to be the most common treatment.[20,64] The Bledsoe boot, costing £212.68, is many times more expensive than tubular bandage and its clinical effectiveness is yet to be proven. The cast was a conventional below knee walking cast and was applied for 10 days. The Aircast brace (£38.19) was chosen from the range of ankle supports available.

Research physiotherapists recruited and randomised participants at the follow-up clinic and undertook baseline assessments. Appropriately trained health professionals applied interventions to a defined standard. All other treatments were standardised and included ice, elevation, crutches and pain-relieving medications if needed. We felt that withdrawal of these treatments would be inappropriate as they constitute normal and accepted care. Outcomes were measured to reflect short- and longer-term recovery and possible complications. A health economics analysis was included.

Method of application

A double layer of tubular bandage was applied from the level of the tibial tuberosity to the base of the toes. Sizing of the tubular bandage was undertaken as per the manufacturer's instructions. Patients were instructed to remove the tubular bandage at night.

The Bledsoe boots were sized and applied according to the manufacturer's instructions (supplied with each device; available at www.bledsoebrace.com) with advice to remove at night.

The Aircast splint was sized and applied according to the manufacturer's instructions (supplied with each device; available at www.aircast.com). The below knee cast was applied from the level of the tibial tuberosity to the base of the toes. A layer of Tubinette® (Mölnlycke Health Care, Göteborg, Sweden) and a layer of padding were applied under a complete synthetic non-flexible cast.

Objectives

The trial had two objectives:

1. to estimate the clinical effectiveness of three different methods of ankle support (below knee cast, Aircast ankle brace and Bledsoe boot) compared with tubular double layer (tubular bandage) in terms of the recovery of function (primary outcome); the recovery of normal occupation, including return to normal work, study, caring or other activities (secondary outcome); and avoidance of residual symptoms including recurrent instability, lasting limitation of physical activity and need for further medical, rehabilitation or surgical treatment (secondary outcomes)
2. to measure the cost-effectiveness of each strategy, including treatment and subsequent health-care costs.

Participants

Participants were recruited from the emergency departments of eight collaborating hospitals: John

Radcliffe Hospital, Oxford; Frenchay Hospital, Bristol; Coventry and Warwickshire Hospital, Coventry; Hospital of St Cross, Rugby; Heartlands Hospital, Birmingham; Alexandra Hospital, Redditch; Solihull Hospital, Solihull; and Warwick Hospital, Warwick.

Inclusion criteria

- Patients attending emergency departments with sprain of the ankle and an inability to weight bear at the time of presentation to the emergency department and their review clinic appointment.
- Age 16 years and older.
- Able to give informed consent.

Exclusion criteria

- Age less than 16 years (because of the possibility of confusion with epiphyseal injuries).
- Ankle fracture (except flake fractures of less than 2 mm as these are normally treated as soft-tissue injuries).
- Any other recent fracture.
- Any contraindication to any of the four arms of the trial (this criterion was added following the pilot study).
- Poor skin viability preventing splinting or casting.
- Injury more than 7 days previously.

Trial procedure

Recruitment

A standard approach was instituted across all participating hospitals. People who attended emergency departments with an ankle sprain were assessed for injury severity by emergency department medical staff who completed a standard proforma (Appendix 2), which recorded details such as the ability to weight bear, talar tilt and anterior draw test to assess stability. Radiography was used to exclude fracture when this was clinically indicated and as guided by the Ottawa guidelines.[65] People able to weight bear and those with a fracture were not eligible for the trial and were managed in accordance with normal practice. All those who could not weight bear (proxy for grade II and III injuries) were referred to a follow-up emergency department clinic, which reflected national normal practice reported in the survey undertaken[20] (*Figure 4*). Emergency department staff were asked to provide participants with information, a letter inviting them to join the trial (Appendix 3) and a patient information sheet (Appendix 4). Between the time of presentation and the clinic all participants had identical self-treatment consisting of analgesia, ice and elevation combined with an exercise regime as tolerated. Patients were advised to mobilise as tolerated and were provided with crutches as appropriate. Written advice was given to all participants (Appendix 5).

The follow-up clinic was 2–3 days after emergency department attendance. This delay was introduced for three reasons. First, a period of elevation and ice is widely advocated to reduce swelling and one of the treatments (the below knee cast) is contraindicated in the first few days because of the risk of developing a compartment syndrome if swelling increases. Second, it is difficult to accurately assess injury severity at initial presentation. The symptoms associated with grade I sprains resolve rapidly and the time delay allowed additional assessment of injury severity. Last, the delay allowed participants sufficient time to consider their involvement in the trial. If clinic attendance was not possible within 7 days of injury the patient was not eligible.

A record was made of all people who had an ankle sprain and were non-weight bearing at presentation in the emergency department to monitor referral and attendance rates at the follow-up clinic. At the follow-up clinic participants were given a full verbal explanation of the trial by the trial research physiotherapists. Informed consent was obtained from eligible and willing participants (Appendix 6). The reasons for declining to participate in the trial were recorded, along with age, sex, ethnicity and severity of injury of all people approached. The research physiotherapist performed a short baseline interview (Appendix 7) to ensure eligibility for randomisation and, after randomisation, the participant completed the baseline questionnaire (Appendix 8). This collected details that included date of birth, age, sex, body mass index (BMI), ethnicity and an assessment of pre-injury abilities including usual levels of mobility, engagement in sporting activity and usual occupation and employment (including hours worked and type of work undertaken), together with a brief examination of weight-bearing status (measured using weighing scales) and pain. Pre-injury quality of life was measured using the EuroQol 5 dimensions (EQ-5D).[66]

Optimising recruitment

A variety of methods were used to optimise recruitment. The challenges to recruitment in this

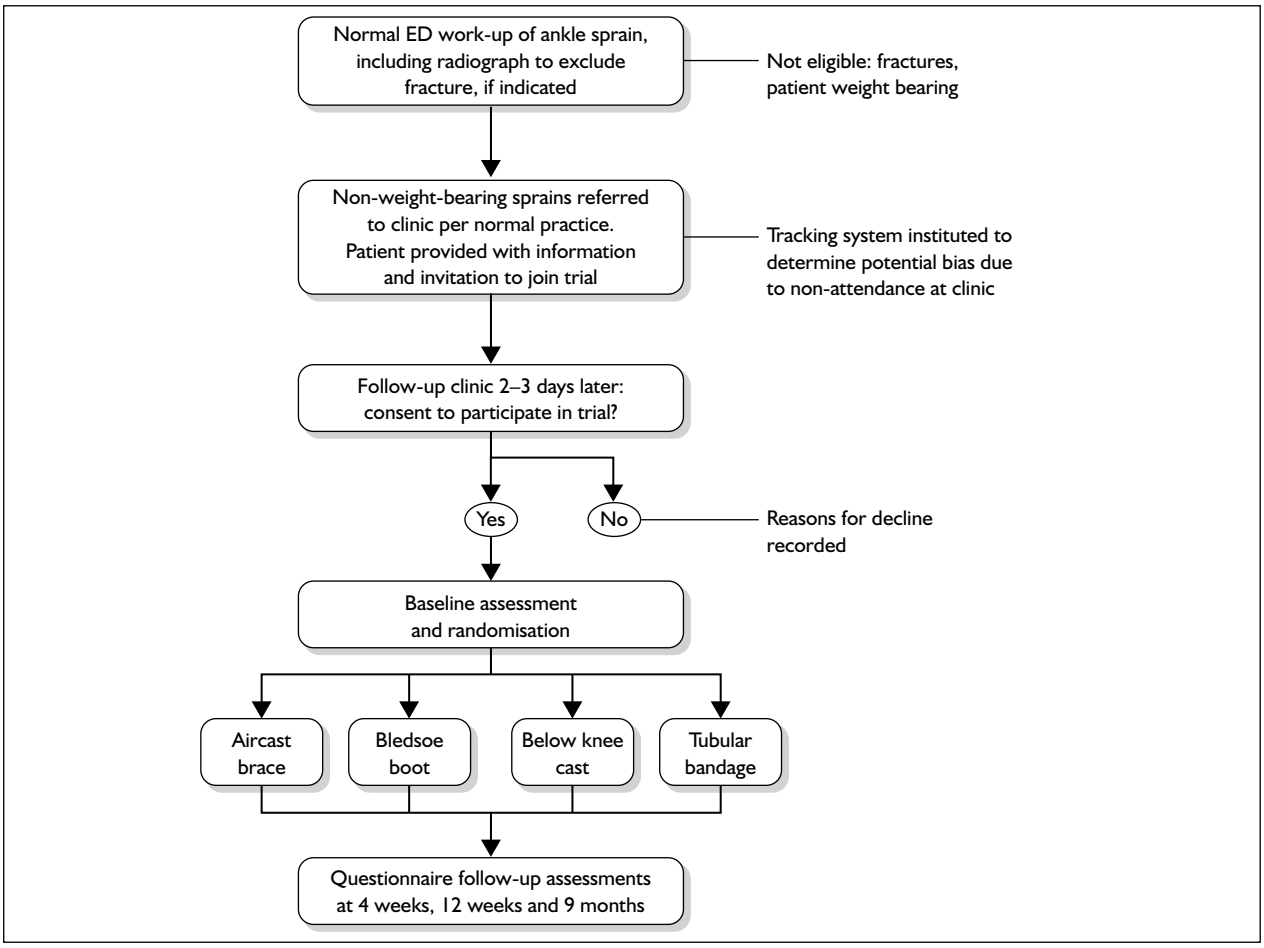

FIGURE 4 *Flow chart of participant progress. ED, emergency department.*

trial have been reported elsewhere (see Appendix 9). Techniques included:

- teaching sessions for emergency department medical staff, emergency nurse practitioners and nurses
- posters within the emergency department
- trial logo screensavers
- regular contact between recruitment physiotherapists and emergency department staff
- audits of recruitment (Appendix 10).

Randomisation

Simple randomisation was used, stratified by centre. This was provided by the Cancer Trials Unit at the University of Birmingham via telephone. Allocation concealment was ensured by using a remote computer-generated randomisation system independently administered and quality controlled. Sealed envelope randomisation was employed over bank holiday periods.

Blinding

A research assistant, independent of all recruitment and randomisation procedures, was responsible for mailing questionnaires and entering responses into the computerised database (Microsoft Access). Blinding of the intervention was maintained until the final analysis of the data was completed.

Interventions

Experimental treatments

The health technologies being assessed were three different methods of mechanical support for ankle sprains. The interventions were applied in the emergency department follow-up clinic by an appropriately trained health professional. Responsibility for application of braces varied

between hospitals, being undertaken by a plaster technician, physiotherapist or nurse; all staff were provided with a standardised training package as part of the trial. Each participant had their Bledsoe boot, Aircast splint, below knee cast or tubular bandage fitted individually to ensure comfort and correct fit. If participants refused the treatment to which they were randomised the default strategy was to give them tubular bandage instead. Participants were provided with standardised written and verbal instructions (Appendix 11) that included continuing reduction of swelling, when to remove the brace, encouragement of normal walking within limits of tolerance, simple exercise advice, what to do in the event of experiencing difficulties with the device and washing instructions. These protocols were established with reference to the manufacturer's recommendations, the results of the national survey[20] and current clinical guidelines. Treatments were applied within 7 days of the injury and within a few hours of randomisation.

Other treatments

The prescription of walking aids, elevation, pain-relieving medications and ice were permitted but were defined by a protocol reflecting current national practice. Physical therapy techniques including musculoskeletal assessment, soft-tissue mobilisations, manipulations, massage, gait re-education, contrast baths, electrotherapy and supervised exercise or exercise classes were not permitted as part of the trial treatment protocol. However, if during or following the trial treatment period participants were considered by the relevant clinician to need physiotherapy, this was permitted but was classed as an outcome.

Follow-up

Handling withdrawals

Participants were free to withdraw from the trial at any time. When possible, reasons for withdrawal were ascertained, including any potential dissatisfaction with the treatment proposed or provided.

Loss to follow-up

Loss to follow-up has been a problem in previous trials of ankle sprain management, particularly when these have involved participants attending follow-up research clinics at the hospital.[67] Postal questionnaires were used in an attempt to minimise loss to follow-up, and a system of reminder letters and telephone calls (*Figure 5*) was instituted to follow up those who did not return their questionnaires. Term-time and holiday addresses were obtained from those participants who were students. If, following completion of the measures shown in *Figure 5*, participants still did not return questionnaires they were telephoned by a researcher and asked to give answers to key questions over the phone. This enabled us to collect core outcome data for analysis.

Questionnaires

The layout of questionnaires was designed to minimise the possibility of systematic missing responses, for example avoidance of single-sided photocopying and other recommendations for increasing the return rate.[68]

Resource use

For data relating to resource use and complications we obtained consent at the beginning of the study to access participant records. This enabled additional information to be gained when participants were lost to follow-up and was used to assess whether data were missing at random and to model the effects of missing data.

Outcome measures

All measures were taken at baseline and at 4 weeks, 12 weeks and 9 months after the injury (*Table 3*). At 12 weeks and 9 months the questionnaire included use of resources.

Primary outcomes

1. Foot and Ankle Outcome Score (FAOS).[69] This questionnaire evaluates symptoms and functional limitations related to ankle injuries and has been validated against objective tests of ankle function.[69] There are five subscales: pain, other symptoms, function in activities of daily living (ADL), function in sport and recreation, and foot- and ankle-related quality of life (QoL). A normalised score (100 indicating no symptoms and 0 indicating extreme symptoms) is calculated for each subscale. The subscales are not summed and, to guide interpretation of the trial, we identified ankle-related quality of life as providing the best overall assessment of quality of recovery of ankle function.
2. The Functional Limitations Profile (FLP) is the British version of the Sickness Impact Profile.[70] The ambulatory subscale was used to provide detailed information on the impact of the injury and treatment. This included information on adaptations that occur after the injury, for example participants returning

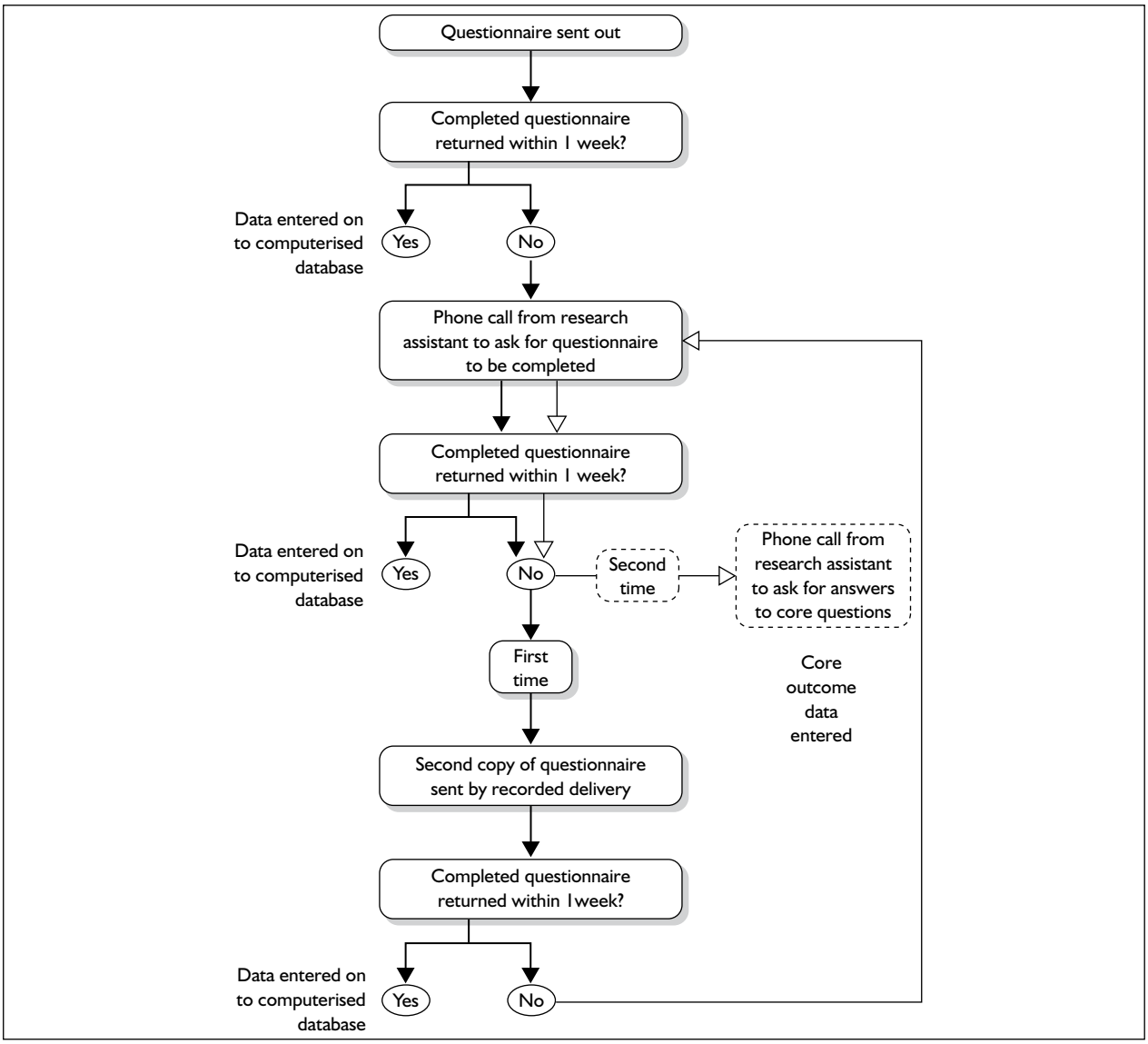

FIGURE 5 *Flow chart of method used to maximise questionnaire return for CAST.*

to a different type of job or to the same job but with reduced function compared with their pre-injury role. Scoring is from 0 to 100, with a lower score meaning a better result. This profile has been used for past injury assessment and has been validated in this environment but it has not been used specifically in ankle injuries.

Secondary outcomes

1. The short form questionnaire with 12 items (SF-12) version 1[71] was used to quantify the recovery of normal occupation and mobility and the broader impact of the treatments on health-related quality of life (HRQoL). The SF-12 was chosen over the the short form questionnaire with 36 items (SF-36) following the pilot study, to reduce the risk of 'questionnaire fatigue'.
2. The EQ-5D[66] measures health on five dimensions and includes a tariff for deriving a single utility score based on time trade-off utility scores. It was used to conduct an economic evaluation.
3. Visual analogue scale (VAS). Participants were asked to mark a vertical point on a 10-cm horizontal line to show how much pain they

TABLE 3 *Primary and secondary outcome measures*

Outcome	Domain	Measures
Primary	Return to function	Foot and Ankle Outcome Score (FAOS), Functional Limitations Profile (FLP) ambulatory assessment
Secondary	Return to mobility and occupation, health-related quality of life (HRQoL) measures	Time to return to occupation, time to return to leisure/sports activities, EQ-5D/SF-12
Secondary	Resource use	Resource use questionnaire

had in their ankle at rest and when weight bearing, with 0 = no pain and 100 = the worst pain imaginable.

4. Benefit scale. Participants were asked to rate the benefit that they had received from their treatment at 12 weeks and 9 months on a scale from 0 to 10, where 0 = no benefit and 10 = maximum benefit.
5. Return to normal occupation and leisure activities. The date that people returned to work and normal activities was recorded.
6. Resource use. At 12 weeks and 9 months an additional questionnaire was completed (see Appendix 12) to determine any additional treatments that had been used for the ankle injury. It identified whether any such treatment was obtained through the NHS or privately and, if privately, whether this had been paid for by the individual or by a private health-care provider. Participants were asked about the number and types of medications and treatments that they had purchased, including pain-relieving medications, gels or other topical agents, bandages, braces or footwear. Participants were asked to distinguish between prescription and out-of-pocket expenses. Hospital notes and records were audited for information on service use. Primary care records were not retrieved.
7. Pre-injury abilities. Participants were asked to provide information on type of occupation and sports and leisure activities in the month before the injury.

Statistical methods

Sample size calculation

This was based on a standard sample size calculation for a two-sample *t*-test with equal variances and a significance level of 0.05, using the mean and variance estimates from the literature and confirmed by the pilot study. For the FAOS a difference of 8–10% was specified as the minimal clinically important difference (MCID). Sample size estimates were calculated using standard methods.[72]

A target of 643 participants was sufficient to provide more than 90% power to detect differences of 10% in the primary outcomes and 80% power to detect differences in a range of secondary outcomes at 4 and 12 weeks assuming a 20% loss to follow-up. This sample size was independently calculated after 6 months of the trial by the Data Monitoring And Ethics Committee (DMEC).

Statistical analysis

Appropriate numerical and graphical summaries of all the data were compiled, including a detailed description of missing data at the clinic visit and the questionnaire and individual level.

The analysis was performed on an intention to treat basis. All participants were analysed in the groups to which they were randomised, regardless of the treatment that they received. An analysis of all people who completed the trial was undertaken and a sensitivity analysis performed to assess the range of potential biases that could result from loss to follow-up or withdrawal.

Analysis was also performed for groups defined by their acceptance of the treatment to which they were randomised.

Calculation of effect sizes

The differences from tubular bandage were transformed into effect sizes (onto a scale of standard deviations) by dividing by the relevant residual standard error.

Recovery

Recovery at each of the time points was monitored with reference to the baseline assessment. Linear regression models were used to provide estimates of the recovery and the prevalence of residual symptoms, with 95% confidence intervals.

Comparison of different treatments

The first comparison was that of each of the three alternative treatments with tubular bandage. Those treatments found to be more effective than tubular bandage were then compared with each other. The

regression modelling allowed an assessment of factors that might indicate the appropriate choice of treatment. As these analyses were prespecified, issues of multiple comparisons are minimal.

The sensitivity of the above analyses to missing data at case level was assessed and quantified using multiple imputation methods. Where data were missing, linear regression was used to fit a model describing the 4-week, 12-week or 9-month outcome in terms of baseline variables (age, sex, pain at rest VAS score and the relevant baseline score). Five draws were then made from the predicted distribution of 4-week scores for each outcome to produce five complete data sets on which the main analyses were repeated. Estimates from these five analyses were combined[73] using the 'mifit' command developed for the statistical analysis software package Stata (StataCorp, College Station, TX). This provided an estimate of effect that incorporated uncertainty due to the missing data.

Economic analysis

Estimates of cost consequences

This analysis sought to estimate the differences in the costs of the resources used by participants in the four arms of the trial, allowing comparisons to be made between different types of ankle support and enabling costs and consequences to be compared from a health-care perspective. Additionally, a wider analysis was conducted that looked at health-care costs plus costs to society as a result of sick leave.

The costs of each ankle support were determined to include staff time, overheads and equipment, and the costs of all subsequent NHS care related to treatment of the severe ankle sprain to include follow-up visits to hospital, GP surgeries, physiotherapists, etc. Other cost consequences for participants in terms of time off work, personal expenditure on aids or private practitioner input were obtained from resource use questions included in the follow-up outcome questionnaires as already described.

Cumulative costs over time associated with each treatment were collated for each of the four groups. The assumption was made that average costs reasonably reflected the long-run marginal costs of provision of services. Primary and hospital services use was costed from a variety of sources, including national sources.[74]

An analysis of the sensitivity of any observed cost differences between areas was undertaken for key cost drivers.

Comparison of costs and consequences

Full economic evaluation was performed based on a comparative assessment of the marginal costs and outcomes of the interventions used.

Cost-effectiveness analysis

A single outcome measure common to all interventions is required to estimate cost-effectiveness. The additional cost per unit improvement can be measured in terms of clinical outcomes such as recovery time or increases in ambulatory scores to estimate incremental cost per unit of improvement.

Cost–utility analysis

The EQ-5D instrument generates time trade-off utility scores[75] and allows determination of the incremental cost of the benefit gained in terms of the cost per quality-adjusted life-year (QALY) gained. Cumulative costs for changes in the health status index measured over the 9 months were calculated for individuals; this was presented in summary form in terms of incremental cost-effectiveness ratios (ICERs). Techniques to deal with missing data in economic analysis were considered;[76–78] however, we adopted a conservative approach such that missing outcome values were imputed only in cases in which EQ-5D data were available for other time points. We chose primarily to analyse complete cases to maintain consistency with the clinical analysis presented in Chapter 3. To ensure the generalisability of any findings we compared the baseline characteristics of the sample used for economic analysis with the sample excluded. For cost data items a non-response was equated to zero resource use only in cases that had reported outcome data. In the cost–utility analysis, uncertainties in the cost and outcomes data were incorporated into a sensitivity analysis.

Study conduct

A Trial Management Committee was set up to monitor the day-to-day running of the trial. It consisted of the chief investigators, statistical team and project co-ordinator. It met monthly for the duration of the project. This was supplemented by weekly meetings of the chief investigators, trial co-ordinator and recruitment physiotherapists.

A Trial Steering Committee (TSC) was set up to: (1) monitor and supervise the progress of the trial towards its interim and overall objectives; (2) review at regular intervals relevant information from other sources; (3) consider the recommendations of the DMEC; and (4) inform the funding body on the progress of the trial. Members of the TSC were Professor Bill Gillespie, Dean, Hull York Medical School (Chair, independent); Professor Sallie Lamb, University of Warwick/University of Oxford (chief investigator); Professor Matthew Cooke, University of Warwick (chief investigator); Professor Jane Hutton, University of Warwick; Dr Jennifer Marsh, University of Warwick; Professor Ala Szczepura, University of Warwick; Professor Jeremy Dale, University of Warwick; Dr Sue Wilson, University of Birmingham; and Vicky Staples (independent lay representative). The committee met at 6-monthly intervals either face-to-face or via teleconference.

A DMEC was set up to: (1) determine if additional interim analyses of trial data should be undertaken; (2) consider data from interim analyses, unblinded if considered appropriate, plus any additional safety issues for the trial and relevant information from elsewhere; (3) ensure that ethical considerations were of prime importance and report to the TSC and recommend on continuation of the trial; (4) consider any requests for the release of interim trial data and to inform the TSC on the advisability of this; and (5) advise on funding issues. Members of the DMEC were Professor Janet Dunn, University of Birmingham (Chair); Professor Damian Griffin, University of Warwick; and Patricia Overton-Brown, University Hospitals Coventry and Warwickshire. The DMEC met 14 and 19 months after recruitment commenced.

Ethical issues

The study was approved by the Northern and Yorkshire Multicentre Research Ethics Committee and all relevant local research ethics committees. Research governance approval was obtained from all NHS trusts involved in recruiting participants.

Informed consent to the trial and access to records was taken from all participants. Participants between the ages of 16 and 18 gave assent to participate in the trial and parents were asked to provide consent.

Pilot study

Rationale

To enable methodological refinement of the study proposal, a pilot study was undertaken. This allowed us to test the methods of collecting costs and outcomes, eliminate redundancy in the outcome measures, identify and overcome any obstacles to participant recruitment and refine the sample size and estimation of project costs.

Methods

A total of 24 participants were recruited from Coventry and Warwickshire Hospital, Coventry, over an 8-week period. The pilot study was conducted according to the methods given earlier in this chapter, with the exception of two questionnaires completed by the participants following randomisation. At the start of the pilot study the Ankle Performance Scale (APS)[79] was used as the best available disease-specific instrument. However, during the pilot study a new measure, based on the APS and by the same authors, was published (the FAOS) and this was phased in to replace the APS. The SF-36 rather than the SF-12 was used throughout the pilot study.

Results

When possible the results from the pilot study participants are included in the final analysis. The first few participants ($n = 17$) in the pilot study only completed the APS at baseline and not the FAOS and the same was true of three participants at 4 weeks. It was therefore not possible to calculate a score for the FAOS for these participants and so they have been excluded from the analyses that use the FAOS but included in all other analyses.

Methodological changes for the main trial

Several minor methodological alterations were made following the pilot study:

1. refinement of the outcome measure package to use the FAOS instead of the APS, and use of the SF-12 instead of the SF-36 to reduce participant questionnaire burden
2. stratification by trial centre
3. refinement of exclusion criteria, including contraindication to any of the four arms of the trial.

Chapter 3
Results

Between 7 April 2003 and 1 July 2005, 1522 potentially eligible participants were referred to the trial clinics at eight centres in the UK. Trial clinics were held 2–3 days following the initial presentation of the participant at the emergency department with severe ankle sprain. Random audits at centres showed that 15–100% of potential patients were referred to the clinics (see Appendix 10). A total of 330 patients who were referred did not attend the clinic; 1192 attended the trial clinic of whom 512 (43%) were ineligible and 584 (49%) were eligible and willing to take part and were randomised to one of the four treatment arms. A small proportion of eligible patients ($n = 79$, 7% of eligible patients attending the clinic) were unwilling to join the trial. The main reason for ineligibility was that the patient was already weight bearing by the time of the trial clinic and thus was deemed to have an ankle sprain less severe than grade II or III. *Figure 6* describes the numbers of participants approached to participate in the trial, randomised and allocated to various treatments and the numbers of withdrawals and losses to follow-up. *Figure 7* shows the numbers of participants recruited from each of the eight centres.

Patients excluded from the analysis were all pilot study participants who initially completed the APS at baseline or 4 weeks rather than the FAOS. These exclusions affected only the analyses using the FAOS scores; all other analyses included all patients. In total, 17 pilot study participants have been excluded from the baseline FAOS analysis and three pilot study participants have been excluded from the 4-week FAOS analysis (one each from the below knee cast, Aircast and Bledsoe groups).

Sample characteristics

The baseline characteristics of the sample are shown in *Table 9*. As anticipated from previous studies there was a greater proportion of men (58%) than women (42%). The mean age of participants was 30 years (SD 10.8, median 27, range 16–72). The majority of the sample was of Caucasian ethnic status (94%), with 68% having O levels/General Certificates of Secondary Education (GCSEs) or A levels as their highest educational qualification, 80% employed for over 25 hours per week and 82% spending greater than 4 hours per day on their feet.

The mean height of participants was 1.7 m (SD 0.1 m) and the mean weight was 78.6 kg (SD 15.4 kg), resulting in a mean BMI of 26.3 kg/m^2 (SD 5.2 kg/m^2).

Almost half of the participants (49%) had experienced an ankle injury previously and 9% of the sample reported recurrent sprain (defined as a previous sprain on three or more occasions, with the most recent incident being within the last year). Pre-existing injuries were generally only of mild to moderate severity and symptoms were intermittent.

Randomisation

Randomisation groups were generally well matched in terms of age, sex, educational level and baseline symptom profile and injury characteristics. There was a slightly larger number of males in the below knee cast group. All analyses have been adjusted for age, sex and baseline score. The median duration between time of injury and application of treatment was 3 days (interquartile range 2), with no differences between the groups.

Baseline injury characteristics

At baseline FAOS ranges indicated that nearly all participants were unable to participate in sports activities, experiencing significant loss of confidence in the ankle, had at least moderate or very frequent pain, and were experiencing at least moderately severe or frequent symptoms including swelling, bruising, instability and inability to weight bear (*Table 10*). Over 75% of participants had scores of less than 50 points for the pain, symptoms, sport and QoL subscales.

Nearly all participants reported at least some difficulty or frequent problems in a range of basic self-care activities of daily living. Mobility, as quantified by both the FLP and FAOS, was significantly impaired. In total, 75% of participants

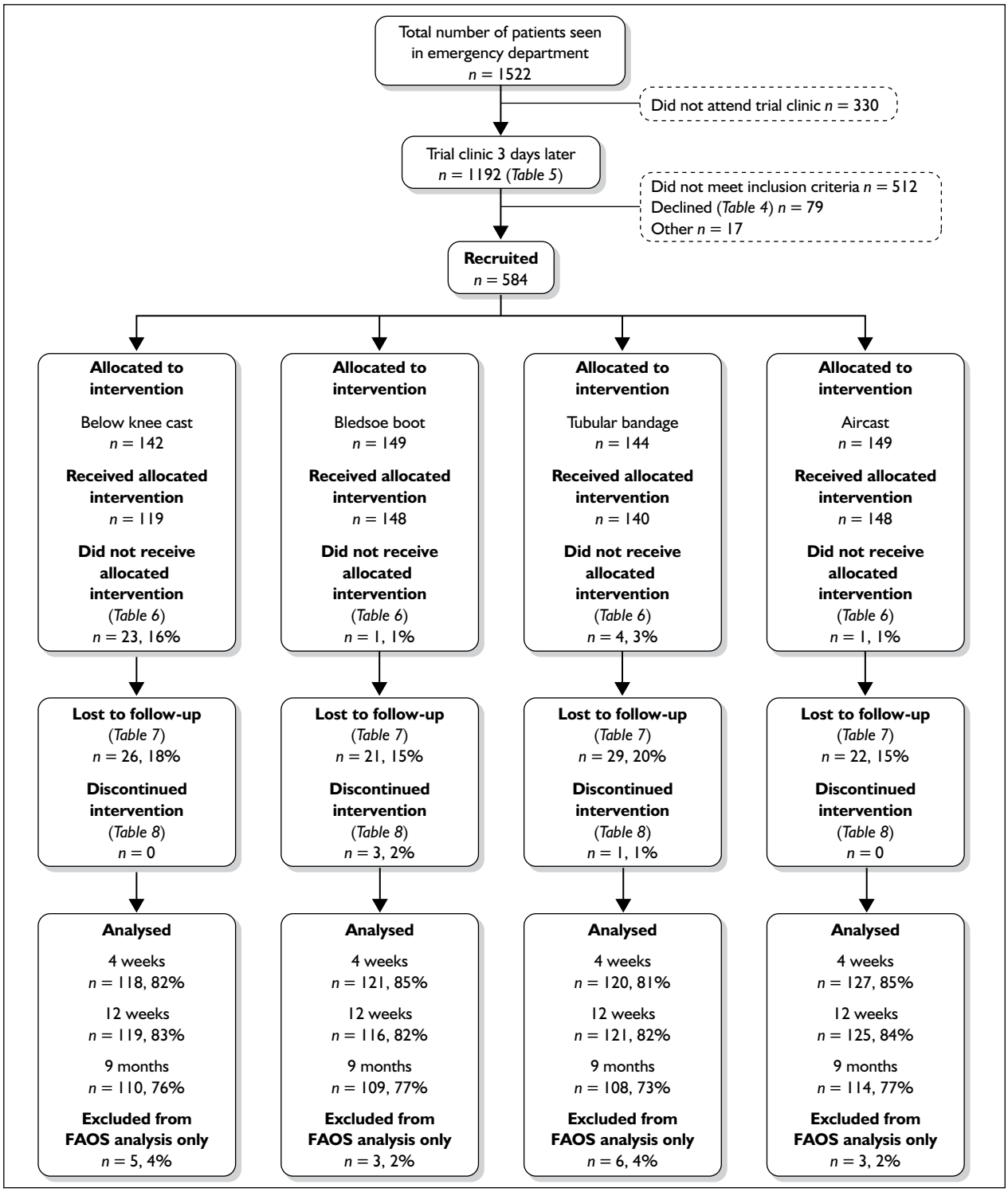

FIGURE 6 *Participant progress through the trial. FAOS, Foot and Ankle Outcome Score.*

TABLE 4 *Delay from injury to randomisation and application of randomised treatment*

	Tubular bandage	Below knee cast	Aircast brace	Bledsoe boot	Total
n	137	135	141	138	551
Mean delay (days)	3.14	3.19	3.01	3.09	3.1
SD	1.33	1.58	1.3	1.4	1.4
Minimum	1	1	1	1	1
1st quartile	2	2	2	2	2
Median	3	3	3	3	3
3rd quartile	4	4	4	4	4
Maximum	7	8	7	8	8

TABLE 5 *Reasons given by 79 participants for declining to take part in the trial*

Reason for decline	Number
Participant unwilling to accept one or more treatment options	57; tubular bandage 4 (7%), below knee cast 46 (81%), Aircast brace 2 (4%), Bledsoe boot 9 (16%)
Did not want to fill in questionnaires	3
Not happy to be part of a research project	6
Felt that the trial would interfere too much with daily life	22
Other unstated reason	26
Total	114

Note: Participants were free to give more than one reason.

TABLE 6 *Reasons for not receiving allocated intervention*

Randomisation group	Reason for not receiving allocated intervention	Number
Tubular bandage (*n* = 4, 3%)	Participant already wearing tubular bandage on arrival at trial clinic and wanting something more effective	1
	No tubular bandage available and given Aircast brace	1
	Reason unknown	2
Below knee cast (*n* = 23, 16%)	Participant refused below knee cast after randomisation	8
	Plaster room closed or technician unavailable	3
	Unable to return for below knee cast removal	1
	Clinical decision following randomisation	2
	Reason unknown	9
Aircast brace (*n* = 1, 1%)	Participant had problems with Aircast brace, physiotherapist decided to use below knee cast	1
Bledsoe boot (*n* = 1, 1%)	Participant moving house and did not want a splint	1

TABLE 7 *Reasons for loss to follow-up or withdrawal after randomisation*

Randomisation group		Number
Reason for loss to follow-up		
Tubular bandage	Loss to follow-up was defined as those participants not sending back their questionnaires and for whom we were unable to obtain core outcomes over the phone. Reasons for this are unknown but include participants moving house or changing phone numbers	26
Below knee cast		21
Aircast brace		29
Bledsoe boot		22
Reason for withdrawal		
Tubular bandage	Participant too busy to fill in questionnaires by 12 weeks	1
Below knee cast	Participant too busy to fill in questionnaires by 12 weeks	1
	Participant refused below knee cast after randomisation and withdrew from trial	1
	Reason unknown	1
Aircast brace	Reason unknown at 9 months	1

TABLE 8 *Reasons for unplanned discontinuation of intervention*

Randomisation group	Reason for discontinuation	Number
Below knee cast	Two participants removed cast themselves at 9 and 5 days respectively	2
	Participant returned after 1 day with discomfort and was given tubular bandage instead	1
Aircast brace	Reason unknown	1

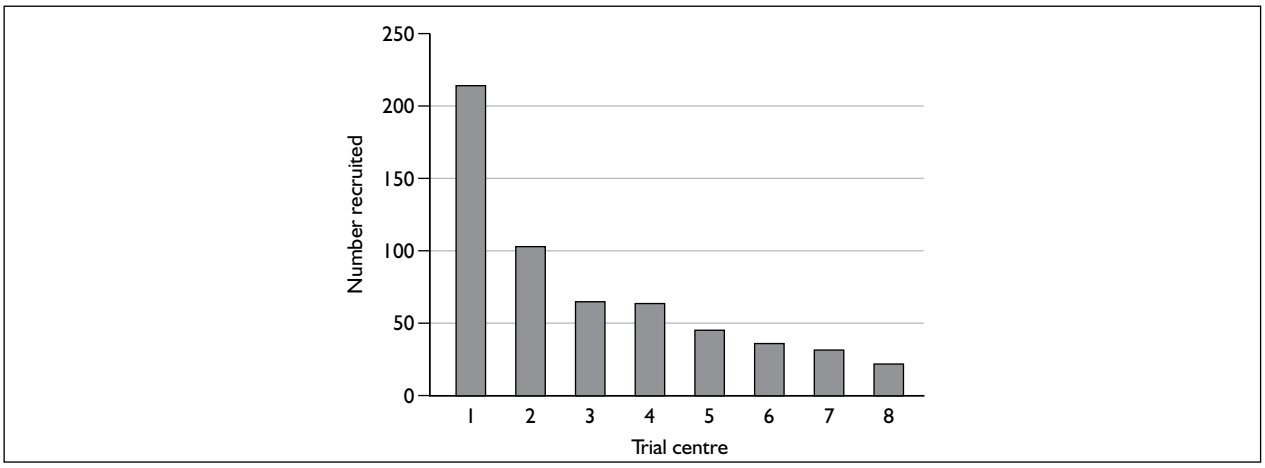

FIGURE 7 *Recruitment by trial centre. Recruitment periods and sizes of centres varied.*

TABLE 9 *Baseline characteristics table*

	Randomisation group				
	Tubular bandage	**Below knee cast**	**Aircast brace**	**Bledsoe boot**	**Total**
n (% of sample)	144 (25)	142 (24)	149 (26)	149 (26)	584
Age (years), mean (SD)	31 (11.2)	30 (10.5)	29 (10.7)	30 (10.7)	30 (10.8)
Gender, n ***(%)***					
Female	64 (44)	54 (38)	65 (44)	64 (43)	247 (42)
Male	80 (56)	88 (62)	84 (56)	85 (57)	337 (58)
Ethnic group, n ***(%)***					
White	135 (94)	133 (94)	140 (94)	141 (95)	549 (94)
Non-white	9 (6)	9 (6)	9 (6)	8 (5)	35 (6)
Education, n ***(%)***					
CSE	9 (6)	10 (7)	8 (6)	11 (8)	38 (7)
O-level/GCSE	59 (42)	57 (41)	67 (48)	66 (46)	249 (44)
A-level	33 (24)	33 (24)	33 (23)	34 (23)	133 (24)
Degree	16 (11)	18 (13)	11 (8)	19 (13)	64 (11)
Higher degree	9 (6)	7 (5)	7 (5)	5 (3)	28 (5)
Other	14 (10)	13 (9)	15 (11)	10 (7)	52 (9)
Employment status, n ***(%)***					
Employed	114 (79)	107 (75)	117 (79)	114 (77)	451 (77)
Unemployed	30 (21)	35 (25)	32 (22)	35 (24)	133 (23)
Hours employed per week					
Less than 10 hours	4 (3)	4 (3)	5 (3)	12 (8)	25 (6)
10–25 hours	14 (10)	14 (10)	17 (11)	17 (11)	62 (14)
25–40 hours	56 (39)	56 (39)	59 (40)	45 (30)	216 (48)
More than 40 hours	39 (27)	33 (23)	34 (23)	37 (23)	143 (32)
Length of day on feet					
Most of day	97 (67)	73 (61)	90 (60)	94 (63)	354 (61)
More than 4 hours	24 (17)	36 (25)	36 (24)	28 (19)	124 (21)
Less than 4 hours	9 (6)	20 (14)	15 (10)	19 (13)	63 (11)
Mostly sitting	14 (10)	12 (9)	8 (5)	8 (5)	42 (7)
Length of time driving					
Most of day	8 (6)	6 (4)	5 (3)	4 (3)	23 (4)
More than 4 hours	6 (4)	9 (6)	13 (9)	4 (3)	32 (25)
Less than 4 hours	41 (29)	29 (20)	40 (27)	38 (26)	148 (25)
Just commuting	35 (24)	35 (25)	32 (21)	44 (30)	146 (25)
Don't drive	54 (38)	62 (44)	59 (40)	58 (39)	233 (40)
BMI (kg/m^2), mean (SD)	26.5 (5)	27.0 (5)	26.1 (6)	25.8 (5)	26.3 (5)

continued

TABLE 9 *Baseline characteristics table*

	Randomisation group				
	Tubular bandage	**Below knee cast**	**Aircast brace**	**Bledsoe boot**	**Total**
Previous instability,* n *(%)					
Yes	30 (21)	23 (16)	26 (17)	31 (21)	110 (19)
No	106 (74)	111 (78)	116 (78)	112 (75)	445 (76)
No answer	8 (6)	8 (6)	7 (5)	6 (4)	29 (5)
Previous ankle injury,* n *(%)					
Yes	70 (49)	71 (50)	76 (51)	66 (44)	283 (49)
No	74 (51)	69 (49)	73 (49)	82 (55)	298 (51)
No answer	0 (0)	2 (1)	0 (0)	1 (1)	3 (1)
Previous recurrent sprain,* n *(%)					
Yes	12 (8)	14 (10)	12 (8)	17 (11)	55 (9)
No	73 (51)	65 (46)	77 (52)	63 (42)	278 (48)
No answer	59 (41)	63 (44)	60 (40)	69 (46)	251 (43)

BMI, body mass index; CSE, Certificate of Secondary Education; GCSE, General Certificate of Secondary Education.

reported scores of 30 points or higher on the FLP ambulatory scale, and nearly all participants (97%) reported at least some problems in getting about.

In comparison with population norms, SF-12 physical performance scores indicated significant impairment. Mental health scores were consistent with age- and sex-adjusted population means. VAS pain scores in all four groups were very similar, with more pain present on weight bearing than at rest. Over 75% of participants had scores well below the population norm as defined by the EQ-5D measure of general health.

Data collection and completeness of follow-up

Loss to follow-up

Case level

Follow-up at individual time points was good: 486 (83%) participants returned a 4-week questionnaire, 481 (82%) returned a 12-week questionnaire and 441 (76%) returned a 9-month questionnaire. There were no differences in follow-up between the four groups (*Table 11*).

Item level

In addition to case-level missing data (no questionnaire returned at all) there were also cases in which, although a questionnaire was returned, it was not sufficiently complete to be able to use the standard algorithms to calculate a score. Missing items were was usually of the order of 2–3%.

In general, questionnaires were well completed for the FAOS pain, symptoms and QoL subscales at all points and less well completed for the FAOS ADL and sport subscales and the SF-12 and EQ-5D scores. Questionnaires were generally better completed at the earlier follow-up points.

Patterns of missing data

There were no differences between randomisation groups with respect to loss to follow-up or patterns of response.

The majority of responses followed a monotonic pattern: once a participant failed to respond at a follow-up point they did not usually respond at any further follow-up point(s). A small proportion of participants responded in a non-monotonic way: having failed to return information at a particular time point(s) they subsequently provided information at later point(s). All available data were incorporated into the analyses for each time point.

Acceptance and receipt of randomised treatment

Acceptance and receipt of randomised treatment was generally high, with only 5% of participants not accepting the treatment to which they were

TABLE 10 *Baseline injury characteristics by randomisation group*

		Randomisation group				
Score		**Tubular bandage**	**Below knee cast**	**Aircast**	**Bledsoe**	**Total**
FAOS, pain	Mean	40.2	40.1	37.6	39.0	39.2
	Median	38.9	41.7	39.0	39.0	38.9
	(Quartiles)	(33.3–50.0)	(25.00–52.8)	(25.0–47.2)	(27.8–50.0)	(27.8–50.0)
FAOS, symptoms	Mean	40.2	42.0	38.7	41.0	40.5
	Median	39.3	39.3	39.3	39.3	39.3
	(Quartiles)	(28.6–50.0)	(32.1–50.0)	(28.6–46.4)	(32.1–50.0)	(28.6–50.0)
FAOS, ADL	Mean	61.5	59.0	57.2	58.6	59.1
	Median	61.8	60.3	57.4	58.8	60.3
	(Quartiles)	(54.4–69.1)	(51.5–66.2)	(50.0–63.2)	(50.0–67.7)	(51.5–66.2)
FAOS, sport	Mean	16.8	14.4	12.3	14.4	14.5
	Median	10.0	5.0	5.0	10.0	10.0
	(Quartiles)	(0.0–25.0)	(0.0–25.0)	(0.0–15.0)	(0.0–20.0)	(0.0–20.0)
FAOS, QoL	Mean	28.0	20.8	21.3	24.4	23.6
	Median	25.0	18.8	18.8	18.8	18.8
	(Quartiles)	(12.5–43.8)	(6.3–25.0)	(6.3–31.3)	(6.3–37.5)	(6.3–37.5)
FLP, ambulatory	Mean	35.4	36.3	37.0	34.0	35.7
	Median	36.4	37.0	36.6	33.1	36.3
	(Quartiles)	(28.3–41.1)	(30.2–45.6)	(30.2–45.5)	(26.3–40.4)	(28.8–42.7)
SF-12, physical	Mean	35.8	36.0	34.0	35.7	35.4
	Median	35.8	37.7	32.3	34.2	34.6
	(Quartiles)	(27.0–43.3)	(28.9–43.1)	(27.5–41.3)	(27.4–43.4)	(27.6–43.0)
SF-12, mental	Mean	51.5	52.0	49.5	51.4	51.1
	Median	53.3	54.3	51.7	54.2	53.3
	(Quartiles)	(43.8–60.6)	(45.8–60.1)	(40.2–58.7)	(43.5–61.5)	(42.8–60.3)
EQ-5D	Mean	0.4	0.3	0.3	0.3	0.3
	Median	0.4	0.3	0.3	0.4	0.3
	(Quartiles)	(0.1–0.7)	(0.1–0.6)	(0.03–0.6)	(0.1–0.6)	(0.1–0.6)
VAS, pain at rest	Mean	37.4	37.8	39.4	36.5	37.8
	Median	32.0	38.5	40.0	32.0	36.0
	(Quartiles)	(18.0–55.0)	(19.5–51.5)	(21.5–55.0)	(18.0–54.5)	(19.0–53.5)
VAS, pain weight bearing	Mean	74.8	74.9	78.4	73.5	75.4
	Median	78.0	77.0	80.0	77.0	78.0
	(Quartiles)	(65.0–90.0)	(67.0–93.0)	(71.0–90.0)	(61.0–90.0)	(66.0–90.0)

ADL, activities of daily living; QoL, quality of life; VAS, visual analogue scale.
The FAOS uses a scale of 0–100 (0 = extreme symptoms, 100 = no symptoms). The FLP ambulatory subsection uses a score of 0–100, with a lower score being better. The SF-12 score ranges from 0 to 100, with a higher score being better. The EQ-5D uses a score from 1 for full health to –0.594 for problems with all five dimensions covered. Baseline VAS scores of pain at rest and on weight bearing are scored from 0 (no pain) to 100 (worst pain imaginable).

TABLE 11 *Missing data proportions: case-level missing data by randomisation group*

		Tubular bandage		Below knee cast		Aircast		Bledsoe		Total	
		n	%	*n*	%	*n*	%	*n*	%	*n*	%
4 weeks	Response	118	82	121	85	120	81	127	85	486	83
	Missing	26	18	21	15	29	20	22	15	98	17
12 weeks	Response	119	83	116	82	121	81	125	84	481	82
	Missing	25	17	26	18	28	19	24	16	103	18
9 months	Response	110	76	109	77	108	73	114	77	441	76
	Missing	34	24	33	23	41	28	35	24	143	25

randomised. Reasons for refusal of randomised treatment were given previously in *Table 4*. There were differences between randomisation groups in the level of acceptance: the Aircast brace and Bledsoe boot had almost total acceptance, with only one participant (1%) in each group refusing the treatment, whereas tubular bandage had a slightly higher rate of non-acceptance with four participants (3%) refusing it. The below knee cast was the least acceptable treatment. The main reason for refusal, when one was given, was an unwillingness to be put in a below knee cast (8 of 23 refusals, 35%), although there were also practical reasons such as not being able to return for cast removal (1 of 23 refusals, 4%). Randomised treatment was not given because of non-availability of the plaster technician on three occasions (3 of 23 refusals, 13%). Two participants were not given a below knee cast for clinical reasons (9%) and nine others (39%) refused for unknown reasons.

The trial protocol stated that participants refusing a randomised treatment should be offered tubular bandage, but for eight out of the 29 participants (28%) who did not receive their randomised treatment a different treatment was applied. Levels of acceptance of randomised treatment, and treatments given in cases of non-acceptance of randomised treatment, are given in *Table 12*, with reasons, when known, previously outlined in *Table 4*.

Withdrawal

Five (1%) participants withdrew their consent for follow-up during the 9-month follow-up period. The reasons for withdrawal are listed in *Table 7*.

Adverse events and serious adverse events

There were seven adverse events in total, of which two were non-serious and five were serious. The two non-serious adverse events were both cases of cellulitis treated with antibiotics, one each in the Aircast brace and Bledsoe boot groups. The five serious adverse events were all either suspected/confirmed deep vein thrombosis (DVT) or pulmonary embolism. These events are not unexpected in this injury and following immobilisation of any type. There were two each in the tubular bandage and Aircast arms and one in the below knee cast arm. Of these, three were possibly related to the trial treatment, one was unrelated and one was of unknown relatedness (the participant had a previous history of recurrent DVT and was taking warfarin but was classified as eligible for the trial and randomised in error). *Table 13* gives full details of the individual cases.

Recovery and estimates of treatment effectiveness

Figures 8 and *9* illustrate recovery (unadjusted medians) by randomisation group for the primary and secondary outcomes. Descriptive statistics are given in Appendix 13.

With the exception of mental health, recovery was incremental over time and most rapid in the first 4 weeks. However, at 9 months nearly 20% of individuals reported persisting difficulties getting around and 50% of participants scored less than 10–20% of the maximum score range on the FAOS subscales. Overall, mental health declined

TABLE 12 *Uptake of treatment by randomisation group*

	Randomisation group				
	Tubular bandage	**Below knee cast**	**Aircast**	**Bledsoe**	**Total**
Total number of participants randomised	144	142	149	149	584
Treatment as intended	140	119	148	148	556
Alternative treatment	4	23	1	1	29
Alternative treatment given					
Tubular bandage	–	20	–	1	–
Below knee cast	–	–	1	–	–
Aircast	4	2	–	–	–
Nothing	–	1	–	–	–
% given alternative treatment	3	16	1	1	5

significantly at 4 weeks in comparison with baseline but had recovered by 12 weeks.

Age was a significant determinant of recovery, which was substantially slower as age increased and less complete by 9 months for all outcomes. Gender was also significant in recovery, particularly at the earlier time points, with men reporting better scores than women on average across all scores. Baseline score was positively related to recovery, with a better score at the outset being associated with better scores later on for all outcomes. No interactions between sex, age or randomisation group were observed.

Estimates of treatment effectiveness – intention to treat analysis

Analysis was controlled for age (centred at 30 years), sex and baseline score (centred at the approximate median of each score). For the FAOS analyses we excluded the 17 pilot study participants who did not complete the FAOS at baseline.

TABLE 13 *Serious adverse events*

Participant ID	Treatment arm	Diagnosis	Age	Sex	Length of time support worn	Related to trial treatment
1060	Tubular bandage	Suspected deep vein thrombosis (DVT)	72	F	1–2 weeks (full questionnaire follow-up returned)	Possibly
1183	Below knee cast	Post-partum pulmonary embolism (PE)	21	F	Less than 1 week (no response to 9-month questionnaire)	Unrelated
2007	Aircast	DVT	28	F	Less than 1 week (full questionnaire follow-up returned)	Possibly
2049	Tubular bandage	PE	51	F	1–2 weeks (full questionnaire follow-up returned)	Unknown. Proforma stated that participant had a history of recurrent DVT and was taking warfarin, but participant was classified as appropriate for the trial and randomised in error
3032	Aircast	DVT	20	M	Unknown, as no questionnaires returned	Possibly

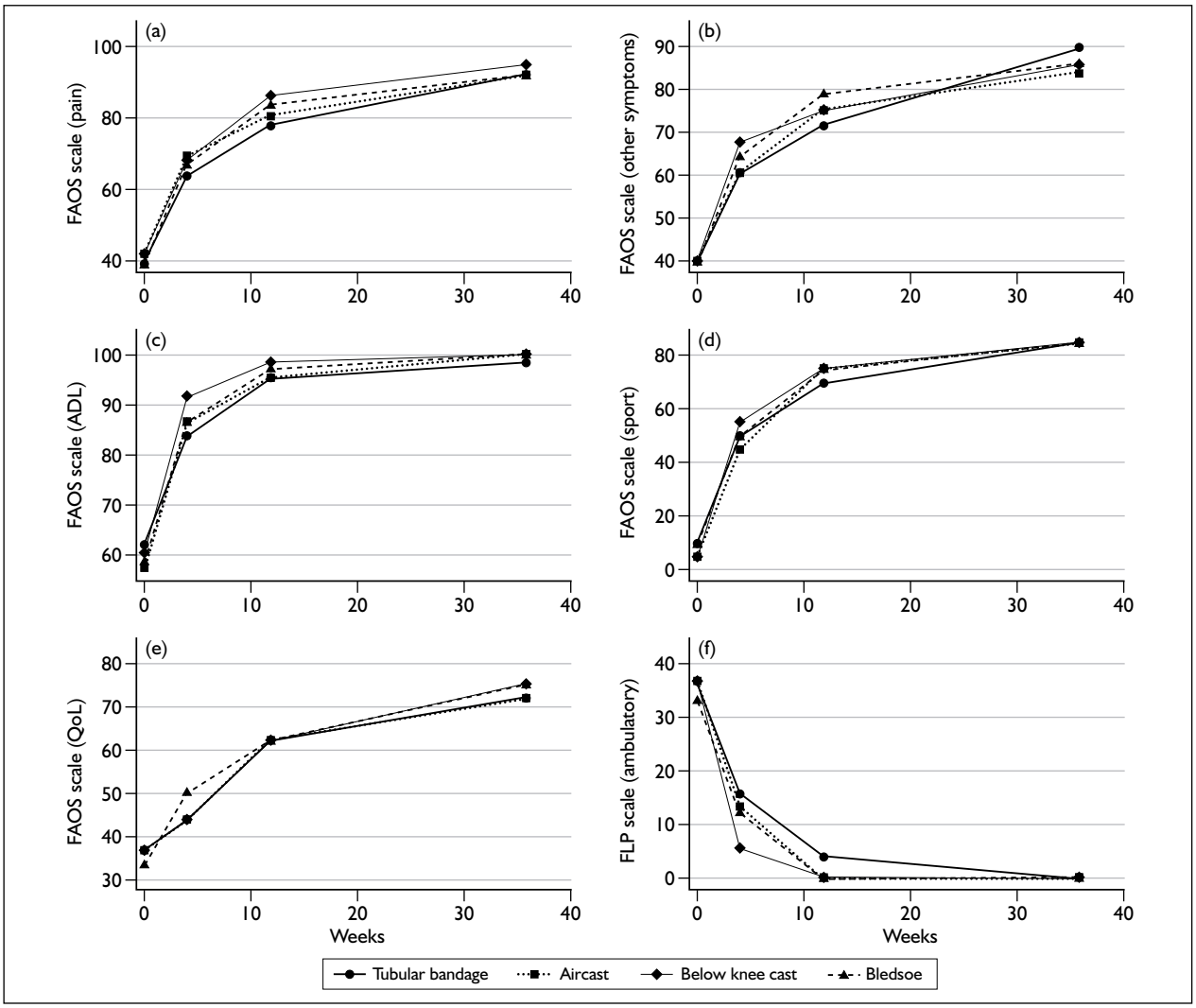

FIGURE 8 *Primary outcome recovery curves for the full 9-month follow-up period. Graphs (a)–(e) show the five FAOS subscales – pain, other symptoms, activities of daily living (ADL), sport and recreation and quality of life (QoL) respectively – and graph (f) shows the FLP ambulatory scale. Figures are unadjusted medians. The FAOS uses a scale of 0–100, in which 0 = extreme symptoms and 100 = no symptoms, whereas the FLP ambulatory subsection uses a score of 0–100, with a lower score being better. (Tables of means, medians and quartiles are given in Appendix 13.)*

Estimates of treatment effectiveness for the primary outcome are presented in *Table 14* on the basis of comparison with tubular bandage.

At 4 weeks the below knee cast was the most effective treatment in the early stages of recovery, its difference compared with tubular bandage being significantly non-zero for the pain and QoL subscales. In terms of clinical significance these differences were small effects. Neither the Aircast brace nor the Bledsoe boot conferred a significant advantage over tubular bandage at 4 weeks.

By 12 weeks the below knee cast was statistically significantly better than tubular bandage on four of the five subscales of the FAOS – pain, ADL, sports and QoL. The differences for the sports scale, QoL scale and ADL scale were moderate, whereas differences in pain were small. The Aircast brace was also significantly more effective than tubular bandage in improving the FAOS QoL subscale, but effects on the other domain scores of the FAOS were not statistically significant. The Bledsoe boot conferred no significant advantage over tubular bandage.

Results of the secondary outcomes are presented in *Table 15* on the basis of comparison with tubular bandage. At 4 weeks the below knee cast was significantly better than tubular bandage for return

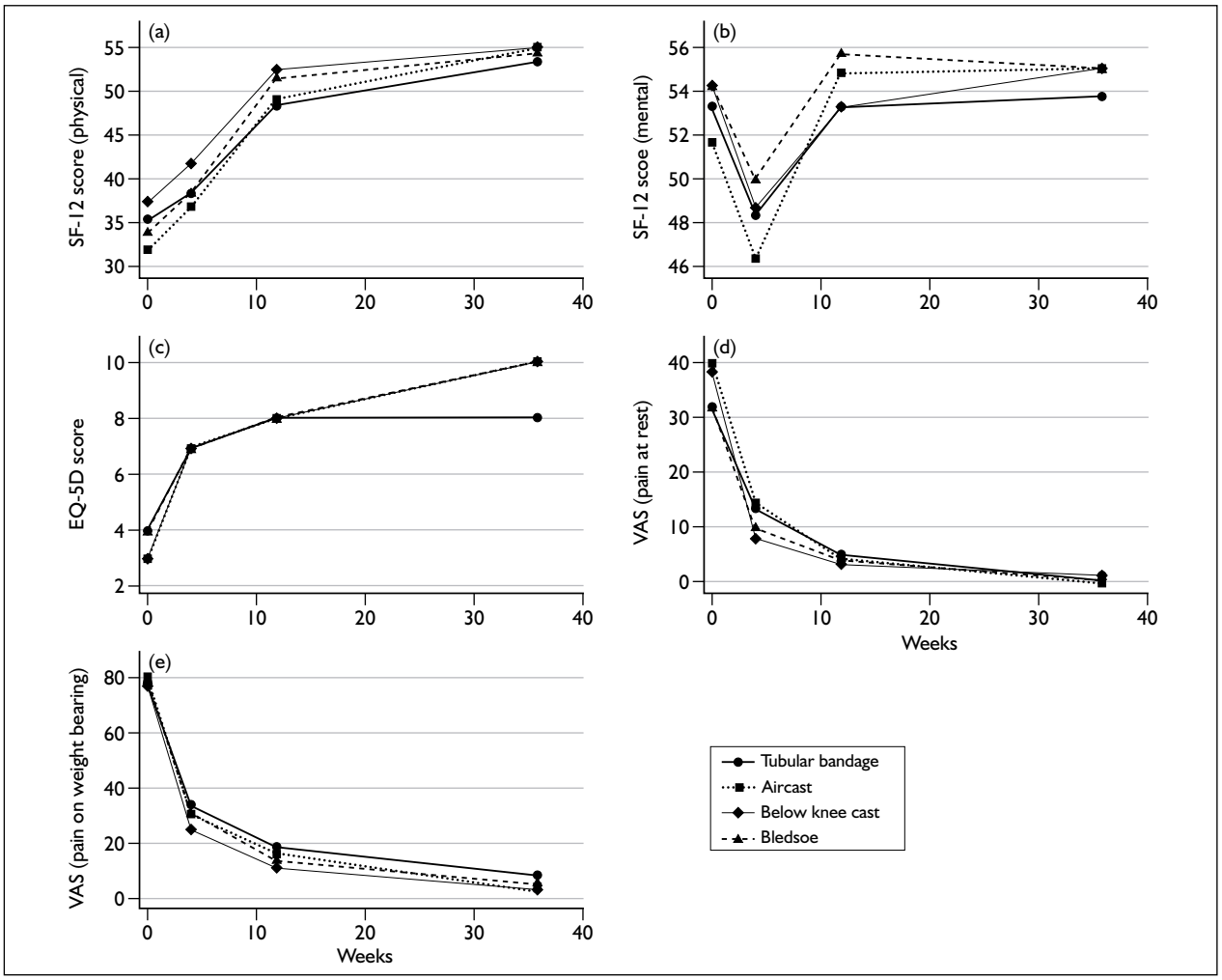

FIGURE 9 *Secondary outcome recovery curves for the full 9-month follow-up period. SF-12 physical (a) and mental (b) component scores (each scale 0–100 with population norm of 50). (c) The EQ-5D (scale –0.594 to 1.0, where a higher score is better). Visual analogue scale (VAS) scores (scale of 0–100 expressed in millimetres, where 0 = no pain and 100 = worst pain imaginable) for pain at rest (d) and pain when weight bearing (e). Figures are unadjusted medians. (Tables of means, medians and quartiles are given in Appendix 13.)*

to physical function (SF-12 physical component), with a small effect size. Mental well-being had decreased in all four groups compared with baseline scores.

By 12 weeks the Aircast brace was significantly better than tubular bandage for return to mental health (SF-12 mental component), with a moderate effect size, with the below knee cast being slightly worse than tubular bandage. On the EQ-5D there was a statistically significant benefit for the below knee cast at both 4 and 12 weeks compared with tubular bandage, with a small to moderate effect size.

Pain at rest, as measured on a VAS, was slightly better with the below knee cast at 4 weeks, and pain when weight bearing was also better with the below knee cast at 12 weeks, compared with tubular bandage.

By 9 months there were no statistically significant differences between the groups on any of the primary or secondary outcome measures.

Self-reported benefit

Participants were asked to rate the benefit that they had received from their treatment at 12 weeks and 9 months on a scale of 0–10. Those in the tubular bandage arm felt that they had received the least benefit of the four groups at both time points, with half of participants reporting a benefit of less than 5 out of 10; the benefit of the other three supports

TABLE 14 *Estimates of clinical effect: primary outcomes, intention to treat analysis*

	4 weeks			12 weeks			9 months		
	Score	**95% CI**	**Effect size[a]**	**Score**	**95% CI**	**Effect size[a]**	**Score**	**95% CI**	**Effect size[a]**
FAOS pain									
Tubular bandage mean	62.3	(58.5–66.1)		72.9	(69.0–76.9)		81.1	(77.0–85.6)	
Bledsoe difference	0.6	(–4.0 to 5.3)	0.03	3.3	(–1.4 to 8.1)	0.18	1.7	(–3.3 to 6.7)	0.09
Aircast difference	3.5	(–1.2 to 8.2)	0.19	3.7	(–1.1 to 8.5)	0.20	1.9	(–3.2 to 7.0)	0.10
Below knee cast difference	5.1	(0.4–9.8)	0.28	5.1	(0.3–10.0)	0.27	4.3	(–0.7 to 9.4)	0.23
n	482			478			440		
FAOS symptoms									
Tubular bandage mean	59.8	(56.0–63.7)		68.70	(64.8–72.6)		79.2	(75.2–83.2)	
Bledsoe difference	–0.8	(–5.4 to 3.9)	–0.04	2.5	(–2.3 to 7.2)	0.13	–1.1	(–5.9 to 3.7)	–0.06
Aircast difference	2.2	(–2.6 to 6.9)	0.12	2.7	(–2.0 to 7.5)	0.15	0.1	(–4.8 to 5.0)	0.01
Below knee cast difference	3.8	(1.0–8.5)	0.21	3.4	(–1.4 to 8.2)	0.18	0.4	(–4.4 to 5.3)	0.02
n	480			478			440		
FAOS ADL									
Tubular bandage mean	82.3	(79.6–85.0)		88.9	(86.4–91.3)		93.1	(90.6–95.6)	
Bledsoe difference	–0.1	(–3.3 to 3.2)	–0.01	2.4	(–0.7 to 5.4)	0.22	0.1	(–3.0 to 3.2)	0.01
Aircast difference	0.6	(–2.7 to 4.0)	0.05	1.1	(–2.0 to 4.2)	0.10	1.0	(–2.1 to 4.1)	0.10
Below knee cast difference	3.0	(–0.3 to 6.3)	0.24	3.5	(0.4–6.6)	0.32	1.2	(–1.9 to 4.3)	0.12
n	453			393			357		

	4 weeks			12 weeks			9 months		
	Score	**95% CI**	**Effect size[a]**	**Score**	**95% CI**	**Effect size[a]**	**Score**	**95% CI**	**Effect size[a]**
FAOS sports									
Tubular bandage mean	44.7	(39.1–50.3)		62.2	(56.5–68.0)		76.8	(70.8–82.7)	
Bledsoe difference	–0.3	(–7.0 to 6.4)	–0.01	5.9	(–1.0 to 12.9)	0.24	1.0	(–6.1 to 8.1)	0.04
Aircast difference	0.0	(–6.7 to 6.8)	0.00	4.8	(–2.3 to 11.9)	0.20	0.8	(–6.5 to 8.0)	0.03
Below knee cast difference	5.0	(–1.7 to 11.8)	0.20	8.7	(1.6–15.7)	0.35	2.4	(–4.8 to 9.6)	0.10
n	438			382			352		
FAOS QoL									
Tubular bandage mean	43.0	(38.2–47.7)		53.5	(48.4–58.6)		64.9	(59.3–70.6)	
Bledsoe difference	1.9	(–3.9 to 7.6)	0.08	6.1	(0.0–12.3)	0.25	4.0	(–2.9 to 10.8)	0.15
Aircast difference	4.9	(–1.0 to 10.7)	0.22	8.0	(1.8–14.2)	0.33	6.1	(–0.9 to 13.0)	0.24
Below knee cast difference	5.9	(0.1–11.8)	0.26	8.7	(2.4–15.0)	0.36	6.3	(–0.7 to 13.2)	0.24
n	481			477			439		
FLP ambulatory									
Tubular bandage mean	16.9	(14.1–19.6)		8.4	(6.2–10.5)		6.3	(4.4–8.3)	
Bledsoe difference	0.1	(–3.3 to 3.4)	0.01	–0.8	(–3.5 to 1.8)	–0.08	–1.5	(–3.9 to 0.9)	–0.18
Aircast difference	–0.1	(–3.4 to 3.3)	0.00	–1.2	(–3.9 to 1.6)	–0.12	–2.2	(–4.6 to 0.3)	–0.26
Below knee cast difference	–3.1	(–6.4 to 0.3)	–0.24	–1.8	(–4.5 to 0.9)	–0.18	–1.7	(–4.1 to 0.7)	–0.21
n	462			401			361		

ADL, activities of daily living; QoL, quality of life.
a Represents effect size difference compared with tubular bandage.
Analysis is adjusted for sex, age and baseline score. Results presented are for female, aged 30 years, with an approximate median baseline score (median score for FAOS pain = 40, symptoms = 40, ADL = 60, sport = 10 and QoL = 20, and for FLP ambulatory = 35). FAOS outcomes are without 17 patients from the pilot study. Scoring is 0–100 for FAOS (higher = better) and 0–100 for FLP (lower = better).

TABLE 15 *Estimates of clinical effect: secondary outcomes, intention to treat analysis*

	4 weeks			12 weeks			9 months		
	Score	**95% CI**	**Effect size[a]**	**Score**	**95% CI**	**Effect size[a]**	**Score**	**95% CI**	**Effect size[a]**
SF-12 physical									
Tubular bandage mean	39.2	(37.4–41.0)		47.3	(45.4–49.3)		49.7	(47.5–52.0)	
Bledsoe difference	–1.3	(–3.5 to 0.8)	–0.16	1.0	(–1.4 to 3.4)	0.11	0.2	(–2.5 to 3.0)	0.03
Aircast difference	–1.4	(–3.6 to 0.8)	–0.17	–0.7	(–3.2 to 1.7)	–0.09	–0.1	(–2.9 to 2.7)	–0.01
Below knee cast difference	2.2	(0.0 to 4.4)	0.27	1.6	(–0.8 to 4.0)	0.18	0.3	(–2.5 to 3.1)	0.04
n	451			396			356		
SF-12 mental									
Tubular bandage mean	43.4	(41.1–45.7)		47.8	(45.6–49.9)		47.7	(45.3–50.1)	
Bledsoe difference	1.0	(–1.8 to 3.8)	0.10	2.6	(–0.0 to 5.2)	0.27	1.4	(–1.5 to 4.3)	0.14
Aircast difference	0.1	(–2.7 to 3.0)	0.01	3.1	(0.3–5.8)	0.33	1.8	(–1.2 to 4.7)	0.18
Below knee cast difference	–0.6	(–3.4 to 2.2)	–0.05	0.0	(–2.7 to 2.7)	0.00	1.2	(–1.8 to 4.2)	0.12
n	451			396			356		
EQ-5D									
Tubular bandage mean	0.60	(0.55–0.65)		0.70	(0.65–0.74)		0.73	(0.68–0.79)	
Bledsoe difference	0.03	(–0.02 to 0.09)	0.14	0.05	(–0.01 to 0.11)	0.28	0.06	(–0.01 to 0.12)	0.28
Aircast difference	0.00	(–0.05 to 0.06)	0.02	0.04	(–0.01 to 0.10)	0.24	0.05	(–0.01 to 0.12)	0.25
Below knee cast difference	0.06	(0.00–0.12)	0.28	0.06	(0.01–0.12)	0.33	0.04	(–0.02 to 0.10)	0.18
n	459			397			359		

	4 weeks			12 weeks			9 months		
	Score	**95% CI**	**Effect size[a]**	**Score**	**95% CI**	**Effect size[a]**	**Score**	**95% CI**	**Effect size[a]**
VAS pain at rest									
Tubular bandage mean	19.2	(15.4–23.0)		12.6	(9.6–15.6)		10.1	(6.7–13.5)	
Bledsoe difference	–0.7	(–5.3 to 3.9)	–0.04	–0.5	(–4.1 to 3.2)	–0.03	0.7	(–3.4 to 4.8)	0.05
Aircast difference	–0.7	(–5.3 to 3.9)	–0.04	–1.2	(–4.9 to 2.5)	–0.09	–2.9	(–7.1 to 1.3)	–0.19
Below knee cast difference	–4.8	(–9.4 to –0.1)	–0.27	–3.2	(–6.9 to 0.4)	–0.23	–0.8	(–4.9 to 3.4)	–0.05
n	461			460			435		
VAS pain weight bearing									
Tubular bandage mean	38.3	(32.9–43.7)		30.1	(25.0–35.2)		25.8	(20.3–31.3)	
Bledsoe difference	0.5	(–6.1 to 7.1)	0.02	–2.4	(–8.6 to 3.8)	–0.10	–1.8	(–8.4 to 4.9)	–0.07
Aircast difference	0.3	(–6.3 to 6.9)	0.01	–4.0	(–10.3 to 2.8)	–0.17	–5.2	(–12.0 to 1.6)	–0.21
Below knee cast difference	–4.4	(–11.1 to 2.2)	-0.18	–6.5	(–12.8 to –0.2)	–0.27	–5.0	(–11.8 to 1.7)	–0.20
n	457			458			433		

a Represents effect size difference compared with tubular bandage.
Analysis is adjusted for sex, age and baseline score. Results presented are for female, aged 30 years, with an approximate median baseline score (median score for SF-12 physical = 35, SF-12 mental = 50, EQ-5D = 0.25, VAS pain at rest = 35 and VAS pain on weight bearing = 80). Scoring is 0–100 for SF-12 (higher = better), –0.594 to 1 for EQ-5D (higher = better) and 0–100 for visual analogue scale (VAS) pain scores (lower = better).

was rated about equally at between 7 and 8 out of 10 (*Table 16*, *Figures 10* and *11*).

Analysis of treatment uptake

Uptake was measured in terms of the numbers of participants who received the application of the treatment to which they were randomised. The analysis was repeated for groups defined by their uptake: that is those who were randomised to a treatment and received it and those who rejected randomisation group treatment. There were no differences between the two groups with respect to sex, age or baseline scores for primary or secondary outcomes (*Table 17*). Overall, the results were consistent with the results of the intention to treat analysis.

TABLE 16 *Self-reported benefit score by randomisation group at 12 weeks and 9 months.*

		Randomisation group			
		Tubular bandage	**Below knee cast**	**Aircast**	**Bledsoe**
Benefit score (12 weeks)[a]	Mean	4.5	6.6	6.7	6.9
	Median	5	7	7	8
	(Quartiles)	(2–7)	(5–9)	(6–8)	(5–9)
	n	116	113	119	120
Benefit score (9 months)[a]	Mean	5.0	6.9	7.0	7.3
	Median	5	8	8	8
	(Quartiles)	(2–8)	(5–9)	(5–9)	(7–9)
	n	109	106	106	111

a Participants reported benefit of the treatment on a scale of 0–10 (0 = no benefit, 10 = maximum benefit).

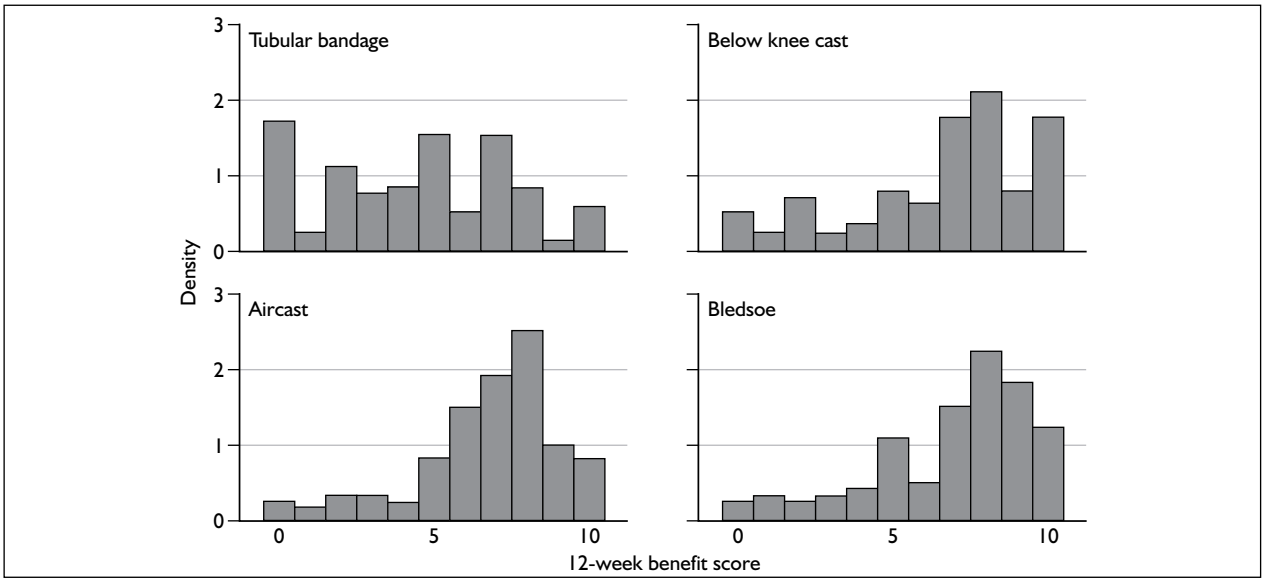

FIGURE 10 *Self-reported benefit of treatment at 12 weeks. Benefit is measured on a scale of 0–10, where 0 = no benefit and 10 = maximum benefit (density = proportion).*

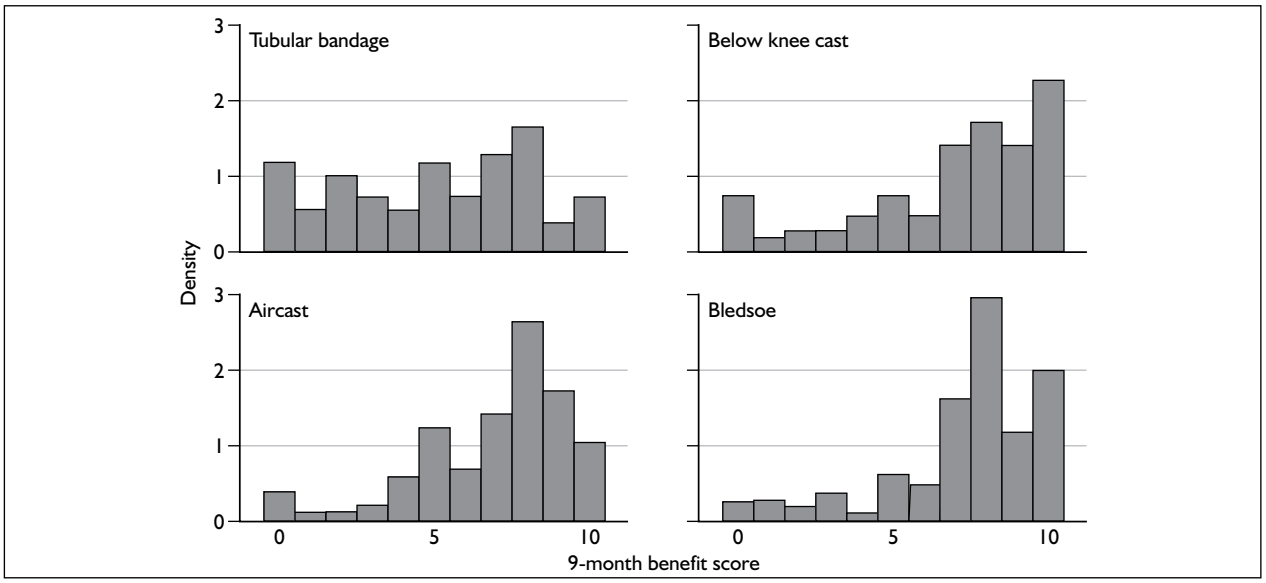

FIGURE 11 *Self-reported benefit of treatment at 9 months. Benefit is measured on a scale of 0–10, where 0 = no benefit and 10 = maximum benefit (density = proportion).*

TABLE 17 *Baseline characteristics of participants who accepted or rejected their randomisation group treatment*

		Rejected randomisation group treatment	Accepted randomisation group treatment
Gender			
Female, *n* (%)		12 (41)	235 (42)
Male, *n* (%)		17 (59)	320 (58)
Age (years)	Mean	33	30
	Median	28	27
	(Quartiles)	(23–41)	(21–37)
FAOS, pain	Mean	43.0	38.1
	Median	45.8	39.0
	(Quartiles)	(33.3–55.6)	(25.0–94.4)
FAOS, symptoms	Mean	45.5	39.2
	Median	42.9	39.3
	(Quartiles)	(32.1–64.3)	(28.6–50.0)
FAOS, ADL	Mean	62.6	57.4
	Median	64.7	58.8
	(Quartiles)	(52.9–72.1)	(50.0–66.2)
FAOS, sport	Mean	13.8	14.0
	Median	7.5	10.0
	(Quartiles)	(0.0–17.5)	(0.0–20.0)
FAOS, QoL	Mean	18.3	23.4
	Median	12.5	18.8
	(Quartiles)	(0.0–34.4)	(6.3–37.5)

continued

TABLE 17 *Baseline characteristics of participants who accepted or rejected their randomisation group treatment (continued)*

		Rejected randomisation group treatment	Accepted randomisation group treatment
FLP, ambulatory	Mean	35.2	35.7
	Median	36.6	36.3
	(Quartiles)	(28.8–45.3)	(28.8–42.7)
SF-12, physical	Mean	35.7	35.4
	Median	35.8	34.3
	(Quartiles)	(26.3–43.1)	(27.7–42.9)
SF-12, mental	Mean	50.0	51.1
	Median	50.5	53.4
	(Quartiles)	(45.6–58.6)	(42.7–60.4)
EQ-5D	Mean	0.38	0.33
	Median	0.36	0.29
	(Quartiles)	(0.16–0.62)	(0.05–0.62)
VAS, pain at rest	Mean	34.9	37.9
	Median	37.5	36.0
	(Quartiles)	(11.0–50.0)	(20.0–54.0)
VAS, pain on weight bearing	Mean	67.4	75.8
	Median	72.0	79.0
	(Quartiles)	(49.0–80.0)	(67.0–90.0)

ADL, activities of daily living; QoL, quality of life; VAS, visual analogue scale.

Sensitivity analysis

Multiple imputation was used to assess the impact of (complete-case) missing data on the analyses. Conclusions from this were not substantially different from those based on the complete-case analysis presented here, and the findings were, as far as can be ascertained, relatively insensitive to missing data.

Chapter 4
Economic evaluation

Introduction

To inform decision-making on the optimum intervention for severe ankle sprain it is necessary to consider not only the measurable benefits or clinical effectiveness of different treatments but also their costs.

Severe ankle sprains can have a range of direct and indirect health-care cost consequences. These include the cost of initial treatment and any subsequent costs incurred in primary and secondary care during the recovery period. Different treatment arms may result in different direct health-care costs and differences in the date at which people return to work, days off work or 'sick leave'.

The most appropriate economic evaluation technique for a clinical trial will depend on the results, and it is recognised that a well-designed economic study should allow for different eventualities.[80] The simplest eventuality would be when the cheaper intervention is found to be better on at least one outcome measure and no worse on any other, in which case it is preferred. Another eventuality is when two interventions have the same outcomes, in which case the economic evaluation required is a cost-minimisation analysis focusing only on costs. When there is the possibility that better outcomes are achieved at a higher cost, or vice versa, or when more than two interventions are being considered, a full economic evaluation is required.

This chapter presents an economic evaluation of the three interventions (below knee cast, Aircast brace and Bledsoe boot) versus tubular bandage as the comparator group. The evaluation explores costs and cost-effectiveness of these three approaches, and the factors influencing this, and is presented in several sections: (1) analysis of health-care costs alone; (2) impact of including indirect costs (sick leave); (3) cost-effectiveness analysis; (4) cost–utility analyses with and without sick leave costs; and (5) sensitivity analyses.

Methods

The primary analysis adopted an NHS perspective as that is of most interest to NHS decision-makers. A societal perspective, including the impact on productivity costs (i.e. time off work), was included in a secondary analysis. Sensitivity analysis was used to examine the impact of uncertainty on the expected cost-effectiveness of each intervention.

Assessment of costs

We considered both the costs of providing each intervention and the costs of all subsequent care related to treatment of the severe ankle sprain, for example pain medication, follow-up visits to the hospital, GP surgery visits, associated investigations, further therapist treatments, hospitalisation, use of gels and other topical agents, and use of bandages, braces or footwear.

A combination of a primary costing approach and cost modelling was used to estimate a total cost for each participant in each group. The resource use associated with fitting each support was obtained through a microcosting study in the emergency department, considering staff time for fitting the item and the materials used. NHS list prices were used for materials (including VAT); bulk buy prices were also obtained from manufacturers for the Bledsoe boot and Aircast brace. Non-health-care costs associated with fitting, such as participant travel costs to the emergency department, were excluded.

Subsequent direct care costs and indirect costs (i.e. time off work) were estimated from responses to resource use questions included in the follow-up questionnaires at 12 weeks and 9 months (see Appendix 12).

Table 18 provides an overview of the resource use recorded, sources of data and means of valuation. More details are provided in Appendix 14.

To estimate subsequent health-care costs and indirect costs, questionnaire responses were

TABLE 18 *Measurement and valuation of resources used*

Resource	Measure	Source of data	Valuation
Intervention	Resources per person fitted	Trial sites	National average unit costs
Post intervention: ambulatory care (outpatients, GP contacts, therapist contacts, investigations, medication)	Number and type	Participant questionnaire	National and local average unit costs
Post intervention: inpatient care (ward stay)	Number and length of stay	Participant questionnaire	National average unit costs
Sick leave	Number of days off work	Participant questionnaire	National average daily wage

combined to provide information on resource use for the full follow-up period. Unit costs for health-care resources were derived from local and national sources and performed in line with best practice.[81] Full details are in Appendix 14.

The total cost for each individual participant was estimated as the sum of:

1. the cost of the ankle support material plus the time required to fit multiplied by the cost per minute of a mid-scale grade E nurse
2. the number of consultant, GP, physiotherapy, osteopath and chiropractor consultations multiplied by the reported cost or average cost per attendance for professional specified, as appropriate
3. the number of scans [radiography, ultrasound, magnetic resonance imaging (MRI), computerised tomography (CT)] multiplied by the reported cost or average price per scan
4. the length of hospital stay multiplied by the cost per participant day
5. specified medications, creams/gels and aids multiplied by the *British National Formulary* (BNF) prices, or participant self-reported prices.

Cases were limited to participants for whom resource use and economic outcome data (EQ-5D) were available or could be imputed over the 9-month period, following established practice.[82]

Costs were summed to provide a total cost estimate for individuals in the three treatment arms and the mean comparative cost was compared with that for tubular bandage participants. Data were analysed separately for direct health-care costs and for direct plus indirect costs. Costs were standardised to 2005–6 prices when possible (see Appendix 14).

Cost-effectiveness analysis

Time to recovery of mobility or increases in ambulatory score had been identified at the outset of the study as an appropriate measure of clinical effectiveness for this purpose. In the event, the time to recovery outcome measure was rejected because the quality of data obtained in questionnaire responses was judged too poor to enable an accurate analysis; participants tended to provide inconsistent responses at consecutive time points, or no response at all. Ambulatory scores examined were the FLP and the FAOS. To assess cost-effectiveness, comparison was made between baseline and 9-month data and, as is established practice, we estimated ICERs comparing interventions with the control group.[83]

Cost–utility analysis

Cost–utility analysis measures the cost of an intervention and expresses its benefit quantitatively, in terms of QALYs. QALYs are calculated by estimating the total life-years gained from a treatment, then weighting each year gained with a quality of life score (from 0, representing worst health, to 1, indicating perfect health). The differences between the costs and effects of two interventions (as measured by QALYs) are expressed as a ratio, the ICER.

The primary outcome measure for the economic evaluation was the EQ-5D. This is a multidimensional measure of HRQoL that can be used to provide a valuation of utilities, or strength of preference of being in a particular health state. The single index figure produced can be used to record HRQoL over time and assess value for money. Changes in EQ-5D scores over the study period were calculated in terms of the area under the curve, assuming linear movement between

four time points, to generate QALYs.[84] For the cost–utility analysis the comparison made was undertaken from baseline to 9 months and only participants for whom we had or could impute figures for EQ-5D were included. However, an analysis of baseline characteristics (EQ-5D index, FLP, age, gender, height, weight), comparing included and excluded cases, indicated no significant differences (95% CI), confirming that the sample used for the economic analyses is representative. Because there are no substantial up-front costs, nor are costs or benefits being tracked over a long period,[85] we did not discount either costs or benefits.

Given that outcomes for the three intervention groups (measured using EQ-5D) looked broadly equivalent, the application of cost-minimisation analysis might appear attractive in the interests of keeping the economic analysis simple. However, there are major shortcomings with this approach,[85] which means that it should not generally be applied except in exceptional circumstances.[76] This supported the case for the use of cost–utility analysis.

Results

Results given in Chapter 3 showed that at 4 weeks the below knee cast was the most effective treatment with respect to reduction of pain and QoL measures but that by 9 months there were no statistically significant differences observed between groups. These observed early differences appear to be clinically significant.

Health-care costs

Mean direct health-care costs per participant are shown for all four groups in *Table 19*. Comparison of the main intervention costs indicated that the Bledsoe boot was the most expensive form of ankle support (£215 including fitting), with tubular bandage the least expensive (£1.44). Of the remaining two interventions the Aircast brace was more than twice as expensive as the below knee cast. For Bledsoe boot participants the intervention cost was the main cost driver overall, accounting for 59% of the total cost. For the other three arms subsequent treatments for ankle sprains were the major cost driver accounting for between 63% and 80% of health-care resources used.

Summing all of the health-care costs in *Table 19* to produce a total health-care cost gave similar results: Bledsoe was the most expensive (£365.01) and tubular bandage the least expensive (£135.09) treatment, whereas the total costs for the below knee cast and the Aircast brace were now comparable. The mean total health-care cost for the Bledsoe boot was higher than that for the tubular bandage group; overall costs associated with the below knee cast and the Aircast brace participants were not significantly different from those associated with tubular bandage participants.

TABLE 19 *Direct health-care costs by resource category*

	Mean participant cost (£) (% of total direct health-care cost)			
Category	**Tubular bandage**	**Below knee cast**	**Aircast**	**Bledsoe**
Intervention cost (including fitting)	1.44 (1)	16.46 (10)	39.23 (24)	215.03 (59)
Incremental treatment cost	–	+15.02	+37.79	+213.59
Subsequent consultation cost for ankle injury	95.33 (71)	137.25 (80)	104.46 (63)	118.77 (33)
Subsequent imaging cost	18.87 (14)	2.02 (1)	2.91 (2)	16.05 (4)
Subsequent hospital admissions cost	4.84 (4)	0 (0)	10.73 (6)	4.56 (1)
Subsequent prescribed medication cost	7.03 (5)	4.17 (2)	3.84 (2)	3.84 (1)
Subsequent purchased medication cost	7.58 (6)	10.64 (6)	5.35 (3)	6.75 (2)
Total direct health-care cost	135.09 (100)	170.54 (100)	166.52 (100)	365.01 (100)[a]
Incremental total cost	–	+35.45	+31.43	+229.92
Number of cases (imputed)	81 (5)	78 (2)	73 (1)	86 (3)

a Significant at 0.05 level relative to tubular bandage (control group).

The figures in *Table 19* are based on cases for which we either had complete EQ-5D outcome data over the 9-month period or had sufficient data points to enable us to estimate cumulative utility so that costs could be related to outcomes in the form of ICERs for the main economic analysis (see Chapter 2 and Cost–utility analyses, below).

Impact of incorporating indirect costs

Indirect costs (i.e. sick leave) were estimated based on the number of days a participant reported being absent from work multiplied by a daily cost figure (£119.70) derived from the mean gross annual UK pay in 2004, assuming 230 working days per year, inflated to 2005 prices.[86] *Table 20* shows that approximately three-quarters of participants were in employment, the remainder being students, retired or unemployed. Of those who were employed an average of 19% worked part-time.

If indirect costs were incorporated the total costs for each of the four arms were raised substantially (*Table 20*). Sick leave costs accounted for between 69% and 87% of the total cost for each group. Because inclusion of indirect costs may not meet the needs of NHS decision-makers and their valuation is contentious,[87,88] the main economic analysis focused on direct health-care costs.

A more detailed breakdown of the pattern of resource use, both direct and indirect items, is shown in *Table 21,* and the resulting estimated costs are listed in *Table 22*. It is widely recognised that clinical trial-related cost data exhibit skewed distributions[90] and so we have presented the median and interquartile range for the total average costs for each of the four arms of the trial.

Cost-effectiveness analysis

The incremental cost per unit improvement in FLP ambulatory score and FAOS score were estimated. The preliminary analysis did not yield conclusive results. Moreover, as we lacked information on how much society (or clinicians) would be willing to pay for a one-unit improvement in these scores it was not possible to draw any conclusions from findings in terms of value for money for the NHS. For this reason, and in the interests of clarity, the only economic analysis results presented in this report are for the cost–utility analyses.

Cost-utility analyses

Table 23 presents the cost–utility analysis findings of the incremental cost per QALY gained for the three interventions relative to tubular bandage. To produce these ICERs we used bootstrapping techniques to generate 1000 replications of actual cost and effect data. *Table 23* presents the point estimates for cost per QALY; more detailed outputs are reported in Appendix 15.

The Aircast brace and below knee cast had similar ICER values, whereas the Bledsoe boot had a much higher figure (over £2000 per QALY gained). Although there is debate about the exact amount society should be willing to pay for a QALY, the National Institute for Health and Clinical Excellence (NICE) employs a threshold of approximately £20,000–£30,000 per QALY when considering new technologies.[89] *Table 23* shows that, considering direct health-care costs only, all three intervention groups were associated with a cost per QALY gained that is well within this range. The most cost-effective means of achieving a QALY was the Aircast brace, although this intervention was only marginally more cost-effective than the below knee cast.

TABLE 20 *Direct health-care and indirect sick leave costs by resource category*

	Mean participant cost (£) (% of sample)			
Category	**Tubular bandage**	**Below knee cast**	**Aircast**	**Bledsoe**
Indirect sick leave cost at £119.70 per diem	805.39 (86)	915.40 (84)	1147.81 (87)	822.59 (69)
Direct health-care cost	135.09 (14)	170.54 (16)	166.52 (13)	365.01 (31)
Total cost including sick leave	940.48 (100)	1085.94 (100)	1314.33 (100)	1187.60 (100)
% in group employed	79	75	78	76
% employed who work part-time (< 25 hour per week)	16	17	19	25
Mean number of days off work	6.9	7.7	9.6	6.9

TABLE 21 *Breakdown of resource use*

	Number recorded (% of patients not using this resource)			
Resource item	**Tubular bandage**	**Below knee cast**	**Aircast**	**Bledsoe**
Number of participants	81	78	73	86
Interventions requiring fitting	81	78	73	86
Consultations				
Emergency department staff (plaster technician)	2	9	7	3
NHS consultant	0	2	19	7
Private consultant	7	8	8	8
GP	52	35	44	66
Osteopathy	0	0	0	0
Chiropractor	2	1	0	0
NHS physiotherapy	44	47	53	68
Private physiotherapy	113	107	60	110
Other	0	3	4	1
Mean number per participant	2.7 (60)	2.7 (60)	2.7 (63)	3.1 (65)
Imaging				
Radiography	5	4	3	6
Magnetic resonance imaging	0	0	0	2
Ultrasound	1	1	2	1
Private imaging	3	0	1	1
Mean number per participant	0.1 (93)	0.1 (94)	0.1 (94)	0.1 (90)
Inpatient episodes				
Inpatient days	1	0	2	1
Mean number per participant	0.0 (99)	0 (100)	0.0 (99)	0.0 (99)
Prescribed medication				
Painkillers	22	9	12	7
Anti-inflammatories	7	5	7	6
Creams/gels	1	0	0	2
Aids/braces/strapping	1	3	4	1
Injection	0	0	0	0
Other	3	2	2	3
Mean number per participant	0.4 (74)	0.2 (83)	0.3 (79)	0.2 (86)
Bought medicines				
Painkillers	25	19	23	16
Anti-inflammatories	11	14	13	8
Creams/gels	12	8	9	8
Aids/braces/strapping	17	34	8	25
Herbal remedies	1	3	1	3
Other	2	3	1	3
Mean number per participant	0.9 (60)	1.0 (45)	0.8 (56)	0.7 (58)
Sick leave				
Days off work	555	596.5	700	591
Mean number per participant	6.9 (65)	7.7 (60)	10.0 (59)	6.9 (63)

TABLE 22 *Breakdown of costs*

Resource item	Cost per participant (£) (total cost for group) [% of participants not using this resource]			
	Tubular bandage	**Below knee cast**	**Aircast**	**Bledsoe**
Number of participants	81	78	73	86
Interventions				
Ankle support intervention	0.34 (27.54)	12.80 (998.40)	38.19 (2787.87)	212.68 (18,290.48)
Cost of fitting the intervention	1.10 (89.10)	3.66 (285.48)	1.04 (75.92)	2.35 (202.10)
Average cost per participant	1.44	16.46	39.23	215.03
Consultations				
Emergency department staff (plaster technician)	0.09 (7.32)	0.42 (32.94)	0.35 (25.62)	0.13 (10.98)
NHS consultant	0 (0)	1.87 (146.00)	19.00 (1387.00)	5.94 (511.00)
Private consultant	10.37 (840.00)	12.31 (960.00)	13.15 (960.00)	22.86 (1965.60)
GP	33.77 (2735.20)	23.60 (1841.00)	31.70 (2314.40)	40.37 (3471.60)
Osteopathy	0 (0)	0 (0)	0 (0)	0 (0)
Chiropractor	0.62 (50.00)	0.52 (40.52)	0 (0)	0 (0)
NHS physiotherapy	4.38 (354.64)	4.86 (378.82)	5.85 (427.18)	6.37 (548.08)
Private physiotherapy	46.11 (3734.58)	49.75 (3880.75)	28.92 (2111.34)	42.76 (3677.30)
Other	0 (0)	43.92 (3425.50)	5.48 (399.99)	0.35 (30.00)
Average cost per participant	95.33 [60]	137.25 [60]	104.46 [63]	118.77 [65]
Total costs for this category	7722	10,706	7626	10,215
Imaging				
Radiography	1.40 (113.60)	1.17 (90.88)	0.93 (68.16)	1.59 (136.32)
Magnetic resonance imaging	0 (0)	0 (0)	0 (0)	7.28 (626.00)
Ultrasound	0.83 (67.00)	0.86 (67.00)	1.84 (134.00)	0.78 (67.00)
Private imaging	16.64 (1348.00)	0 (0)	0.14 (10.00)	6.41 (551.00)
Average cost per participant	18.87 [93]	2.02 [94]	2.91 [94]	16.05 [90]
Total costs for this category	1529	158	212	1380
Inpatient episodes				
Inpatient days	4.84 (391.81)	0 (0)	10.73 (783.62)	4.56 (391.81)
Average cost per participant	4.84 [99]	0 [100]	10.73 [99]	4.56 [99]
Total costs for this category	392	0	784	392
Prescribed medication				
Painkillers	5.46 (442.58)	2.36 (184.40)	2.48 (180.92)	2.20 (189.46)
Anti-inflammatories	0.78 (63.00)	0.99 (77.40)	0.75 (54.56)	0.65 (56.20)
Creams/gels	0.10 (8.00)	0 (0)	0 (0)	0.22 (18.60)
Aids/braces/strapping	0.12 (9.99)	0.41 (32.04)	0.13 (9.68)	0.07 (6.35)
Injection	0 (0)	0 (0)	0 (0)	0 (0)
Other	0.57 (45.96)	0.40 (31.08)	0.48 (35.00)	0.70 (60.00)
Average cost per participant	7.03 [74]	4.17 [83]	3.84 [79]	3.84 [86]
Total costs for this category	570	325	280	331

continued

TABLE 22 *Breakdown of costs*

	Cost per participant (£) (total cost for group) [% of participants not using this resource]			
Resource item	**Tubular bandage**	**Below knee cast**	**Aircast**	**Bledsoe**
Bought medicines				
Painkillers	3.51 (284.17)	2.12 (165.28)	1.70 (123.86)	1.76 (151.00)
Anti-inflammatories	0.68 (54.79)	1.33 (103.42)	1.71 (124.69)	0.51 (43.67)
Creams/gels	0.90 (72.54)	1.07 (83.46)	0.88 (64.05)	0.44 (37.44)
Aids/braces/strapping	2.03 (164.59)	5.56 (433.64)	0.89 (64.96)	3.52 (302.61)
Herbal remedies	0.04 (3.00)	0.32 (25.05)	0.11 (8.00)	0.41 (35.01)
Other	0.43 (35.00)	0.24 (19.00)	0.07 (5.00)	0.13 (10.99)
Average cost per participant	7.58 [60]	10.64 [45]	5.35 [56]	6.75 [58]
Total costs for this category	614	830	391	581
Sick leave				
Average cost per participant	805.39 [65]	915.40 [60]	1147.81 [59]	822.59 [63]
Total costs for this category	65,236	71,401	83,790	70,743
Average cost per participant				
Mean	940.48	1085.94	1314.99	1187.60
Median	123	113.48	124.07	257.45
(Interquartile range)	(1.44–881.87)	(16.46–960.68)	(39.23–1697.33)	(215.03–1518.20)
Total costs for this category	76,179	84,703	95,946	102,133

TABLE 23 *Cost–utility analysis: incremental cost-effectiveness ratios (ICERs), direct health-care costs only*

	Tubular bandage	Below knee cast	Aircast	Bledsoe
Number of participants	81	78	73	86
ICER (direct health-care costs only)	–	£339[a]	£301	£2116

a Simulation output (1000 trials) ICERs.

There are some methodological problems associated with the application of ICERs,[91] and summarising clinical trial results in terms of ICERs can be misleading when there are more than two comparators. A particular arm may have the most favourable cost per QALY gained but a lower level of effectiveness than other intervention(s). In these circumstances an alternative intervention that is more effective but also associated with a higher cost may actually represent a more favourable option if the effectiveness gain justifies the additional marginal cost.

In such a situation, and to summarise uncertainty around ICER estimates, the use of cost-effectiveness acceptability curves (CEACs) is becoming increasingly accepted within clinical trials to assess different options.[92] CEACs have the advantage that the curves convey information from which inferences can be made about the statistical significance or otherwise of cost-effectiveness results.[93] For multiple comparators one can attempt to rank the options by cost and then remove the options by simple and extended dominance.[94] However, to do this discernible differences must

exist in effectiveness between comparators. In this instance, the differences in average effects between intervention groups (as measured using EQ-5D) are so small that they are not statistically significant. Therefore, although we could assume that the control group was not a cost-effective option (because of the relatively small incremental cost per QALY associated with all of the intervention groups relative to the control group) we lacked a basis to rank interventions using either simple or extended dominance. Thus, we considered the cost-effectiveness of all options relative to the control group.

A CEAC curve (*Figure 12*) indicates the probability (on the vertical axis) that an intervention is cost-effective relative to the comparator group for a range of possible societal valuations of a QALY (on the horizontal axis). If, for any given valuation of a QALY, the CEAC reaches or exceeds a 95% probability then it is possible to conclude (at the 5% significance level) that this intervention is cost-effective relative to the control group. Several interventions can be displayed on the same graph and thus CEACs can shed light upon cost-effectiveness in more complex decision-making contexts.

The CEAC curves in *Figure 12* demonstrate that there is a high probability that all three interventions are more cost-effective than the control (tubular bandage) for most reasonable cost per QALY thresholds. Both the below knee cast and the Aircast brace were virtually the same, indicating that these two interventions had a comparable cost-effectiveness. The Bledsoe boot curve lay below these two, indicative of lower cost-effectiveness.

Appendix 16 provides scattergrams illustrating cost-effectiveness for the 1000 simulations under the different treatment regimes for direct care costs only (*Figures 14–16*). Similar benefits accrued on use of the Bledsoe boot as a treatment for greater health-care costs than for Aircast or below knee cast in almost all simulations.

Impact of indirect costs on ICERs

To take the costs associated with absence from work into account we could use either a friction cost or a human capital approach. Although the friction cost approach has its advocates,[95,96] it lacks a foundation in economic theory.[97,98] Therefore, in the interests of simplicity we used a human capital approach.

When the costs of days off work because of illness were included, a different picture emerged (*Table 24*). The Aircast brace was now the least cost-effective intervention and the below knee cast remained the best in terms of value for money.

The CEACs shown in *Figure 13* suggest that, once costs arising through sick leave were included, the Aircast brace was the least cost-effective option and that, once society values a QALY at around £7500, both the Bledsoe boot and below knee cast appeared to be equally cost-effective. All three interventions were cost-effective compared with the control group (tubular bandage) assuming a cost-effectiveness threshold of £20,000 per QALY.

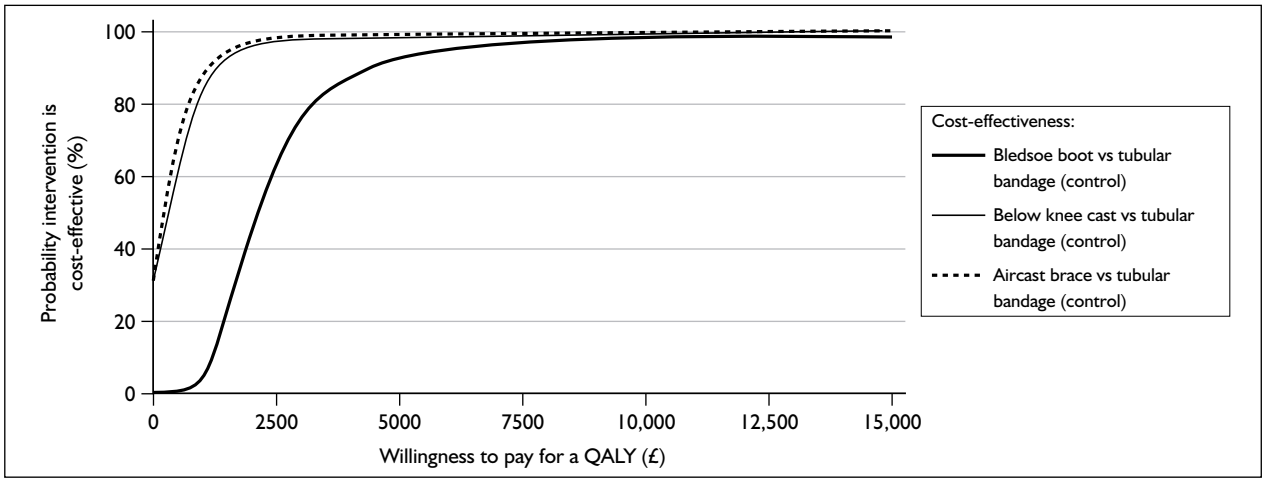

FIGURE 12 *Simulation output (1000 trials) cost-effectiveness acceptability curves (CEACs). Graph showing the probability of an intervention being cost-effective relative to tubular bandage at different levels of willingness to pay for an additional quality-adjusted life-year (QALY) (direct health-care costs only; excludes sick leave costs).*

TABLE 24 *Cost–utility analysis: incremental cost-effectiveness ratios (ICERs), direct health-care and indirect sick leave costs*

	Tubular bandage	Below knee cast	Aircast	Bledsoe
Number of participants	81	78	73	86
ICER (direct health-care and indirect sick leave costs)	–	£1393[a]	£3585	£2275

a Simulation output (1000 trials) ICERs.

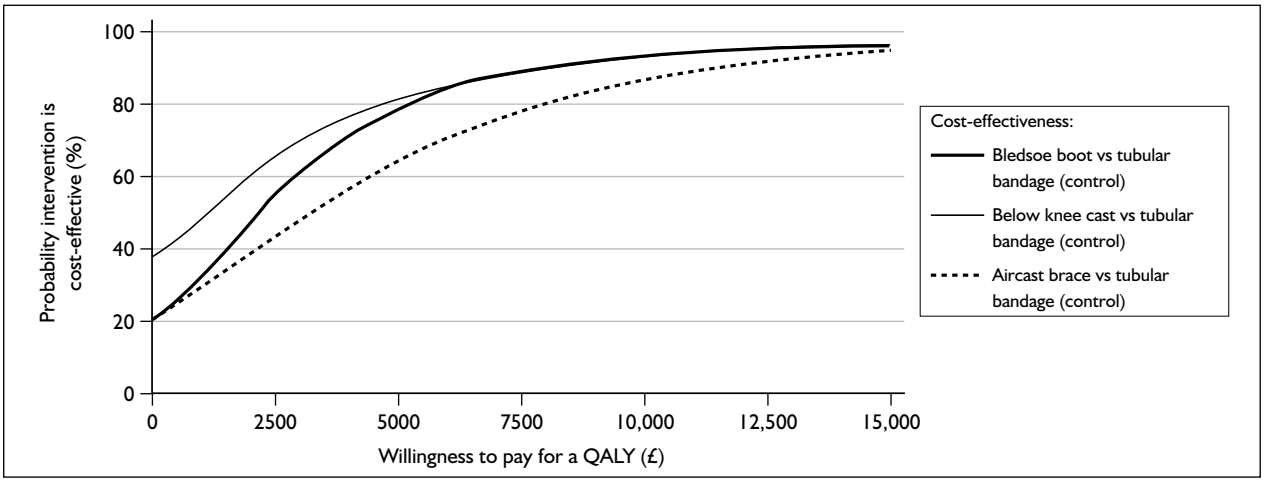

FIGURE 13 *Simulation output (1000 trials), cost-effectiveness acceptability curves (CEACs). Graph showing the probability of an intervention being cost-effective relative to tubular bandage at different levels of willingness to pay for an additional quality-adjusted life-year (QALY) (direct health-care and indirect sick leave costs).*

Appendix 16 provides scattergrams illustrating cost-effectiveness for the different ankle support regimes including indirect costs (*Figures 17–19*), showing that, if sick leave costs were included, there was little to discriminate between the three interventions in terms of costs or benefits accrued.

Sensitivity analyses

There will be uncertainties in many of the estimates above and in some of the assumptions made (e.g. the average cost per day off work). In addition to the bootstrapped probabilistic sensitivity analysis described above, one-way sensitivity analyses for a range of input parameters were used to examine the uncertainty in any conclusions drawn on relative cost-effectiveness.[99] Analyses considered key cost drivers and factors that might affect the outcomes measured.

In terms of costs the main health system cost driver was the cost of the interventions themselves (from 34p for tubular bandage to £212.68 for Bledsoe boots). Staff costs for fitting interventions were not key drivers (£1.10 and £2.35 per participant for these same supports respectively). For intervention costs, prices were not adjusted to make any allowance for bulk discounts because this would require very large orders, which it was judged that individual NHS trusts were unlikely to be able to sustain. However, for the purpose of sensitivity analysis we established with manufacturers how costs might be affected if NHS trusts could obtain either Aircast braces or Bledsoe boots at a bulk buy discount (e.g. through some centralised purchasing arrangement via NHS supplies). For Aircast braces the suppliers offered a bulk buy price of £22.56 (list price £38.19 including VAT) but only for bulk orders of 500 braces on a 3-year contract. For Bledsoe boots bulk buy costs would be £58.75 (list price £212.68 including VAT) for orders of over 100 per year. Bulk purchase was not appropriate for either tubular bandage (cost too low at 34p) or below knee casts (relatively inexpensive at £12.80

and available from a variety of suppliers so prices are competitive).

The main uncertainty in the measures of benefit used was the use of imputation for missing EQ-5D data, although the number of cases involved was very small (1–3% depending upon treatment arm).

Health-care cost perspective

The following one-way sensitivity analyses were undertaken.

Impact on health-care cost of removal of imputed cases

Removal of participants for whom imputed values had been used had no effect on the ranking of the three interventions (*Table 25*).

Impact on health-care cost of assuming bulk buy prices

Table 25 shows that bulk buy of the Bledsoe boot or the Aircast brace reduced the respective ICER value. However, the Bledsoe boot still ranked as the least cost-effective intervention, whereas the Aircast brace became substantially more favourable than the below knee cast.

Societal cost perspective

The inclusion of sick leave costs meant that it was no longer possible to draw clear conclusions regarding the cost-effectiveness of the comparator arms and so sensitivity of the analysis to various assumptions about sick leave was explored rigorously.

Impact on societal cost of varying assumptions on sick leave cost

Sick leave was clearly a major cost driver, accounting for between 69% and 87% of the overall societal costs. There are a number of sources of uncertainty associated with this cost estimate.

Reported days off work and their cost

Estimation of sick leave cost raised two principal concerns. First, the cost of a day off work may have been overvalued. In cases in which some of the population is unemployed or when individuals can 'catch up' on missed work or other staff can provide cover, the real value to society of the cost of time off work may be less than that based on the value of a day off work.[87] Second, when respondents specified a given number of days or weeks off work it was sometimes unclear whether they had adjusted this figure to account for the part-time nature of their work, and thus the total number of days off work may have been overestimated. An average of 19% of working trial participants reported that they were employed part-time. We assumed in a one-way sensitivity analysis that the actual cost of a reported day off work was half the value used in the earlier analysis (£59.85). *Table 26* shows that if this lower cost for reported days off work is assumed, the below knee cast performed best, with the Aircast brace next best and the Bledsoe boot performing the worst. The cost per QALY improved and the Bledsoe boot fell from second to third in rank order, with the below knee cast and the Aircast brace remaining unchanged.

Sick leave outliers

In all groups there were a small number of people who reported a large number of weeks off work (up to 9 months). Clinical opinion was sought on how best to interpret these observations. Incapacity requiring time off work greater than 6 weeks (30 days) was thought by clinicians to be highly unusual. Recovery data from the trial were generally consistent with time to recovery not

TABLE 25 *Sensitivity analysis (incremental cost effectiveness ratios): direct health-care costs only*

	Cost per participant[a]			
	Tubular bandage	**Below knee cast**	**Aircast brace**	**Bledsoe boot**
ICER (baseline)	–	£339[b] (2)	£301 (1)	£2116 (3)
ICER (imputed cases removed)	–	£392 (2)	£323 (1)	£2184 (3)
Number of participants with imputed data	5/81 (6%)	2/78 (3%)	1/73 (1%)	3/86 (3%)
ICER (bulk buy price for Aircast and Bledsoe)	–[c]	£339[b] (2)	£151 (1)	£699 (3)

a Cost per participant is ranked from 1 to 3, with 1 being the most favourable option.
b Incremental cost-effectiveness ratios (ICERs) based on simulation output (1000 trials).
c No bulk buy price for these items.

TABLE 26 *Sensitivity analysis (incremental cost effectiveness ratios): direct health-care and indirect sick leave costs*

	Cost per participant[a]			
	Tubular bandage	**Below knee cast**	**Aircast brace**	**Bledsoe boot**
ICER (baseline, sick pay at £119.70 per diem)	–	£1393[b] (1)	£3585 (3)	£2275 (2)
ICER (sick pay at £59.85 per diem)	–	£866 (1)	£1943 (2)	£2195 (3)
ICER[c] (cap person days off work at 30 days)	–	£58 (1)	£1746 (2)	£2596 (3)
Sick leave > 30 days	5/81 (6%)	4/78 (5%)	5/73 (7%)	3/86 (3%)
ICER[c] (imputed cases removed)	–	£1031 (1)	£3024 (3)	£1794 (2)
Number of participants with imputed data	5/81 (6%)	2/78 (3%)	1/73 (1%)	3/86 (3%)
ICER[c] (bulk buy price for Aircast brace and Bledsoe boot)	–[d]	£1393[d] (2)	£3435 (3)	£858 (1)

a Cost per participant is ranked from 1 to 3, with 1 being the most favourable option.
b Incremental cost-effectiveness ratios (ICERs) based on simulation output (1000 trials).
c Sick pay assumption maintained at £119.70 per diem.
d No bulk buy price for these items.

requiring more than 12 weeks. Thus, the effect of introducing a 30-day cap to the number of sick days attributable to ankle injury was explored in a further sensitivity analysis. *Table 26* shows that removing these outliers had a similar effect to reducing the value attached to a reported day off work, with a major impact on the below knee cast ICER value (£58), and the Bledsoe boot ICER once again becoming the least favourable (rising to £2596 per QALY).

Impact on societal cost of removal of imputed cases

The impact of removing from the analysis any participants for whom imputations were made is also shown in *Table 26*. This had no effect on the ranking of different interventions relative to tubular bandage.

Impact on societal cost of assuming bulk buy prices

Table 26 also shows that assuming bulk buy prices were in operation improves significantly the ICER value for the Bledsoe boot, making it the most cost-effective intervention. For the Aircast brace there was a small improvement in the ICER value, which was not large enough to change its ranking.

Summary of societal cost perspective

Table 26 shows that the below knee cast remained the most cost-effective intervention compared with tubular bandage, ranking number one under all conditions except for bulk buy. The Bledsoe boot and Aircast brace gave similar rankings overall, each with two second places and two third places, with the Bledsoe boot ranking first under bulk buy conditions.

Discussion

From a health-care cost perspective the Aircast brace and below knee cast represented the most cost-effective interventions, with the Bledsoe boot ranked third. The cost–utility analyses also demonstrated that the Bledsoe boot was least cost-effective but that all three interventions were highly cost-effective compared with treatments for other types of condition. The cost per QALY figures extended up to a maximum of just above £2000 per QALY for the Bledsoe boot, which was well below the threshold set by bodies such as NICE of £20,000–£30,000.

To capitalise on any reduced prices associated with bulk buy arrangements some centralised purchasing arrangement would need to be established. For Aircast the suppliers offered a bulk buy price of £22.56 (list price £38.19 including VAT), but only for bulk orders of 500 braces on a 3-year contract. The eight trial clinics saw 1522 potentially eligible participants over a period of

27 months, equating to approximately 85 patients annually per centre; therefore, a throughput of 500 braces per annum would only be feasible at a five-centre level. The transaction, storage and transport costs involved in a centralised supply chain would then need to be balanced against any cost savings. The feasibility of such an arrangement is doubtful.

Conclusion

When considered from a health-care perspective alone the below knee cast and Aircast brace are the most cost-effective options for the management of severe ankle sprains. If purchased under bulk buy conditions the Aircast brace is more cost-effective than the below knee cast; however, the feasibility of a bulk buy system is doubtful. If the decision-maker's main concern is to maximise effectiveness relative to total health-care costs then the Aircast brace may have a marginal cost-effectiveness advantage over the below knee cast. The lack of a clear front-runner in terms of cost-effectiveness reinforces the case for giving patients an informed choice.

When considering societal costs as well, the below knee cast is the most cost-effective treatment for severe ankle sprains. This finding persists throughout analyses using a range of assumptions about sick leave.

The sensitivity of rank order to changes in the assumptions made about sick leave means that results from this wider cost perspective should be treated with some caution.

Chapter 5

Acceptability of a deposit system

Introduction

A component of the original brief commissioned by the National Coordinating Centre for Health Technology Assessment (NCCHTA) was to explore the feasibility of a deposit system to promote return of the mechanical supports and reuse. The manufacturers of the Bledsoe boot and Aircast brace do not recommend reuse, although both allow washing of the device.

In the context of a clinical trial it was felt that, given the manufacturer's recommendations, and the many barriers that already exist to recruitment into trials, implementing a deposit system was impractical. It was agreed with NCCHTA that a small series of interviews would be undertaken as a preliminary exploration of the topic. We undertook a small qualitative study to examine participants' opinions of the viability of a refundable deposit system for expensive items such as the Bledsoe boot.

Method

A total of 19 CAST trial participants (10 males and 9 females) undertook semistructured interviews. They were conducted by a single researcher (RN). Participants were asked four questions:

1. How would you have felt if we had asked for a refundable deposit on the boot/brace to encourage you to return it?
2. How big a deposit would encourage you to return the boot/brace? £0–5, £5–10, £10–15, £15–20, more than £20?
3. Would you have been willing to pay this amount if asked?
4. If you had been asked to pay a deposit, do you think this would have affected your willingness to take part in the trial? Please explain.

All interviews were audio tape recorded with the participant's consent and later transcribed verbatim. The key questions were designed to give yes/no responses but a subsequent explanation of the answer was open. Thematic analysis of these responses was undertaken.

Participants

The mean age of participants was 34 (range 16–62). Eight participants were non-drivers. The level of sporting activity of participants ranged from no participation in sport to regular participation in three or more sporting activities. The majority of participants (12, 63%) had injured their ankle between 3 and 6 months before the qualitative study. Four participants were randomised to tubular bandage, four received a below knee cast, six received a Bledsoe boot and five received an Aircast brace. Analysis was performed using the approach of framework analysis.[100]

Results

The idea of a refundable deposit to encourage return of the boots was explained to the participants and they were then asked whether they would have been willing to pay (*Table 27*).

The majority of participants had no problem with the idea of paying a deposit. Some participants had previous experience of shortages of hospital equipment and were willing to participate in a

TABLE 27 *Frequencies of those willing or not to pay a deposit*

	Yes		No		Not sure	
	n	%	*n*	%	*n*	%
Willing to pay deposit	16	73	1	5	2	9

scheme to help prevent this. Two participants were unsure and expressed expectations of 'free' health care. Having to pay a deposit (even if refundable) went against these expectations. One participant was flatly against the deposit system, stating that paying a deposit 'goes against the grain'. Two of the participants suggested that they felt a social obligation to return hospital equipment and that they felt a deposit would not make any difference to them. Most participants ($n = 14$, 64%) felt that a deposit of between £15 and £20 would be fair considering the cost of the Bledsoe boot. Although most participants would be willing to pay they were then asked whether they would have had sufficient funds on them at the time of their emergency department attendance. About half of the participants felt that they would not have had enough cash to pay such a deposit, although many would have had either a cheque book or credit/debit cards.

Conclusion

This is a small study that aims only to give an initial exploration of the acceptability of a deposit system. Participants were generally happy with the concept of paying a deposit for a device like the Bledsoe boot. However, the mechanical integrity of the devices over prolonged periods of use and different cleaning regimes is unknown and would have to be established before reuse could be recommended. If the device had proven a more clinically effective option, a deposit and reuse system may have reduced the overall cost. No further modelling was undertaken given the results of the trial. The costs of implementing a deposit system for the Aircast brace are likely to outweigh any benefits if the device was reusable. Neither the tubular bandage nor below knee casts are fit for reuse.

Further research is required to determine the effects of deposits in clinical trials.

Chapter 6
Discussion

Main findings of the trial

This is the first large RCT of three types of mechanical support for ankle sprains of sufficient severity to prevent weight bearing. Results showed a clinically and statistically significant advantage for the use of a below knee cast compared with tubular bandage in relation to symptom resolution and return of normal activity and function in the first 3 months. Benefits were maximal in the first 3 months of recovery. The differences between tubular bandage and the Aircast ankle brace and the Bledsoe boot had less clear clinical relevance, although the Aircast brace gave significantly better results for mental well-being in the early stages. The economic evaluation indicates that from a health-care perspective the Aircast brace and below knee cast perform similarly in terms of cost-effectiveness. The Bledsoe boot is the least cost-effective (relative to tubular bandage).

External validity and generalisability of the findings

This multicentred trial recruited from eight centres ranging from teaching hospitals to district hospitals, with a range of sizes of emergency departments, in a variety of metropolitan, urban and semirural environments. The services available in these hospitals reflected the normal services in UK hospitals, with none having specific specialist services applicable to this type of injury. The level of training in application of braces was consistent with what would be expected in routine clinical practice, with some being applied by plaster technicians but most being applied by other clinical staff, as is normal practice for these units. No special instructions regarding the type of below knee casts were given, but all sites used synthetic casts.

The interventions before application of the tubular bandage or mechanical support were standardised to ensure equality between treatment arms. This minimised risk, including compartment syndrome associated with excessive swelling, and ensured that injuries were of sufficient severity to meet the case definition. Injury severity is particularly difficult to ascertain until time has passed and swelling has had a chance to resolve. Audit has demonstrated that there was variable referral into the trial by clinicians, with between 15% and 100% of potential participants being referred to the clinic for consideration of recruitment. It was not possible to collect detailed information about these potential participants. We have no reason to believe that there was a systematic bias in those approached. Of those unable to weight bear at the time of presentation who were given a clinic appointment, 512 (43%) had symptom resolution by the time of clinic attendance and were therefore not eligible for the trial. In practice, it is possible that the tubular bandage, Bledsoe boot or Aircast brace could be applied at the time of emergency department presentation. However, this is highly unlikely to affect the results that we obtained. Larger numbers of less severe self-limiting injuries would have been included. A study of current practice[20] showed low usage of mechanical supports at initial presentation, and it is believed that current practice in emergency medicine is for delayed application.

Loss to follow-up was minimal for the first 3 months of the trial and the internal validity of the study was not compromised. Slightly higher losses occurred by the 9-month follow-up; however, the main purpose for continuing follow-up until 9 months was not to detect differences between treatment but to ensure that, overall, no one treatment was associated with a consistently poor profile. Otherwise, internal validity of the study was good (see comments in the section on limitations of the study).

Overall, we believe that the generalisability of this trial is good, with valid representation of severe injury (represented by the inability to weight bear as a proxy for grade II and III injuries), a wide range of hospitals and substantial numbers of participants. It is not known whether the spectrum of patients presenting to emergency departments is similar to those presenting to minor injury units, primary care or sports injury facilities. However, the number of patients with the severity of injury

studied here who are treated at these facilities is likely to be small, as all of these patients require radiography.[65] It is believed that the results of this trial should be applicable to all patients conforming to the inclusion/exclusion criteria of the trial.

It is important to note that this trial is related to the subgroup of patients who presented to emergency departments with an ankle sprain of such severity that they were unable to weight bear on that leg at the time of presentation and were still unable to weight bear at a review clinic a few days later. The population in this study had a slightly higher proportion of males than females, similar to previous studies, but average age was slightly higher than in previous studies because of the inclusion criteria (no upper age limit and all types of injuries). All participants received advice to elevate the limb, use ice, rest and undertake gentle non-weight-bearing exercises in the days between emergency department attendance and the clinic appointment. This initial period of 2–3 days may be important for the subsequent outcome, as it results in reduced swelling and also promotes early movement. The reduction in swelling is important both to speed up the healing process and to reduce pain, and also to allow proper fitting of any external support devices. The Aircast brace can be applied in the presence of oedema and gradually adjusted as swelling reduces, but the Bledsoe boot and tubular bandage may be oversized if applied early in the presence of swelling. A cast that can be weight bearing is contraindicated in the first few days because of the risk of compartment syndrome.

Internal validity and limitations of the trial

The trial groups were comparable for age, sex, educational status, baseline symptoms and injury characteristics and we do not believe that there has been any bias in allocation to the four treatment groups. Overall, the trial group was comparable to the English population for sex, height, BMI, employment, educational status and ethnicity, based on 2001 census data and data from the 2004 Health Survey for England. Comparative data for previous ankle injuries and symptoms are not available.

Uptake of treatment varied between groups. The below knee cast is the only treatment that participants cannot remove themselves. The majority of those who declined the trial because they did not want a particular treatment cited plaster as their reason for declining (46 out of 57 participants, 81%) (see *Table 4*). Insignificant numbers did not receive the allocated intervention for other reasons, were lost to follow-up or discontinued their treatment. The compliance rate over the following 2 weeks is not known; participants in the non-cast group could remove their splints either intermittently or permanently after leaving the clinic.

The follow-up rates in the study were high compared with similar clinical trials, with follow-up rates of 83%, 82% and 76% for the 4-week, 12-week and 9-month questionnaires respectively.

At the time of randomisation (a few days after injury), most participants were abstaining from sport, were not confident in walking, had moderate or frequent pain and had moderately severe symptoms. Nearly all participants reported some difficulty in basic self-care and mobility. In comparison with age- and sex-adjusted population norms, the participants had significantly impaired mobility but similar mental health scores.

We confirm the findings of other investigators in smaller studies that ankle sprains presenting with the inability to weight bear do not recover quickly; many participants still had limited mobility and function resulting from their injuries at 9 months. Patients with ankle sprains who initially present with an inability to weight bear should be given a cautious prognosis and warned of potential long-term effects on their mobility and activities. Recovery is slower and less complete with increasing age. At all follow-up points and across all randomisation groups the scores of men were better than those of women on all primary outcome measures.

Three participants in the study developed DVT and two suffered pulmonary emboli (although one was probably related to pregnancy rather than the injury and the other had a past history of thromboembolic disease and was taking warfarin and was randomised in error). These adverse events were not associated with any particular treatment arm. Thromboembolic events are a recognised but unquantified event after ankle injury. Our study suggested a rate of 1% (4/584) of ankle injuries having a clinically apparent thromboembolic event within 9 months of injury. Numbers were too small to give differential rates

by treatment. The risks/benefits of the use of prophylactic anticoagulation in lower limb injury are uncertain[101] and could usefully be investigated in future studies.

Clinical findings

The differences observed between treatments were broadly consistent across all physical measures and their subscales.

Mental health status at 4 weeks fell to below the norm for all treatment groups, suggesting that this injury has an adverse effect on mental well-being regardless of the support method used. For mental health the results suggest that the removable supports may give better results than either tubular bandage or the fixed below knee cast. By 9 months only the tubular bandage group had mental health scores below the population norm. Psychological issues will result from a combination of the effects of the injury, the recovery and the treatment. Although the below knee cast resulted in quicker recovery it did not give the best mental health scores early on; however, by 9 months the scores were comparable for all groups except for tubular bandage. It is possible that the inability to remove the boot, for either comfort or hygiene purposes, may be responsible for this effect.

Trials that use disability and HRQoL outcomes face significant challenges in interpreting the clinical meaningfulness of the observations made. There are some benchmarks against which we can assess the clinical importance of the differences between treatments. Changes in scores of between 2.5 and 4.0 points on the SF-12 are generally considered clinically meaningful in terms of the individual.[102] Studies of the use of visual analogue scales for pain severity in the emergency care setting indicate that a change of 13 mm is the accepted level for indicating a clinically significant change.[103,104] There is little evidence to determine clinically significant changes in the FAOS, although the authors have suggested that an 8- to10-point difference, as used in the Knee injury and Osteoarthritis Outcome Score, is clinically significant.[105] These guidelines suggest that differences between the treatments observed on the FAOS scores were small at baseline and of moderate size at 12 weeks. Differences between tubular bandage and the below knee cast were commensurate with a clinically significant change. An alternative method is to express the differences between groups in relation to the standard deviation.[106] Effect sizes of 0.25 are considered small but may be of clinical relevance, and those of 0.25–0.5 are considered moderate but are likely to be of clinical relevance. Overall, our interpretation of findings of the CAST study are that the benefits afforded by below knee casts in relation to tubular bandage are clinically small at 4 weeks, but clinically more substantial by 12 weeks, affording greater recovery of mobility, comfort and confidence in the ankle.

Present medical opinion has suggested the importance of early mobilisation and the role of early return of proprioceptive stimulation as key determinants of recovery in ankle sprains. Results from our study contradict this theory by demonstrating that the treatments producing most immobilisation resulted in quicker recovery, without any longer-term disadvantage. However, although we used a below knee cast, it was for a relatively short period compared with that in many studies. There are various pathophysiological mechanisms that could explain our findings that a period of immobilisation may be beneficial, including a decreased risk of further reinjury and rebleeding even at the microscopic level, an early decrease in pain encouraging better mobilisation once the cast is removed, short-term abolition of pain reducing plastic changes in the central nervous system that can lead to increased vigilance of the ankle and the development of centrally sensitised pain, decreased swelling because of increased elevation of the cast compared with other patients, a better proprioceptive response when the cast is removed because of decreased swelling and loss of abnormal stimulus that may occur in the early recovery phase, and a decreased inflammatory response with decreased abnormal fibrosis and a recovery period allowing return of tensile strength of ligaments before mobilisation. The initial 2-day period may be important in dispersing initial haematomata that could lead to a fibrotic response.

It is possible that long-term instability (becoming apparent after 9 months) occurs, but this would not be detected in this study. It is well recognised that a period of initial movement can prevent stiffness in joints that are subsequently immobilised. We do not know how much exercise people undertook when in each form of splint or how much/when they removed the device. If a period of relative immobility is the reason for the improved outcome

then it is possible that the other groups performed less well because they could remove the splint and therefore moved the ankle more. It would only be possible to determine this by trials of varying regimes of usage of the various splints, to inform any instructions on splint usage. The below knee cast completely immobilises, and therefore gives better analgesia during its use, but this benefit persists at 4 weeks (over 2 weeks after removal). Early diminution of pain may have important consequences for encouraging recovery and could potentially be duplicated by better analgesia. The below knee cast is the only device for which the period of support is guaranteed and which cannot be varied by the patient or by the clinician's instructions. It may also have other reasons for improved outcome that could be independently manipulated, such as indirectly encouraging more elevation, less dependency and less use of the whole limb, being more likely to be elevated at night and providing better analgesia.

With no benefit in outcome and with worse mental health scores this study does not recommend the use of tubular bandage in severe ankle sprains. It is unlikely that severe injuries would be appropriately treated by the widely used RICE (rest, ice compression, elevation) regime.

Cost and economic analysis

Mean direct health-care costs per participant indicated that the Bledsoe boot was the most expensive form of ankle support, with tubular bandage the least expensive.

Cost–utility analysis, comparing incremental costs with differential impact on HRQoL over 9 months, demonstrated that from a health-care perspective the Aircast brace (£301 per QALY) and below knee cast (£339 per QALY) were more cost-effective than the Bledsoe boot (£2116 per QALY). Simulations generated CEACs, which were indistinguishable for the Aircast brace and below knee cast, indicating that these two interventions had comparable cost-effectiveness; the Bledsoe boot was least cost-effective.

Cost–utility analysis was necessarily based on the sample of patients for whom we had cumulative outcome data over the study period or for whom we had a sound basis for imputation for missing utility data. We used imputation techniques in a small number of cases in which we considered we could reliably make predictions about utility changes, despite some missing data. A conservative approach using average values was adopted as more sophisticated approaches are recognised to lead to varying predictions.[77,78] We assume that attrition of the sample is unlikely to have affected final estimates of relative cost–utility in any systematic manner as analysis of baseline characteristics indicated no significant differences. This was confirmed by analysis of sample characteristics such as baseline utility measures. Other uncertainty around ICER estimates was addressed by the use of CEACs and sensitivity analysis.

Although the Aircast brace and below knee cast could not be differentiated in terms of cost-effectiveness, they differed in terms of participant preference. Differential compliance rates suggested that the below knee cast was the least popular intervention. In a non-trial population, participants' responses to the offer of this treatment could be even less favourable unless the benefits are explained carefully. Bearing in mind that both types of support were similarly cost-effective, decision-makers may favour the Aircast brace over the below knee cast for routine implementation. We did not formally assess preference or acceptability and so these suggestions should be interpreted with caution. The results of this trial may give participants a greater amount of information with which to make a choice. The cost of a fitted below knee cast was less than half of that for the Aircast brace; however, total health-care costs (including subsequent care costs) did not differ significantly between the two treatment groups and so the below knee cast lost its cost advantage.

If the Aircast brace was acquired at a discount price through bulk purchase it had half the ICER value of the below knee cast. Centralised purchasing arrangements would have to be established to enable this price advantage to be realised; storage and transport costs would need to be added to the intervention cost, although these are unlikely to eliminate purchase cost savings.

From a societal perspective the inclusion of indirect costs associated with sick leave indicated that there was little to discriminate between the three interventions in terms of costs or benefits accrued (CEACs). Because the valuation of indirect costs was contentious, sensitivity analyses were undertaken to include varying the assumed cost of a single day off work and capping reported sick

leave attributable to ankle injury at 30 working days. The sensitivity of the economic evaluation conclusions to the assumptions made about sick leave means that the results from this wider cost perspective should be treated with some caution.

Overall, the economic evaluation results of this trial indicated that, if the decision-maker's main concern is to maximise effectiveness relative to total health-care costs, the Aircast brace and below knee cast perform similarly. The Aircast brace may also be the optimal pragmatic option in terms of universal use unless patients can be offered the two treatment options.

Chapter 7
Conclusions

Ankle sprains with an inability to weight bear have a prolonged recovery. Older people have slower and less complete recovery. Prognosis should be cautious, explaining that the injury, independent of treatment, has a significant risk of some disability in the form of symptoms, mobility or limitation of activities at 9 months.

Such patients, initially treated with 2–3 days of elevation, ice and non-weight bearing exercise, had more rapid resolution of symptoms and return to normal activities in the first 3 months when treated with a below knee cast for 10 days than with tubular bandage. By 9 months all treatments were equally effective. Mental health deteriorated in the early stages of recovery but returned to normal by 12 weeks. This study suggests that choice of treatment may affect speed of recovery but not long-term outcome. The below knee cast was not universally popular from the patient's perspective and, therefore, the clinician and patient need to have an informed discussion to determine the best treatment for each individual.

Implications for health care

This study demonstrates that severe ankle sprains, as defined by an inability to weight bear 2–3 days following injury, have long-term effects that can be influenced by treatment. Current treatment could be improved by the use of mechanical supports.

This study recommends the use of either a short-term below knee cast or an Aircast brace, following an initial period of several days to allow swelling reduction and non-weight-bearing exercise, for the treatment of severe ankle sprains. The choice between the two depends on a balance of clinical effectiveness, patient acceptability and cost.

Chapter 8

Recommendations for future research

The role of physiotherapy is not known in these injuries. In view of their poor prognosis in relatively active people it is important to be aware of an appropriate regime of exercise and physiotherapy during and after the period of functional support.

There are still no adequately powered studies of less severe ankle sprains.

In the UK, anticoagulants are not routinely used in lower limb injury, whereas this is standard practice in most of mainland Europe. More research is needed to determine the risk–benefit of such strategies.

The timing of interventions and the role of an initial period of relative rest, elevation and ice application have not been considered by this research and require further investigation.

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The CAST trial group

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Contribution of authors

Matthew Cooke, Professor of Emergency Medicine, participated in the design of the original experiment, had input into the original grant application, networking to establish clinical sites and supervision of clinical sites, and was the lead author for the final report.

Jennifer Marsh, Lecturer in Medical Statistics and Health Informatics, was involved in the design of the study, discussions on the pilot study, analysis of data from the pilot study, changes in the light of analysis of the pilot study data, discussions on data collection, data cleaning and management for the main study, implementation of data cleaning and management, analysis of data and discussions on analysis and interpretation, discussions on the statistics sections write-up, and undertaking the write-up. Also made a major contribution to the preparation of DMEC reports and attended TSC meetings, DMEC meetings and management and other meetings.

Michael Clark, Senior Research Fellow in Health Economics, undertook the economic components of the study, including having input into the design of data collection tools and the microcosting study, attended regular study meetings, was responsible for economic data analysis and interpretation, and undertook the final economic analysis and economic write-up.

Rachel Nakash, Research Fellow, was trial co-ordinator for the planning and set-up phase and to the end point of recruitment and led on the qualitative study and analysis.

Rose Jarvis was the clinical trials co-ordinator for the final stages of the study and was involved in data cleaning and management, analysis and co-ordination of report writing.

Jane Hutton, Professor of Medical Statistics, was involved in the design of the study, discussions on the pilot study, collection of data for the pilot study, changes in the light of analysis of pilot study data, discussions with statistician on data collection, cleaning and management, discussions with statistician and others on data analysis and interpretation, and writing of the results chapter. Also attended TSC meetings and some management and other meetings.

Ala Szczepura, Professor of Health Services Research, wrote the economics section of the original application, attended TSC and other management meetings and was responsible for the economic analysis and the writing of the economics elements in the report.

Sue Wilson, Professor of Clinical Epidemiology, had input into the original grant application and provided comments on the final draft of the report.

Sallie Lamb, Professor of Rehabilitation, led the design of the original experiment, had responsibility for writing the original grant

application, gathered comments from other applicants and integrated them into the grant application, set up the trial, appointed and supervised the trial co-ordinator and administrator, supervised the trial on a day-to-day basis in close liaison with Matthew Cooke, participated in analysis and participated in the writing of reports.

Other roles fulfilled

Bill Gillespie, Chairman of TSC; Sue Wilson, member of TSC; Vicky Staples, member of TSC; Jeremy Dale, member of TSC; Janet Dunn, Chairman of DMEC; Damian Griffin, member of DMEC; Pat Overton-Brown, member of DMEC; Gulnaz Begum and team, randomisation; Emma Withers, trial administrator; Lisa Craven, follow-up; Chris McCabe, advice on economic evaluation; Simon Gates, reviewer for systematic review.

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Appendix 1

Search strategy for literature reviews

The search strategy used in the relevant Cochrane reviews[28,29] was replicated but limited to the years 2000–5 to identify new studies. The databases searched were MEDLINE, EMBASE and the Cochrane Central Register of Controlled Trials (CENTRAL). The National Research Register and the International Standard Randomised Controlled Trial Number register were searched to identify relevant research projects.

The following subject-specific search was used in MEDLINE:

1. Ankle Injuries/
2. Ligaments, Articular/
3. "Sprains and Strains"/
4. or/1–3
5. ankle$.tw.
6. ligament$.tw.
7. and/5–6
8. (sprain$or strain$or injur$or rupture$or tear or torn).tw
9. and/7–8
10. and/4,9
11. Lateral Ligament, Ankle/
12. or/10–11

The reference lists of identified trials and reviews were also searched. The BioMail MEDLINE search service (http://biomail.sourceforge.net/biomail) was used with the search terms of 'ankle AND (injur* OR sprain*)' to alert for new trials.

Appendix 2

Ankle injury proforma

Ankle injury
(age 16 years or over)

Attach patient sticker

History

Mechanism of injury _____

Date and time of injury _____

Location of pain

Ability to walk: unable/with pain/ minimal pain/no pain

Previous injuries Y/N

Any pain or injury elsewhere Y/N

PMH

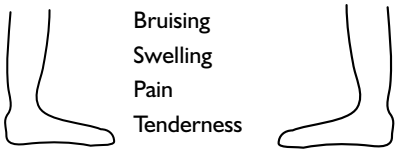
Drugs

Allergies

Contraindications to NSAIDs Y/N

Examination

R or L



Bruising
Swelling
Pain
Tenderness

Anterior drawer test: positive/painful/negative
Talar tilt test: positive/painful/negative
Proximal fibula tender: Y/N

Achilles tendon intact: Y/N

Circulation:
Cap refill time =

Sensation in foot =

Weight bearing/partial weight bearing/non-weight bearing

Investigation

Radiography of ankle/foot: Y/N

Indication of radiography if not as in adjacent box:
_____

Indicators for radiography:

Tenderness at posterior or tip of either malleolus
Unable to weight bear (at evaluation and at time of accident)
Tender 5th metatarsal
Tender navicular
Age over 60 years and pain

Management (Radiograph normal or fragment ≤ 2 mm)

- ❑ Relative rest for 2 days
- ❑ Ice
- ❑ Elevation
- ❑ Advice leaflet
- ❑ Exercises explained
- ❑ Analgesia (specify)_____
- ❑ Other (specify) _____

If non-weight bearing or minimal bearing
- ❑ review clinic*
- ❑ crutches

Chronic instability and weight bearing → Physiotherapy referral

Radiograph findings:

Management if radiograph abnormal
(note: exclude # fragments < 2 mm)

Consult local guidelines

- ❑ POP
- ❑ Fracture clinic
- ❑ On call orthopaedic team

Other reason for orthopaedic referral:

Diagnosis _____

***Appropriate for ankle trial?** **Yes ❑** **No ❑** **If 'Yes', trial information and invite given?** **Yes ❑** **No ❑**

(Check inclusion/exclusion criteria)

Record reasons here if patient declines ankle trial: _____

Appendix 3

Invitation letter

Trial of treatment of severe ankle sprains

This hospital is taking part in a study to determine the best treatment of ankle sprains. We would like to invite you to participate in this trial.

The trial is looking at four different treatments, which are explained in the accompanying leaflet. People taking part would be allocated randomly to these four treatments.

The doctor who sees you today will explain about the trial. Treatment today will not be affected by the trial, as it is the same for everyone, whether participating in the trial or not. You will also be given a leaflet. Please read this leaflet carefully.

If you are prepared to take part in the trial we would arrange to see you in 2–3 days' time. A physiotherapist would then explain the trial in more detail and you would have the opportunity to ask more questions. If you agree, the physiotherapist would then start your treatment.

Your treatment will not be affected if you do not wish to participate in the trial.

Thank you for considering taking part.

A&E Consultant

Appendix 4

Patient information sheet

Study title: study of four ways of treating severe ankle sprains

You are being invited to take part in a research study. Before you decide it is important for you to understand why the research is being done and what it will involve. Please take time to read the following information carefully and discuss it with others if you wish. Ask us if there is anything that is not clear or if you would like more information. Take time to decide whether or not you wish to take part.

Thank you for reading this.

What is the purpose of the study?

This study aims to determine the best treatment for severe ankle injuries. We are comparing four treatments – a simple elastic bandage as is commonly used at present, a plaster of Paris cast, a plastic splint and a boot-like support.

Why have I been chosen?

All patients attending this hospital, and several others, with your type of injury are being invited to take part in this trial. Eventually 600 patients will be taking part.

Do I have to take part?

It is up to you to decide whether or not to take part. If you do decide to take part you will be given this information sheet to keep and asked to return to a clinic in 2–3 days' time. At that clinic you will be given a further explanation of the trial and have an opportunity to ask questions. If you agree to participate in the trial you will be asked to sign a consent form. If you decide to take part you are still free to withdraw at any time and without giving a reason. A decision to withdraw at any time, or a decision not to take part, will not affect the standard of care you receive. If you decide not to take part the researcher may ask you why, but you do not have to answer this question.

What will happen to me if I take part?

When you attend the clinic you will be given the opportunity to ask further questions before deciding whether you want to take part in this trial. If you decide to participate you will be allocated to one of the four treatments and given appropriate instructions and advice. We do not know which way of treating patients is best; that is why we need to make comparisons. People will be put into groups and then compared. A computer using an approach similar to tossing a coin selects the groups. Patients in each group then have a different treatment and these are compared.

At the clinic appointment a short examination of your ankle will be performed and you will be asked to complete a short questionnaire with the help of the research physiotherapist. This will take about 30–45 minutes. Your further treatment will then be explained.

At about 4 weeks and 12 weeks after injury we will send you another copy of the questionnaire by post and would like you to complete this and post it back to us (we pay the postage). This will then be repeated 9 months after your injury. The researcher may contact you by phone soon after you receive the questionnaire to see if you need help completing it.

What do I have to do?

We will give you advice on what exercise you can undertake whilst in the trial. If you still have problems after 6 weeks we will arrange further treatment for you, although this will not be part of the trial. This will be standard treatment by the NHS. During the trial we will ask you to make note of certain events such as when you return to work or to playing sport.

What is the treatment that is being tested?

The four different treatments are:

- an elastic bandage worn during the day
- a plaster of Paris cast, like that used when people break a bone
- a plastic splint that supports the side of the ankle
- a boot that looks like a ski boot that supports the ankle.

What are the side effects of any treatment received when taking part?

We do not know of any side effects from these treatments. Anybody with an ankle injury can develop severe swelling, and occasionally this can affect the circulation in the leg. By the time you receive one of the trial treatments the swelling should be going down. There is a small risk that the swelling could worsen or cause problems when the treatment is applied. If the pain worsens after your treatment is started or your foot becomes numb then you should contact the A&E department immediately.

What are the possible disadvantages and risks of taking part?

We do not know which of these treatments gives the best results. The only risk that we know of is the swelling mentioned above.

What are the possible benefits of taking part?

We hope that the treatments will help you. However, this cannot be guaranteed. The information we get from this study may help us to treat future patients with severe ankle sprains.

What if new information becomes available?

Sometimes during the course of a research project, new information becomes available about the treatment that is being studied. If this happens your research physiotherapist will tell you about it and discuss with you whether you want to continue in the study. If you decide to withdraw your physiotherapist will make arrangements for your care to continue. If you decide to continue in the study you will be asked to sign an updated consent form. Also, on receiving new information the research physiotherapist might consider it to be in your best interests to withdraw you from the study. He/she will explain the reasons and arrange for your care to continue.

What happens when the research study stops?

You will be continuing with the treatment for 6 weeks. If you are still having problems at this time we will arrange for you to have an appointment with an appropriate specialist to continue your care.

What if something goes wrong?

If taking part in this research project harms you there are no special compensation arrangements. If you are harmed because of someone's negligence then you may have grounds for a legal action but you may have to pay for it. Regardless of this, if you wish to complain, or have any concerns about any aspect of the way you have been approached or treated during the course of this study, the normal NHS complaints mechanism is available to you.

Will my taking part in this study be kept confidential?

All information that is collected about you during the course of the research will be kept strictly confidential. Any clinical information about you that leaves the hospital will have your name and address removed so that you cannot be recognised from it. We would like to inform your general practitioner of your involvement in this trial so that he or she is fully aware of your situation. We will confirm that you are prepared for us to do this when you see the physiotherapist in the clinic.

What will happen to the results of the research study?

This study is expected to last 3 years. At the end of the study we will publish the findings in medical journals and at medical conferences. We will also put the results on the trial website at www.warwick.ac.uk/go/ankle. No individual patient will be identifiable in any results.

Who is organising and funding the research?

The NHS funds this study. The research team will receive salaries from the grant but these do not depend on the recruitment of patients or on the results that are produced. The study is being organised by the Universities of Warwick and Birmingham.

What will happen if I decide not to participate in the research study?

If you decide not to participate in the research study you will be treated using the standard treatment used at your hospital, that is elastic bandaging and provision of a pair of crutches with follow-up arranged by the A&E department.

Who has reviewed the study?

Your local research ethics committee has reviewed this study. If you have any concerns you may contact them on [to be inserted]

Contacts for further information

If you would like further information please contact the local researcher, Rachel Nakash, on telephone number 02476 000000. Alternatively, you can speak to Dr Cooke, who is leading the project, by telephoning 02476 000000.

Please keep this information sheet for your future use. If you join the study you will also be given a copy of your consent form.

Appendix 5

Advice to participants prior to trial clinic

1. **Elevate** to reduce swelling, keeping your foot well up above the level of your bottom. In bed, rest it on a couple of pillows.
2. **Apply ice** to ease pain, swelling and bruising. **Method**: Use frozen peas or crushed ice in a damp towel. Place around elevated ankle for 10 minutes. Repeat 4–6 times a day. Caution: Ice can cause a burn. Protect sensitive skin. Follow instructions.
3. **Exercise every 2 hours** for 10 minutes, especially after ice treatment, if it is not too painful. If you hold your ankle stiff in an awkward position it will become more difficult to move it from that position, i.e. it will stiffen up. Do what exercises you can manage but if it is too painful, stop and try again later. Point foot up towards you and point it down again. Circle ankle keeping knee straight. Keep feet together. Turn soles of feet towards and away from each other.

Bandages can make your ankle go stiff. Most people should not use a bandage on an injured ankle – this allows you to do your exercises better.

Take simple **painkillers** for the first few days, e.g. paracetamol or ibuprofen, if you feel you need help with the pain. These are available from the chemist.

Walking – You may try to walk if it is not too painful. Try to walk with even strides (heel first, then toe). Put as much weight through the foot as pain allows. Use stick/crutches as advised to help you walk.

If pain increases or swelling gets worse, contact your GP.

Sports – You may benefit from ankle strapping whilst playing sport, for a few weeks after the injury. Remove the strapping at the end of the game.

IMPORTANT
Sometimes the swelling in the ankle can cause problems with the circulation. This is rare but needs urgent treatment.

If you get increasing pain despite following the instructions above or your foot goes blue, or it becomes numb, then contact either NHS Direct on 0345 46 47 or your local A&E department IMMEDIATELY.

Appendix 6

Consent form

Trial centre:
Patient's centre ID:

Title of project: A randomised controlled trial to estimate the clinical and cost-effectiveness of four different methods of mechanical support in severe ankle sprains.

Name of researchers: Professor Sallie Lamb, University of Warwick and
Dr Matthew Cooke, University of Warwick

Please initial box

1. I confirm that I have read and understand the information leaflet dated 17/12/03 version 3 for the above study and have had the opportunity to ask questions. ☐
2. I understand that my participation is voluntary and that I am free to withdraw at any time, without giving any reason, without my medical care or legal rights being affected. ☐
3. I understand that sections of any of my medical notes relating to the trial may be looked at by responsible individuals from the University of Warwick. ☐
4. I give permission for these individuals to have access to my records, which will be dealt with in a confidential manner. ☐
5. I agree to take part in the above study. ☐
6. As part of the study a sample of patients will be given a 'trial calendar'* to help with questionnaire completion and also a very small number of people will be asked to be interviewed by a member of the research team. I give my consent for this. ☐

Name of patient	Date	Signature
Name of person taking consent	Date	Signature
Name of researcher	Date	Signature

One for patient; one for researcher; one to be kept with hospital notes.

*The calendar was part of an embedded methodology trial that will be reported separately.

Appendix 7

Pre-randomisation eligibility form

Patient's centre ID: **Trial centre:**

Research physiotherapist name:

Patient details

Name: Hospital number:

Date of birth: Sex:

Home address: Other address (e.g. student):

Patient contact number(s): H:

W:

Mob:

E-mail:

GP name and surgery details:

Eligibility checklist

1. Patient aged 16 years or over ❑
2. Patient non-weight bearing/or weight bearing with aid ❑
3. One week or less since injury ❑
4. No contraindications to any of the four arms of the trial ❑
5. No fracture or other significant injuries present ❑
6. Written informed consent gained ❑

Trial Number
(Given by Randomisation Centre)

Telephone 0800 000 000 or 0800 000 000 for randomisation onto the CAST trial

Appendix 8

Background information

Q1. Age: ☐☐ Years

Q2. Sex: ❑ Male ❑ Female

Q3. Ethnic group: (Please tick one box)

1. White ❑
2. Black-Caribbean ❑
3. Black-African ❑
4. Black-Other ❑
5. Indian ❑
6. Pakistani ❑
7. Bangladeshi ❑
8. Chinese ❑
9. Other (Please specify) ❑

Q4. What is your first language? (Please tick one box)

1. English ❑
2. Other European ❑
3. Gujarati ❑
4. Hindi ❑
5. Punjabi ❑
6. Urdu ❑
7. Bengali ❑
8. Other (please specify) ❑

Will you be able to fill in questionnaires in English? Yes/No

Q5. Employment status:

An important part of the study is to determine how much your ankle injury has affected you in terms of days off work. This is why the next question asks about your employment.

5.1 Are you currently employed? (If you are a full-time student but also work, complete this section and also tick question 5.6 on page 4)
Yes – part time ❑
Yes – full time ❑
No (go to 5.2 on page 4) ❑

(a) Is this employment:
Paid ❑
Unpaid ❑

(b) How many hours a week do you work?

Less then 10	❑
10–25	❑
25–40	❑
More than 40	❑

(c) Which of the following categories do you think best describes your employment?

Unskilled manual	❑	
Skilled manual	❑	
Unskilled non-manual	❑	
Skilled non-manual	❑	
Professional	❑	Please describe: _____
Other	❑	Please describe: _____
Decline to answer	❑	

If you are *not* currently employed which of the following applies to you:

5.2. Retired	❑
5.3. At home and not looking for paid employment (e.g. looking after home, family or others)	❑
5.4. Unable to work because of illness or disability	❑
5.5. Unemployed and looking for work	❑
5.6. In full-time education	❑
5.7. Other (please specify):	❑

Q6. What is the highest qualification you have achieved?

CSE (or equivalent)	❑
O-level/GCSE (or equivalent)	❑
A-level (or equivalent)	❑
Degree (or equivalent)	❑
Higher degree (or equivalent)	❑
Other (Please specify):	❑

Q7. During your usual daily routine (e.g. work, caring for others, daily activities) *approximately* how much time do you spend:

(a) On your feet?

Most of the day	❑
More than 4 hours a day	❑
Less than 4 hours a day	❑
Not much time – mostly sitting	❑

(b) Driving?

Most of the day	❑
More than 4 hours a day	❑
Less than 4 hours a day	❑
Usually just to/from work	❑
Don't drive	❑

Q8. Are you currently taking any medication for pain or inflammation?

Only since ankle injury	❑
Prior to injury for a separate condition	❑
No	❑
Did not answer	❑

Q9. Which of the following activities do you participate in: (before injuring your ankle)

	More than once weekly	Less than once weekly	Never
Swimming	❑	❑	❑
Weight training	❑	❑	❑
Aerobics/keep-fit	❑	❑	❑
Cycling	❑	❑	❑
Jogging/running	❑	❑	❑
Team sport (e.g. football, rugby, hockey, netball)	❑	❑	❑
Racquet sport (e.g. tennis, squash, badminton)	❑	❑	❑
Yoga	❑	❑	❑
Athletics	❑	❑	❑
Walking (2 miles or more)	❑	❑	❑
Heavy DIY, housework, gardening	❑	❑	❑
Other sports or exercise (please specify):			

Q10. How tall are you? _____ feet _____ inches *or* _____ cm

Q11. How much do you weigh? _____ stone _____ pounds *or* _____ kg

Q12. Pain:

On a scale of 0–10, where 0 is no pain and 10 is the worst pain you can imagine, how painful is your ankle now? (please circle)

At rest: 0 – 1 – 2 – 3 – 4 – 5 – 6 – 7 – 8 – 9 – 10

Weight bearing: 0 – 1 – 2 – 3 – 4 – 5 – 6 – 7 – 8 – 9 – 10

Q13. Previous injuries:

Apart from your current injury, have you sprained or twisted your ankle in the last 3 months?

Yes ❑ No ❑

If 'Yes', did you need to attend A&E for this injury?

Yes ❑ No ❑

Q14. Weight bearing:

Using the weighing scales, whilst sitting in a chair, how much weight are you able to put through your ankle at the moment?

_____ kg

Appendix 9

Challenges of recruitment

Abstract from Faculty of Accident and Emergency Medicine meeting, London, 2003.

Authors(s): Nakash R, Lamb S, Cooke MW, on behalf of the CAST project team
ADDRESS:
BODY OF ABSTRACT:
Title: Conducting clinical trials in ED – a pilot study highlights recruitment challenges. **Introduction** Conducting clinical research in the ED environment poses particular challenges. The pilot study of a randomised controlled trial of mechanical supports following severe ankle sprains was used to gauge the difficulties of recruitment. **Methods** ED physicians and emergency nurse practitioners were asked to identify patients with severe ankle sprains using pre-specified inclusion criteria and refer these patients to a 'trial clinic'. These clinics were run by research physiotherapists 2–3 days later where consent and randomisation was undertaken. An assessment proforma was designed to assist with assessment and act as a tracking instrument and 'aide-mémoire' for staff to refer appropriate patients to the trial clinic. **Results** During the 5-week pilot phase, 85 patients were referred to the trial clinic as fulfilling the criteria at the time of initial examination. 29 patients (34%) were recruited onto the study, 29 patients (34%) either failed to attend or cancelled their trial clinic appointment, 19 patients (22%) attended the trial clinic but were excluded from the study due to significant improvement in symptoms and 8 patients (9%) declined to return to the trial clinic. The high rate of exclusion at the trial clinic was due to the 'severe' sprains diagnosed in ED turning out to be less serious injuries when the patient returned. This could also explain the high rate of trial clinic non-attendance. **Discussion** The assessment proforma has been well received and has proved a useful tool for tracking recruitment. Recruiting patients in ED may overestimate the severity of soft tissue injuries and a 2- to 3-day period before recruitment can ensure patients fulfil clinical criteria of severe injury. One-third of patients failed to return to the clinic; mechanisms for encouraging patients to return need to be employed.
ED, emergency department.

Appendix 10

Audits

The nature of the recruitment process for this trial meant that we were reliant upon emergency department staff to identify potentially appropriate patients and then refer them to the trial recruitment clinics. Considerable time and effort were invested by the trial team to encourage emergency department staff to co-operate with the trial procedures, but it was apparent that some difficulties with recruitment were partly due to potentially appropriate patients attending emergency departments but not being referred to the recruitment clinics, meaning that the patients were then lost to the trial.

To gauge how well individual members of the emergency department team understood the trial and co-operated with trial procedures, audits were carried out of patients' emergency department notes. On days selected at random, and with the help of emergency department reception staff, lists were obtained of patients coded as 'ankle injury' throughout the 24-hour period. Each patient's notes were then retrieved and evaluated for whether the patient was potentially appropriate for the trial. The results of these audits are summarised in the table below.

As the audit process was a time-consuming activity, the local trial centres received more attention than the remote centres. Members of the trial team were able to conduct the local audits whereas at the more distal centres we relied on the help of the collaborating clinicians.

Although the audits were not systematically conducted they gave us a valuable insight into the approach used by emergency department clinicians. We were able to establish reasons why patients with ankle sprains were not referred to the recruitment clinics. The most useful outcome was that we were able to identify individual emergency department staff who appeared to be unaware of the trial procedures and who failed to refer appropriate patients to the recruitment clinics. It was then possible to approach these staff members personally and remind them of the trial. The trial team endeavoured to conduct a training session at each trial centre following senior house officer rotations, but the audit process was particularly useful following such rotations, to identify new emergency department staff who required training in the trial procedures.

Details of audits undertaken

Trial centre	Days audited	Total adult ankle injuries	Not appropriate[a]	Potentially appropriate	Potentially appropriate and referred to CAST, *n* (%)	Other[b]
1	64	380	233	98	29 (30)	49
2	103	404	242	94	23 (24)	68
3	62	165	108	31	8 (26)	26
4	209	539	377	81	48 (59)	81
5	75	359	186	95	14 (15)	78
6	11	67	29	21	4 (19)	17
7	9	32	23	2	1 (100)	7
8	0	–	–	–	–	–

a 'Not appropriate' includes those patients who were fully weight bearing, who were wrongly categorised on arrival at the emergency department, who had a non-acute ankle injury or a fractured ankle or other bone, or who had other past medical history that made them ineligible.
b 'Other' includes no notes or insufficient information available for the audit, referred elsewhere for treatment, or declined information about the trial in the emergency department.

Appendix 11

Ankle support instructions to participants

1. Tubular bandage advice sheet

The research physiotherapist will show you how to apply your tubular bandage whilst you are in the Ankle Trial Clinic.

You may want to wear your tubular bandage continuously for the first few days but you can remove it when:

- bathing
- applying ice
- doing the exercises you have been instructed to do.

Remove your tubular bandage at night when you go to bed

The tubular bandage should be hand washed only, using warm water and detergent for delicate fabrics such as Lux soap flakes, then rinsed, squeezed and dried.

Stop using the tubular bandage as soon as your ankle feels comfortable and you feel confident to do so.

If you are having any problems contact: Rachel Nakash, Study Trial Co-ordinator: Tel: 024 7657 4650

2. Aircast/Air-stirrup advice sheet

Your physiotherapist will show you how to apply your brace whilst you are in the Ankle Trial Clinic.

If you have any problems, follow the fitting instructions you have been given.

Apply the Air-stirrup brace over an absorbent long sock and wear a laced shoe such as a trainer.

You may want to wear your Air-stirrup brace continuously for the first few days but you can remove it when:

- bathing
- applying ice
- doing the exercises you have been instructed to do.

Remove your Air-stirrup brace at night when you go to bed

When your ankle starts to feel more comfortable, wear the brace only when walking.

Stop using the brace when your ankle feels comfortable and you feel confident to do so.

If you are having any problems contact: Rachel Nakash, Study Trial Co-ordinator: Tel: 024 7657 4650

3. Bledsoe boot advice sheet

The research physiotherapist will show you how to apply your boot whilst you are in the Ankle Trial Clinic.

If you have any problems, follow the fitting instructions you have been given.

Your boot may feel more comfortable if you wear it over an absorbent long sock.

You may want to wear your boot continuously for the first few days but you can remove it when:

- bathing
- applying ice
- doing the exercises you have been instructed to do.

Remove your boot at night when you go to bed

The straps and the foam wrap should be hand washed only, using warm water and detergent for delicate fabrics such as Lux soap flakes, then rinsed, squeezed and line dried.

Stop using the boot when your ankle feels comfortable and you feel confident to do so.

If you are having any problems contact: Rachel Nakash, Study Trial Co-ordinator: Tel: 024 7657 4650

4. Below knee cast advice sheet

Each participant was given the standard advice sheet from the plaster room at the relevant hospital.

Appendix 12

Resource use questionnaire

Q1. Is your ankle better, just the same or worse after the treatment you received 9 months ago?

Better ❑ Same ❑ Worse ❑

On a scale of 0–10, how much benefit do you think you have gained from the treatment?
Circle your answer (0 = no benefit, 10 = maximum benefit).

0 1 2 3 4 5 6 7 8 9 10

Q2. During the past 6 months, have you consulted a doctor or therapist or received any further treatment for your ankle (apart from the treatment you received as part of the trial)?

Yes ❑ No ❑

If 'Yes', please specify which treatment by placing a tick in the appropriate box:

A&E staff, e.g. plaster technician	❑	How many times? _____
NHS consultant	❑	How many times? _____
Private consultant	❑	How many times? _____
GP	❑	How many times? _____
Osteopathy	❑	How many times? _____
Chiropractic	❑	How many times? _____
NHS physiotherapy	❑	How many times? _____
Private physiotherapy	❑	How many times? _____
Other (please specify): _____		

Did you pay for this treatment? Yes ❑ No ❑

If 'Yes', was payment made by yourself or a private insurance company?

Self ❑ Insurance company ❑

How much did it cost? _____

Q3. Over the past 6 months have you had any scans or radiographs because of your ankle?

Yes ❑ No ❑

If 'Yes', what type of radiograph or scan? (Tick more than one box if needed)

Normal radiograph	❑
MRI scan	❑
Ultrasound scan	❑

Did you pay for this/these scan(s)? Yes ❑ No ❑

If 'Yes', was payment made by yourself or a private insurance company?
Self ❑ Insurance company ❑

How much did it cost? _____

Q4. Over the past 6 months have you been admitted to hospital because of your ankle?

Yes ❑ No ❑

If 'Yes', how many days did you spend in hospital? _____

Q5. Has your doctor prescribed any medicines, creams or other treatments (e.g. brace/strapping) for your ankle over the past 6 months? (Do not include the brace/support you wore as part of the trial)

Prescribed medicines/creams:

Item description	**Name of item (e.g. ibuprofen)**	**Cost to you (e.g. prescription charge or other cost)**
Painkillers		£
Anti-inflammatories		£
Creams/gels		£
Aids/braces/strapping		£
Injection		£
Other		£

Q6. Over the past 6 months, have you bought any medicines, creams or other treatment (e.g. brace) for your ankle?

Medicines/creams bought *without prescription*:

Item description	**Name of item**	**Cost to you**
Painkillers		£
Anti-inflammatories		£
Creams/gels		£
Aids/braces/strapping		£
Herbal remedies		£
Other		£

Q7. Over the past 6 months have you had to take any sick leave from work because of your ankle?

Yes ❑ No ❑ Not applicable ❑

If 'Yes', how many sick days did you take? _____

Q8. Have you been involved in any exercise/sport over the last 6 months?

Yes ❑ No ❑

If 'Yes', which ones? (Please tick all boxes that apply).

Swimming	❑
Weight training	❑
Aerobics/keep-fit	❑
Cycling	❑
Jogging/running	❑
Team sport (e.g. football, rugby, hockey, netball)	❑
Racquet sport (e.g. tennis, squash, badminton)	❑
Yoga	❑
Athletics	❑
Walks of 2 miles or more	❑
Heavy housework/DIY/gardening	❑
Other sports or exercise (please specify): _____	

Approximately how many times in the last 6 months have you done any of these activities?

Less than once a month	❑	Once a week	❑
Once a month	❑	Twice a week	❑
Once a fortnight	❑	More than twice a week	❑

Appendix 13
Results tables

Primary outcomes

Data are summary statistics and exclude the 17 pilot study patients for the FAOS analyses only.

Four weeks

		Randomisation group			
Score		**Tubular bandage**	**Below knee cast**	**Aircast brace**	**Bledsoe boot**
FAOS, pain	Mean	63.6	66.9	67.1	65.5
	Median	63.9	67.9	69.4	66.7
	(Quartiles)	(47.2–80.6)	(51.8–82.1)	(50.0–83.3)	(50.0–83.3)
FAOS, symptoms	Mean	61.0	66.9	63.0	61.6
	Median	60.7	67.9	60.7	64.3
	(Quartiles)	(46.4–75.0)	(51.8–82.1)	(46.4–78.6)	(46.4–82.1)
FAOS, ADL	Mean	83.0	87.0	83.4	83.7
	Median	83.8	91.9	86.8	86.8
	(Quartiles)	(72.1–97.1)	(79.4–98.5)	(75.0–95.6)	(73.5–95.6)
FAOS, sport	Mean	48.9	55.2	48.5	48.8
	Median	50.0	55.0	45.0	50.0
	(Quartiles)	(30.0–70.0)	(30.0–75.0)	(30.0–70.0)	(25.0–75.0)
FAOS, QoL	Mean	44.3	49.5	48.6	46.4
	Median	43.8	43.8	43.8	50.0
	(Quartiles)	(25.0–62.5)	(31.3–68.8)	(31.3–62.5)	(25.0–62.5)
FLP, ambulatory	Mean	16.0	11.7	15.3	14.7
	Median	15.6	5.9	13.4	12.6
	(Quartiles)	(3.9–24.5)	(0.0–22.5)	(0.0–24.1)	(0.0–22.7)

ADL, activities of daily living; FAOS, Foot and Ankle Outcome Score; FLP, Functional Limitations Profile; QoL, quality of life.

Twelve weeks

Score		Randomisation group			
		Tubular bandage	Below knee cast	Aircast brace	Bledsoe boot
FAOS, symptoms	Mean	70.6	75.6	73.9	74.6
	Median	71.4	75.0	75.0	78.6
	(Quartiles)	(57.1–85.7)	(60.7–92.9)	(58.9–92.9)	(60.7–92.9)
FAOS, pain	Mean	74.2	79.8	77.7	78.0
	Median	77.8	86.1	80.6	83.3
	(Quartiles)	(55.6–94.4)	(69.4–97.2)	(63.9–94.4)	(66.7–91.7)
FAOS, ADL	Mean	89.3	92.8	90.6	92.1
	Median	95.6	98.5	95.6	97.1
	(Quartiles)	(80.9–100.0)	(89.7–100.0)	(85.3–100.0)	(88.2–100.0)
FAOS, sport	Mean	63.5	72.8	68.7	69.3
	Median	70.0	75.0	75.0	75.0
	(Quartiles)	(45.0–85.0)	(60.0–95.0)	(55.0–85.0)	(55.0–90.0)
FAOS, QoL	Mean	55.5	63.5	63.5	61.8
	Median	62.5	62.5	62.5	62.5
	(Quartiles)	(37.5–75.0)	(50.0–81.3)	(43.8–81.3)	(43.8–75.0)
FLP, ambulatory	Mean	8.1	5.7	6.3	5.9
	Median	3.88	0.0	0.0	0.0
	(Quartiles)	(0.0–14.3)	(0.0–6.2)	(0.0–8.2)	(0.0–9.2)

ADL, activities of daily living; FAOS, Foot and Ankle Outcome Score; FLP, Functional Limitations Profile; QoL, quality of life.

Nine months

Score		Randomisation group			
		Tubular bandage	Below knee cast	Aircast brace	Bledsoe boot
FAOS, symptoms	Mean	80.7	82.6	80.9	81.0
	Median	89.3	85.7	83.9	85.7
	(Quartiles)	(64.3–100.0)	(75.0–96.4)	(69.6–100.0)	(71.4–96.4)
FAOS, pain	Mean	82.1	87.0	83.6	84.2
	Median	91.7	94.4	91.7	91.7
	(Quartiles)	(69.4–100.0)	(80.6–100.0)	(75.0–100.0)	(75.0–100.0)
FAOS, ADL	Mean	93.2	95.1	94.4	94.2
	Median	98.5	100.0	100.0	100.0
	(Quartiles)	(92.7–100.0)	(95.6–100.0)	(95.6–100.0)	(92.7–100.0)
FAOS, sport	Mean	77.5	80.8	78.9	79.1
	Median	85.0	85.0	85.0	85.0
	(Quartiles)	(67.5–100.0)	(75.0–100.0)	(70.0–100.0)	(70.0–100.)
FAOS, QoL	Mean	67.0	72.8	72.8	71.2
	Median	71.9	75.0	75.0	75.0
	(Quartiles)	(50.0–93.8)	(56.3–100.0)	(50.0–100.0)	(50.0–93.8)
FLP, ambulatory	Mean	6.0	3.7	3.3	3.4
	Median	0.0	0.0	0.0	0.0
	(Quartiles)	(0.0–7.1)	(0.0–0.0)	(0.0–0.0)	(0.0–0.0)

ADL, activities of daily living; FAOS, Foot and Ankle Outcome Score; FLP, Functional Limitations Profile; QoL, quality of life.

Secondary outcomes

Data are summary statistics.

Four weeks

		Randomisation group			
Score		**Tubular bandage**	**Below knee cast**	**Aircast brace**	**Bledsoe boot**
SF-12, physical	Mean	39.5	42.5	38.4	38.9
	Median	38.6	42.0	37.2	38.8
	(Quartiles)	(32.6–46.7)	(34.5–49.7)	(32.5–43.4)	(32.1–44.8)
SF-12, mental	Mean	45.6	45.7	45.1	47.3
	Median	48.4	48.7	46.4	50.0
	(Quartiles)	(35.7–55.0)	(37.2–55.7)	(38.3–54.0)	(39.1–56.7)
EQ-5D	Mean	0.6	0.7	0.7	0.7
	Median	0.7	0.7	0.7	0.7
	(Quartiles)	(0.6–0.8)	(0.6–0.8)	(0.6–0.8)	(0.6–0.8)
VAS, pain at rest	Mean	20.4	15.1	19.6	18.1
	Median	13.5	8.0	14.5	10.0
	(Quartiles)	(2.0–32.5)	(0.0–23.0)	(3.0–29.0)	(2.0–25.0)
VAS, pain weight bearing	Mean	37.2	31.7	37.6	35.1
	Median	33.0	25.0	30.5	30.5
	(Quartiles)	(12.5–60.0)	(6.0–50.0)	(14.5–62.0)	(9.0–60.0)

EQ-5D, EuroQol 5 dimensions; SF-12, short form questionnaire with 12 items; VAS, visual analogue scale.

Twelve weeks

		Randomisation group			
Score		**Tubular bandage**	**Below knee cast**	**Aircast brace**	**Bledsoe boot**
SF-12, physical	Mean	47.0	49.1	46.5	48.7
	Median	48.7	52.5	49.2	51.7
	(Quartiles)	(41.5–55.2)	(42.2–56.4)	(38.6–54.5)	(43.5–56.5)
SF-12, mental	Mean	49.5	49.8	52.2	52.5
	Median	53.3	53.3	54.9	55.7
	(Quartiles)	(42.3–57.7)	(44.1–57.7)	(47.3–58.6)	(49.4–58.6)
EQ-5D	Mean	0.7	0.8	0.8	0.8
	Median	0.8	0.8	0.8	0.8
	(Quartiles)	(0.6–1.0)	(0.7–1.0)	(0.7–1.0)	(0.7–1.0)
VAS, pain at rest	Mean	12.7	9.0	10.8	10.6
	Median	5.0	3.5	4.0	4.0
	(Quartiles)	(0.0–20.0)	(0.0–11.0)	(0.0–16.0)	(0.0–15.0)
VAS, pain weight bearing	Mean	27.9	20.3	23.9	23.3
	Median	18.5	11.0	16.0	13.5
	(Quartiles)	(3.0–49.5)	(1.0–30.0)	(3.0–35.0)	(2.0–40.0)

EQ-5D, EuroQol 5 dimensions; SF-12, short form questionnaire with 12 items; VAS, visual analogue scale.

Nine months

Score		Randomisation group			
		Tubular bandage	**Below knee cast**	**Aircast brace**	**Bledsoe boot**
SF-12, physical	Mean	49.9	50.8	50.1	50.9
	Median	53.5	55.1	54.9	54.5
	(Quartiles)	(44.6–57.0)	(47.1–57.7)	(44.5–57.0)	(50.0–57.0)
SF-12, mental	Mean	49.4	51.2	51.2	51.6
	Median	53.8	55.1	55.0	55.1
	(Quartiles)	(44.3–57.7)	(46.9–58.6)	(47.1–57.7)	(49.1–58.4)
EQ-5D	Mean	0.8	0.8	0.8	0.9
	Median	0.8	1.0	1.0	1.0
	(Quartiles)	(0.7–1.0)	(0.7–1.0)	(0.7–1.0)	(0.8–1.0)
VAS, pain at rest	Mean	9.9	8.7	6.5	9.8
	Median	1.0	1.0	0.0	1.0
	(Quartiles)	(0.0–9.0)	(0.0–8.5)	(0.0–6.0)	(0.0–8.0)
VAS, pain weight bearing	Mean	23.5	16.9	18.2	19.3
	Median	8.0	3.5	4.0	5.0
	(Quartiles)	(0.0–45.0)	(0.0–29.0)	(0.0–29.0)	(0.0–25.0)

EQ-5D, EuroQol 5 dimensions; SF-12, short form questionnaire with 12 items; VAS, visual analogue scale.

Analyses of covariance (ANCOVAS) of primary outcomes, intention to treat analysis, all participants, showing the influence of age, sex and baseline score

Four weeks

		Tubular bandage	**Below knee cast**	**Aircast brace**	**Bledsoe boot**	**Male**	**Age**	**Baseline score**
FAOS, pain	Coefficient	62.23	5.03	3.64	0.69	5.04	–0.55	0.37
	SE	1.93	2.38	2.38	2.34	1.71	0.07	0.05
FAOS, symptoms	Coefficient	59.52	3.28	2.46	–0.99	4.21	–0.33	0.40
	SE	1.97	2.43	2.43	2.39	1.74	0.07	0.05
FAOS, ADL	Coefficient	82.32	2.96	0.27	0.02	2.88	–0.40	0.24
	SE	1.40	1.73	1.74	1.70	1.23	0.05	0.04
FAOS, sport	Coefficient	44.59	4.78	–0.37	–0.20	5.27	–0.66	0.34
	SE	2.84	3.44	3.45	3.42	2.47	0.11	0.07
FAOS, QoL	Coefficient	42.67	5.52	5.06	1.74	0.97	–0.45	0.28
	SE	2.40	2.97	2.96	2.90	2.13	0.09	0.04
FLP	Coefficient	16.86	–3.06	–0.06	0.06	–3.39	0.39	0.14
	SE	1.38	1.71	1.71	1.68	1.23	0.05	0.05

ADL, activities of daily living; FAOS, Foot and Ankle Outcome Score; FLP, Functional Limitations Profile; QoL, quality of life.

Twelve weeks

		Tubular bandage	Below knee cast	Aircast brace	Bledsoe boot	Male	Age	Baseline score
FAOS, pain	Coefficient	72.93	5.13	3.70	3.33	3.51	–0.33	0.31
	SE	2.00	2.46	2.42	2.40	1.77	0.07	0.05
FAOS, symptoms	Coefficient	68.70	3.38	2.74	2.46	5.32	–0.35	0.31
	SE	1.98	2.44	2.42	2.40	1.76	0.07	0.05
FAOS, ADL	Coefficient	88.86	3.48	1.09	2.35	1.95	–0.26	0.17
	SE	1.25	1.57	1.58	1.53	1.12	0.05	0.04
FAOS, sport	Coefficient	62.24	8.68	4.78	5.94	1.71	–0.61	0.12
	SE	2.91	3.59	3.61	3.51	2.56	0.12	0.08
FAOS, QoL	Coefficient	53.48	8.68	8.01	6.11	2.40	–0.43	0.18
	SE	2.59	3.19	3.15	3.12	2.30	0.10	0.05
FLP	Coefficient	8.36	–1.76	–1.16	–0.81	–2.02	0.30	0.14
	SE	1.10	1.37	1.39	1.34	0.98	0.04	0.04

ADL, activities of daily living; FAOS, Foot and Ankle Outcome Score; FLP, Functional Limitations Profile; QoL, quality of life.

Nine months

		Tubular bandage	Below knee cast	Aircast brace	Bledsoe boot	Male	Age	Baseline score
FAOS, pain	Coefficient	81.11	4.33	1.91	1.71	2.91	–0.29	0.27
	SE	2.09	2.56	2.58	2.53	1.87	0.08	0.05
FAOS, symptoms	Coefficient	79.19	0.42	0.10	–1.08	4.52	–0.24	0.28
	SE	2.01	2.47	2.48	2.44	1.80	0.08	0.05
FAOS, ADL	Coefficient	93.14	1.20	0.99	0.09	2.00	–0.17	0.13
	SE	1.27	1.58	1.59	1.55	1.13	0.05	0.03
FAOS, sport	Coefficient	76.77	2.39	0.78	0.97	2.25	–0.31	0.16
	SE	3.01	3.68	3.69	3.61	2.63	0.11	0.08
FAOS, QoL	Coefficient	64.92	6.26	6.07	3.95	2.89	–0.28	0.20
	SE	2.88	3.54	3.54	3.47	2.57	0.11	0.05
FLP	Coefficient	6.32	–1.68	–2.15	–1.49	–2.26	0.21	0.09
	SE	0.99	1.23	1.23	1.21	0.88	0.03	0.03

ADL, activities of daily living; FAOS, Foot and Ankle Outcome Score; FLP, Functional Limitations Profile; QoL, quality of life.

ANCOVAs of primary outcomes, intention to treat analysis, excluding pilot study participants who did not complete the FAOS at baseline, showing the influence of age, sex and baseline score

Four weeks

		Tubular bandage	Below knee cast	Aircast brace	Bledsoe boot	Male	Age	Baseline score
FAOS, pain	Coefficient	62.28	5.12	3.53	0.62	3.68	–0.33	0.38
	SE	1.94	2.38	2.39	2.35	1.73	0.07	0.05
FAOS, symptoms	Coefficient	59.80	3.78	2.18	–0.75	4.95	–0.55	0.38
	SE	1.95	2.41	2.41	2.37	1.72	0.07	0.05
FAOS, ADL	Coefficient	82.26	3.02	0.63	–0.07	3.01	–0.42	0.21
	SE	1.36	1.68	1.69	1.65	1.21	0.05	0.04
FAOS, sport	Coefficient	44.69	5.02	0.04	–0.26	5.22	–0.68	0.33
	SE	2.83	3.43	3.44	3.41	2.47	0.11	0.07
FAOS, QoL	Coefficient	42.95	5.91	4.86	1.85	0.53	–0.46	0.28
	SE	2.40	2.96	2.96	2.90	2.13	0.09	0.04
FLP	Coefficient	16.86	–3.06	–0.06	0.06	–3.39	0.39	0.14
	SE	1.38	1.71	1.71	1.68	1.23	0.05	0.05

ADL, activities of daily living; FAOS, Foot and Ankle Outcome Score; FLP, Functional Limitations Profile; QoL, quality of life.

Twelve weeks

		Tubular bandage	Below knee cast	Aircast brace	Bledsoe boot	Male	Age	Baseline score
FAOS, pain	Coefficient	72.93	5.13	3.70	3.33	3.51	–0.33	0.31
	SE	2.00	2.46	2.42	2.40	1.77	0.07	0.05
FAOS, symptoms	Coefficient	68.70	3.38	2.74	2.46	5.32	–0.35	0.31
	SE	1.98	2.44	2.42	2.40	1.76	0.07	0.05
FAOS, ADL	Coefficient	88.86	3.48	1.09	2.35	1.95	–0.26	0.17
	SE	1.25	1.57	1.58	1.53	1.12	0.05	0.04
FAOS, sport	Coefficient	62.24	8.68	4.78	5.94	1.71	–0.61	0.12
	SE	2.91	3.59	3.61	3.51	2.56	0.12	0.08
FAOS, QoL	Coefficient	53.48	8.68	8.01	6.11	2.40	–0.43	0.18
	SE	2.59	3.19	3.15	3.12	2.30	0.10	0.05
FLP	Coefficient	8.36	–1.76	–1.16	–0.81	–2.02	0.30	0.14
	SE	1.10	1.37	1.39	1.34	0.98	0.04	0.04

ADL, activities of daily living; FAOS, Foot and Ankle Outcome Score; FLP, Functional Limitations Profile; QoL, quality of life.

Nine months

		Tubular bandage	Below knee cast	Aircast brace	Bledsoe boot	Male	Age	Baseline score
FAOS, pain	Coefficient	81.11	4.33	1.91	1.71	2.91	–0.29	0.27
	SE	2.09	2.56	2.58	2.53	1.87	0.08	0.05
FAOS, symptoms	Coefficient	79.19	0.42	0.10	–1.08	4.52	–0.24	0.28
	SE	2.01	2.47	2.48	2.44	1.80	0.08	0.05
FAOS, ADL	Coefficient	93.14	1.20	0.99	0.09	2.00	–0.17	0.13
	SE	1.27	1.58	1.59	1.55	1.13	0.05	0.03
FAOS, sport	Coefficient	76.77	2.39	0.78	0.97	2.25	–0.31	0.16
	SE	3.01	3.68	3.69	3.61	2.63	0.11	0.08
FAOS, QoL	Coefficient	64.92	6.26	6.07	3.95	2.89	–0.28	0.20
	SE	2.88	3.54	3.54	3.47	2.57	0.11	0.05
FLP	Coefficient	6.32	–1.68	–2.15	–1.49	–2.26	0.21	0.09
	SE	0.99	1.23	1.23	1.21	0.88	0.03	0.03

ADL, activities of daily living; FAOS, Foot and Ankle Outcome Score; FLP, Functional Limitations Profile; QoL, quality of life.

ANCOVAs of primary outcomes, compliance analysis, all participants, showing the influence of age, sex and baseline score

Four weeks

		Tubular bandage	Below knee cast	Aircast brace	Bledsoe boot	Male	Age	Baseline score
FAOS, pain	Coefficient	62.36	3.80	3.40	0.15	5.40	–0.56	0.34
	SE	1.97	2.51	3.41	2.37	1.76	0.08	0.05
FAOS, symptoms	Coefficient	59.44	2.86	2.38	–1.33	4.62	–0.33	0.38
	SE	2.00	2.55	2.46	2.42	1.79	0.08	0.05
FAOS, ADL	Coefficient	82.37	1.98	0.18	–0.30	3.07	–0.41	0.23
	SE	1.42	1.83	1.76	1.72	1.28	0.06	0.04
FAOS, sport	Coefficient	44.34	3.32	–0.35	–0.53	6.29	–0.64	0.33
	SE	2.85	3.59	3.46	3.42	2.53	0.12	0.07
FAOS, QoL	Coefficient	42.98	4.56	4.50	1.01	1.26	–0.45	0.28
	SE	2.44	3.13	2.99	2.94	2.20	0.10	0.04
FLP	Coefficient	16.61	–1.66	0.20	0.55	–3.56	0.38	0.12
	SE	1.40	1.80	1.73	1.70	1.26	0.05	0.05

ADL, activities of daily living; FAOS, Foot and Ankle Outcome Score; FLP, Functional Limitations Profile; QoL, quality of life.

Twelve weeks

		Tubular bandage	Below knee cast	Aircast brace	Bledsoe boot	Male	Age	Baseline score
FAOS, pain	Coefficient	72.78	4.35	3.53	3.21	3.69	–0.32	0.29
	SE	2.05	2.64	2.47	2.45	1.84	0.08	0.05
FAOS, symptoms	Coefficient	68.84	3.08	2.80	2.39	4.86	–0.38	0.30
	SE	2.02	2.58	2.45	2.43	1.81	0.08	0.05
FAOS, ADL	Coefficient	88.89	2.69	0.75	2.11	2.23	–0.26	0.14
	SE	1.28	1.68	1.61	1.55	1.17	0.05	0.04
FAOS, sport	Coefficient	62.23	7.65	4.11	5.56	2.50	–0.58	0.10
	SE	2.94	3.78	3.63	3.53	2.64	0.12	0.08
FAOS, Q0L	Coefficient	53.57	8.84	7.44	5.48	2.86	–0.42	0.16
	SE	2.64	3.40	3.20	3.17	2.38	0.10	0.05
FLP	Coefficient	7.90	–0.50	–0.55	–0.31	–2.18	0.03	0.12
	SE	1.10	1.42	1.38	1.33	1.00	0.04	0.04

ADL, activities of daily living; FAOS, Foot and Ankle Outcome Score; FLP, Functional Limitations Profile; QoL, quality of life.

Nine months

		Tubular bandage	Below knee cast	Aircast brace	Bledsoe boot	Male	Age	Baseline score
FAOS, pain	Coefficient	81.69	2.93	1.67	1.38	2.31	–0.30	0.27
	SE	2.14	2.73	2.63	2.58	1.93	0.08	0.05
FAOS, symptoms	Coefficient	79.51	–0.64	0.05	–1.38	4.28	–0.26	0.27
	SE	2.06	2.63	2.53	2.49	1.86	0.08	0.05
FAOS, ADL	Coefficient	93.20	0.72	0.97	0.05	1.85	–0.18	0.13
	SE	1.30	1.70	1.63	1.59	1.18	0.05	0.04
FAOS, sport	Coefficient	77.58	–0.39	0.32	0.17	1.67	–0.36	0.16
	SE	3.06	3.90	3.74	3.67	2.72	0.12	0.08
FAOS, QoL	Coefficient	65.93	3.43	5.58	3.15	2.00	–0.30	0.20
	SE	2.92	3.72	3.58	3.51	2.64	0.12	0.06
FLP	Coefficient	5.94	–0.69	–1.80	–1.07	–2.29	0.20	0.07
	SE	1.00	1.30	1.24	1.22	0.91	0.04	0.04

ADL, activities of daily living; FAOS, Foot and Ankle Outcome Score; FLP, Functional Limitations Profile; QoL, quality of life.

ANCOVAs of primary outcomes, compliance analysis, excluding pilot study participants who did not complete the FAOS at baseline, showing the influence of age, sex and baseline score

Four weeks

		Tubular bandage	Below knee cast	Aircast brace	Bledsoe boot	Male	Age	Baseline score
FAOS, pain	Coefficient	62.41	3.91	3.30	0.09	5.31	–0.56	0.35
	SE	1.97	2.52	2.42	2.38	1.77	0.08	0.05
FAOS, symptoms	Coefficient	59.74	3.41	2.10	–1.11	4.07	–0.33	0.37
	SE	1.98	2.54	2.44	2.40	1.78	0.08	0.05
FAOS, ADL	Coefficient	82.31	2.02	0.53	–0.43	3.22	–0.43	0.19
	SE	1.38	1.79	1.71	1.67	1.25	0.05	0.04
FAOS, sport	Coefficient	44.44	3.61	0.07	–0.58	6.26	–0.66	0.32
	SE	2.83	3.58	3.45	3.40	2.52	0.12	0.07
FAOS, QoL	Coefficient	43.26	5.03	4.30	1.12	0.81	–0.46	0.27
	SE	2.43	3.13	2.99	2.93	2.20	0.10	0.04
FLP	Coefficient	16.61	–1.66	0.20	0.55	–3.56	0.38	0.12
	SE	1.40	1.80	1.73	1.70	1.26	0.05	0.05

ADL, activities of daily living; FAOS, Foot and Ankle Outcome Score; FLP, Functional Limitations Profile; QoL, quality of life.

Twelve weeks

		Tubular bandage	Below knee cast	Aircast brace	Bledsoe boot	Male	Age	Baseline score
FAOS, pain	Coefficient	72.78	4.35	3.53	3.21	3.69	–0.32	0.29
	SE	2.05	2.64	2.47	2.45	1.84	0.08	0.05
FAOS, symptoms	Coefficient	68.84	3.08	2.80	2.39	4.86	–0.38	0.30
	SE	2.02	2.58	2.45	2.43	1.81	0.08	0.05
FAOS, ADL	Coefficient	88.89	2.69	0.75	2.11	2.23	–0.26	0.14
	SE	1.28	1.68	1.61	1.55	1.17	0.05	0.04
FAOS, sport	Coefficient	62.23	7.65	4.11	5.56	2.50	–0.58	0.10
	SE	2.94	3.78	3.63	3.53	2.64	0.12	0.08
FAOS, QoL	Coefficient	53.57	8.84	7.44	5.48	2.86	–0.42	0.16
	SE	2.64	3.40	3.20	3.17	2.38	0.10	0.05
FLP	Coefficient	7.90	–0.50	–0.55	–0.31	–2.18	0.03	0.12
	SE	1.10	1.42	1.38	1.33	1.00	0.04	0.04

ADL, activities of daily living; FAOS, Foot and Ankle Outcome Score; FLP, Functional Limitations Profile; QoL, quality of life.

Nine months

		Tubular bandage	Below knee cast	Aircast brace	Bledsoe boot	Male	Age	Baseline score
FAOS, pain	Coefficient	81.69	2.93	1.67	1.38	2.31	–0.30	0.27
	SE	2.14	2.73	2.63	2.58	1.93	0.08	0.05
FAOS, symptoms	Coefficient	79.51	–0.64	0.05	–1.38	4.28	–0.26	0.27
	SE	2.06	2.63	2.53	2.49	1.86	0.08	0.05
FAOS, ADL	Coefficient	93.20	0.72	0.97	0.05	1.85	–0.18	0.13
	SE	1.30	1.70	1.63	1.59	1.18	0.05	0.04
FAOS, sport	Coefficient	77.58	–0.39	0.32	0.17	1.67	–0.36	0.16
	SE	3.06	3.90	3.74	3.67	2.72	0.12	0.08
FAOS, QoL	Coefficient	65.93	3.43	5.58	3.15	2.00	–0.30	0.20
	SE	2.92	3.72	3.58	3.51	2.64	0.12	0.06
FLP	Coefficient	5.94	–0.69	–1.80	–1.07	–2.29	0.20	0.07
	SE	1.00	1.30	1.24	1.22	0.91	0.04	0.04

ADL, activities of daily living; FAOS, Foot and Ankle Outcome Score; FLP, Functional Limitations Profile; QoL, quality of life.

Appendix 14

Methods of derivation of individual costs

Unit resource costs between baseline and 9 months

Health-care resource	Unit	Actual cost given if not in 2005–6 prices (for date see footnotes)	Actual cost inflated to 2005–6 prices (if applicable)[a]
Aircast braces	Per brace		List price to NHS: £32.50 + VAT = £38.19 Bulk buy price: £19.20 + VAT = £22.56 for orders of 500 braces a year on a 3-year contract[b]
Bledsoe boots	Per boot		List price to NHS = £212.68 including VAT Bulk buy price of £58.75 including VAT for large orders (over 100 per year)[c]
Elasticated stockings (tubular bandage)	Per elasticated stocking		NHS price: 34p[d]
Below knee cast	Per participant: two rolls of polyresin casting tape required[e]		NHS price: £12.80[f]
Cost of fitting			
Aircast braces	Fitting a brace		£1.04[g]
Bledsoe boots	Fitting a boot		£2.35[h]
Elasticated stockings (tubular bandage)	Fitting elasticated stockings		£1.10[i]
Below knee cast	Cost of applying polyresin casting tape		£3.66[j]
Staff costs (NHS)			
NHS consultant	Consultation		£73.00 (quartile range £63.00–£89.00)[k]
GP	Consultation	£49 (quartile range £31–£44)[l]	£52.60 (quartile range £33.28–£47.23)[m]
Osteopath	Session	£40.29[n]	£43.25[o]
Chiropractor	Session	£37.75[p]	£40.52[q]
NHS physiotherapy	Consultation		£8.06[r]
Other: attendances at deep vein thrombosis clinic	Consultation		£189 (quartile range £130–£242)[s]
Staff costs (private)[t]			
Private consultant	Consultation		£120[u]
Osteopathy	Session	£40.29[v]	£43.25[w]
Chiropractor	Session	£37.75[x]	£40.52[y]
Private physiotherapy	Session	£33.86[z]	£36.35[aa]

continued

Health-care resource	Unit	Actual cost given if not in 2005/6 prices (for date see footnotes)	Actual cost inflated to 2005/6 prices (if applicable)[a]
Imaging because of ankle injury (NHS)			
Normal radiograph	Scan	£22.57[bb]	£22.72[cc]
MRI scan	Scan		£313 (quartile range £187–£527)[dd]
Ultrasound scan	Scan		£67 (quartile range £51–£89)[ee]
CT scan	Scan		£160 (quartile range £107–£195)[ff]
Imaging because of ankle injury (private)[t]			
Normal radiograph	Scan		£74.50[gg]
MRI scan	Scan		£556.20[hh]
Ultrasound scan	Scan		£212.50[ii]
CT scan	Scan		£518.75[jj]
Hospital admissions			
Cost of days hospital admission (orthopaedics)	Inpatient day in orthopaedic care: regular day/night admissions	£365[kk]	£391.81[ll]
Prescribed medicine			
Various prescribed medicine			Prices sourced from the *British National Formulary* (BNF) website[mm]
Privately purchased medicine			
			Prices self-reported by patients[nn]
Sick leave due to ankle injury			
Cost of 1 day off work (based on national average wage)	Day	£114.60[oo]	£119.70[pp]

a If unit costs not already in 2005/6 prices.
b For the equivalent product (i.e. trial version no longer available), which has the advantage over the existing one in that it fits both legs but is otherwise comparable. Supplied by Aircast Ltd Partnership, Brant House, Scragglethorpe, Lincs, LN5 0QZ, February 2006.
c Up-to-date costs (list and bulk buying prices) supplied by Bhraum Medical, Thorncliffe Park, Sheffield, S35 2PW.
d Cost provided relates to prevailing costs of elasticated stockings supplied to Coventry and Warwickshire hospital (part of UHCW NHS Trust).
e Information confirmed by Coventry and Warwickshire hospital plastering department in 2006.
f Cost information provided by Coventry and Warwickshire hospital plastering department in 2006 for two rolls.
g Average total time to apply 4 minutes [standard deviation = 0.97: using the formula for CIs for difference between the means comparing the control group (elasticated stockings) with Aircast braces gives 4.5 minutes vs 4.0 minutes, a difference between means of 0.5 minutes (CI –1.35 minutes to 2.41 minutes)], assuming 3 minutes of a Senior II physiotherapist's time [mid-scale (average of points 3 and 4 salaries for 2004/5 with on-costs at 9.3% for employers national insurance and 14% for superannuation)]. Nurse time taken as E-grade nurse on point 4 of 7, with on-costs for 2005/6.
h Average total time to apply 9 minutes [standard deviation = 5.0: using the formula for CI for difference between the means comparing the control group (elasticated stockings) with Bledsoe boots gives 4.5 minutes vs 9 minutes, a difference between means of –4.6 minutes (CI –1.66 to –7.56)], assuming 5 minutes of physiotherapist time and 4 minutes of nursing time. Grades and costing procedures as for Aircast braces.
i Average total time to apply 4.5 minutes (standard deviation = 4.17), assuming a mid-scale E-grade nurse on an average of points 3 or 4 of 6 for 2005/6, with on-cost percentages as for Aircast brace and elasticated stockings.

j Average total time to apply 15 minutes [standard deviation = 7.34: using the formula for CI for difference between the means comparing the control group (elasticated stockings) with below knee cast gives 4.5 minutes vs 15 minutes, a difference in means of –10.5 minutes (CI –6.80 minutes to –14.20 minutes)], assuming a mid-scale E-grade nurse on the average of points 3 or 4 of 6 for 2005/6, with on-cost percentages as for Aircast brace and elasticated stockings.
k National schedule of reference costs – NHS trusts and primary care trusts – Outpatient follow-up attendance data. Reference costs 2005. Figure taken for Trauma and Orthopaedics: Trauma.
l National schedule of reference costs – Primary care trusts – Outpatient follow-up attendance data. Reference costs 2004 (published March 2005).
m Based on National schedule of reference costs – Primary care trusts – Outpatient follow-up attendance data. Reference costs 2004 (published March 2005), inflated using an average of the 5-year annual percentage increase in health and community health services inflation factors for pay.
n Lack of information on NHS figures meant that private sector figures were used. The average cost of a session at seven private osteopaths consulted about their 2004 prices. All these osteopaths were selected because they were close to sites involved in the study.
o 2004 costs of osteopathy inflated using an average of the 5-year annual percentage increase in health and community health services inflation factors for pay.
p Approach to costing as for osteopaths but using costs for chiropractors, using eight private chiropractors and 2004 prices.
q 2004 costs of chiropractors inflated using an average of the 5-year annual percentage increase in health and community health services inflation factors for pay.
r Using physiotherapy pay scales (2005/6); based on a 30-minute consultation and a 37.5-hour working week for 46 weeks per year, assuming a Senior II physiotherapist on the average of point 3 or 4 out of 6, costed with on-costs for national insurance and superannuation.
s Based on National schedule of reference costs – NHS trusts – Outpatient first attendance data. Reference costs 2004 (published March 2005).
t Figures used if respondents did not supply a cost. If a cost was supplied this was used. Such costs were not inflated because of (a) the relatively short time period of the trial; (b) the absence of a readily available cost inflation index applying directly to such private sector services; (c) the fact that use of such services was not a major cost driver.
u Cost for use if patient did not specify cost: Walsgrave Hospital, Coventry; cost in 2006 for a 15-minute consultation with an orthopaedic surgeon.
v Cost for use if patient did not specify cost: average cost of a session at seven private osteopaths consulted about their 2004 prices.
w Cost for use if patient did not specify cost: 2004 costs of osteopathy inflated using an average of the 5-year annual percentage increase in health and community health services inflation factors for pay.
x Cost for use if patient did not specify cost: average cost of a session at eight private chiropractors using 2004 prices.
y Cost for use if patient did not specify cost: 2004 costs for a chiropractor inflated using an average of the 5-year annual percentage increase in health and community health services inflation factors for pay.
z Cost for use if patient did not specify cost: average cost of a session at seven private physiotherapists using 2004 prices.
aa Cost for use if patient did not specify cost: 2004 costs for private physiotherapy inflated using an average of the 5-year annual percentage increase in health and community health services inflation factors for pay.
bb Based on average of 2004/5 prices for ankle imaging without radiologist support.
cc Based on average of 2004/5 prices for ankle imaging without radiologist support. This figure was then inflated to 2005/6 prices using an average of the 5-year trend for 2000–5 of the price component of the health and community health services pay and price inflation index.
dd National schedule of reference costs – NHS trusts – Direct access: radiology services test data – Banding code RBF1. Reference costs 2005 (published April 2006).
ee National schedule of reference costs – NHS trusts – Direct access: Radiology services test data – Banding code RBC2. Reference costs 2005 (published April 2006).
ff National schedule of reference costs – NHS trusts – Direct access: radiology services test data – Banding code RBD1. Reference costs 2005 (published April 2006).
gg Cost for use if patient did not specify cost: based on the average price of a radiograph in late 2005 with BUPA (Whalley Range, Manchester); MedTel (City of London); BMI Healthcare (nationwide costs); and Alliance Medical (nationwide costs).
hh Cost for use if patient did not specify cost: based on the average price of an MRI in late 2005 with BUPA (Whalley Range, Manchester); MedTel (City of London); MedTel (Cardiff); BMI Healthcare (nationwide costs); and Alliance Medical (nationwide costs).
ii Cost for use if patient did not specify cost: based on the average price of an ultrasound in late 2005 at BUPA (Whalley Range, Manchester) and MedTel (City of London).
jj Cost for use if patient did not specify cost: based on the average price of a CT scan in late 2005 with BUPA (Whalley Range, Manchester); MedTel (City of London); BMI Healthcare (nationwide costs); and Alliance Medical (nationwide costs).
kk National schedule of reference costs – NHS trusts (regular admissions data). Reference costs 2004 (published March 2005).
ll 2004 reference cost inflated using an average of the 5-year annual percentage increase in health and community health services inflation factors for pay.

continued

mm BNF website: www.bnf.org (costs sourced in early 2006).
nn No attempt was made to inflate self-reported costs to 2005/6 prices if items were obtained before this period. This was because, when the trial began in November 2002, the Health Service Cost Index (available from the Resource Planning Acquisition Team at the Department of Health) for drugs was 77.86; in March 2005, just before the 2005/6 financial year for which we wanted to standardise prices, the figure was 76.97. Thus, drug prices were practically static over the period, suggesting inflating or deflating such costs was unnecessary. On occasions, if respondents volunteered information about purchasing an item but failed to indicate a cost then we sometimes assumed a cost figure supplied by another respondent, or used personal knowledge about the retail price of such an item, or obtained a cost from the BNF website.
oo Data sourced from Dobbs.[86] Using Table 3, Make-up of mean gross weekly pay, United Kingdom, April 1998–2004 – column 2004 – implies a weekly wage of £506.90. This figure was multiplied by 52 and then divided by 230 (allowing for 6 weeks of holidays and assuming 230 working days). This yielded a daily rate of £114.60.
pp The 2004 pay data has been inflated to 2005 prices (because of the paucity of data available) using the average percentage increase over the 5-year series 1999–2004 obtained from the same data set (and row) as the actual 2004 pay information.

Appendix 15

Cost–utility analysis results

Cost–utility analysis (ICERs) related to cost per QALY (health-care costs only)

	Tubular bandage	Below knee cast	Aircast brace	Bledsoe boot
Effect, mean	0.3254	0.4299	0.4297	0.4341
Effect, SD	0.2678	0.2802	0.2491	0.2902
Effect, SE	0.0298	0.0317	0.0292	0.0340
Cost, mean	£135.09	£170.54	£166.52	£365.00
Cost, SD	£371.51	£394.51	£366.64	£381.72
Cost, SE	£41.28	£44.67	£42.91	£44.68
Difference (effect), mean		0.1044	0.1043	0.1086
Difference (effect), SE		0.0435	0.0417	0.0452
Difference (effect), lower 95% CI		0.0192	0.0227	0.0201
Difference (effect), upper 95% CI		0.1897	0.1859	0.1971
Difference (cost), mean		£35.44	£31.43	£229.91
Difference (cost), SE		£60.82	£59.54	£60.83
Difference (cost), lower 95% CI		–£83.76	–£85.28	£110.69
Difference (cost), upper 95% CI		£154.65	£148.13	£349.13
ICER		£339	£301	£2116

CI, confidence interval; ICER, incremental cost-effectiveness ratio; QALY, quality-adjusted life-year.

Cost–utility analysis (ICERs) related to cost per QALY (health-care costs only) comparing below knee cast with Aircast brace and with Bledsoe boot

	Below knee cast	Aircast brace	Bledsoe boot
Effect, mean	0.4299	0.4297	0.4341
Effect, SD	0.2802	0.2491	0.2902
Effect, SE	0.0317	0.0292	0.0340
Cost, mean	£170.54	£147.33	£365.00
Cost, SD	£394.51	£366.64	£381.72
Cost, SE	£44.67	£42.91	£44.68
Difference (effect), mean		–0.0001	0.0042
Difference (effect), SE		0.0431	0.0465
Difference (effect), lower 95% CI		–0.0846	–0.0869
Difference (effect), upper 95% CI		0.0843	0.0953
Difference (cost), mean		–£23.21	£194.47
Difference (cost), SE		£61.94	£63.18
Difference (cost), lower 95% CI		–£144.61	£70.64
Difference (cost), upper 95% CI		£98.20	£318.29
ICER		£159,214	£46,324

CI, confidence interval; ICER, incremental cost-effectiveness ratio; QALY, quality-adjusted life-year.

Cost–utility analysis (ICERs) related to cost per QALY (health-care costs and indirect sick leave cost)

	Tubular bandage	Below knee cast	Aircast brace	Bledsoe boot
Effect, mean	0.3254	0.4299	0.4297	0.4341
Effect, SD	0.2678	0.2802	0.2491	0.2902
Effect, SE	0.0298	0.0317	0.0292	0.0340
Cost, mean	£940.48	£1085.94	£1314.33	£1187.60
Cost, SD	£1903.39	£2842.05	£3254.27	£1918.34
Cost, SE	£211.49	£321.80	£380.88	£224.53
Difference (effect), mean		0.1044	0.1043	0.1086
Difference (effect), SE		0.0435	0.0417	0.0452
Difference (effect), lower 95% CI		0.0192	0.0227	0.0201
Difference (effect), upper 95% CI		0.1897	0.1859	0.1971
Difference (cost), mean		£145.45	£373.85	£247.11
Difference (cost), SE		£385.07	£435.66	£308.45
Difference (cost), lower 95% CI		–£609.28	–£480.03	–£357.43
Difference (cost), upper 95% CI		£900.18	£1227.72	£851.65
ICER		£1393	£3585	£2275

CI, confidence interval; ICER, incremental cost-effectiveness ratio; QALY, quality-adjusted life-year.

Cost–utility analysis (ICERs) related to cost per QALY (health-care costs and indirect sick leave cost) comparing below knee cast with Aircast brace and with Bledsoe boot

	Below knee cast	Aircast brace	Bledsoe boot
Effect, mean	0.4299	0.4297	0.4341
Effect, SD	0.2802	0.2491	0.2902
Effect, SE	0.0317	0.0292	0.0340
Cost, mean	£1085.94	£1314.33	£1187.59
Cost, SD	£2842.05	£3254.27	£1918.34
Cost, SE	£321.80	£380.88	£224.53
Difference (effect), mean		–0.0001	0.0042
Difference (effect), SE		0.0431	0.0465
Difference (effect), lower 95% CI		–0.0846	–0.0869
Difference (effect), upper 95% CI		0.0843	0.0953
Difference (cost), mean		£228.39	£101.66
Difference (cost), SE		£498.62	£392.38
Difference (cost), lower 95% CI		–£748.89	–£667.40
Difference (cost), upper 95% CI		£1205.68	£870.72
ICER		–£1566,824	£24,216

CI, confidence interval; ICER, incremental cost-effectiveness ratio; QALY, quality-adjusted life-year.

Sensitivity analysis: cost–utility analysis (ICERs) related to cost per QALY (health-care costs) excluding cases for which imputation necessary

	Tubular bandage	Below knee cast	Aircast brace	Bledsoe boot
Effect, mean	0.3275	0.4225	0.4320	0.4294
Effect, SD	0.2651	0.2798	0.2516	0.2889
Effect, SE	0.0304	0.0321	0.0296	0.0317
Cost, mean	£136.38	£173.66	£170.11	£358.93
Cost, SD	£379.31	£399.21	£371.20	£386.66
Cost, SE	£43.51	£45.79	£43.75	£42.44
Difference (effect), mean		0.0950	0.1045	0.1019
Difference (effect), SE		0.0442	0.0419	0.0434
Difference (effect), lower 95% CI		0.0083	0.0223	0.0168
Difference (effect), upper 95% CI		0.1817	0.1866	0.01870
Difference (cost), mean		£37.27	£33.72	£222.54
Difference (cost), SE		£63.17	£60.93	£60.00
Difference (cost), lower 95% CI		–£86.54	–£85.70	£104.95
Difference (cost), upper 95% CI		£161.08	£153.14	£340.14
ICER		£392	£323	£2184

CI, confidence interval; ICER, incremental cost-effectiveness ratio; QALY, quality-adjusted life-year.

Sensitivity analysis: cost–utility analysis (ICERs) related to cost per QALY (health-care costs at bulk buy discounted prices) comparing tubular bandage with Aircast brace and with Bledsoe boot

	Tubular bandage	Aircast brace at bulk buy price	Bledsoe boot at bulk buy price
Effect, mean	0.3254	0.4297	0.4341
Effect, SD	0.2678	0.4291	0.2902
Effect, SE	0.0298	0.0292	0.0340
Cost, mean	£135.09	£150.89	£211.07
Cost, SD	£371.51	£366.64	£381.72
Cost, SE	£41.28	£42.91	£44.68
Difference (effect), mean		0.1043	0.1086
Difference (effect), SE		0.0417	0.0452
Difference (effect), lower 95% CI		0.0227	0.0201
Difference (effect), upper 95% CI		0.1859	0.1971
Difference (cost), mean		£15.80	£75.98
Difference (cost), SE		£59.54	£60.83
Difference (cost), lower 95% CI		–£100.91	–£43.24
Difference (cost), upper 95% CI		£132.50	£195.20
ICER		£151.00	£699.00

CI, confidence interval; ICER, incremental cost-effectiveness ratio; QALY, quality-adjusted life-year.

Sensitivity analysis: cost–utility analysis (ICERs) related to cost per QALY (health-care costs and indirect sick leave cost at £59.85 per diem)

	Tubular bandage	Below knee cast	Aircast brace	Bledsoe boot
Effect, mean	0.3254	0.4299	0.4297	0.4341
Effect, SD	0.2678	0.2802	0.2491	0.2902
Effect, SE	0.0298	0.0317	0.0292	0.0340
Cost, mean	£537.79	£628.24	£740.42	£776.30
Cost, SD	£1038.87	£1543.73	£1688.57	£1103.98
Cost, SE	£115.43	£174.79	£197.63	£129.21
Difference (effect), mean		0.1044	0.1043	0.1086
Difference (effect), SE		0.0435	0.0417	0.0452
Difference (effect), lower 95% CI		0.0192	0.0227	0.0201
Difference (effect), upper 95% CI		0.1897	0.1859	0.1971
Difference (cost), mean		£90.45	£202.64	£238.51
Difference (cost), SE		£209.47	£228.87	£173.26
Difference (cost), lower 95% CI		–£320.10	–£245.95	–£101.07
Difference (cost), upper 95% CI		501.00	651.22	£578.10
ICER		£866	£1943	£2195

CI, confidence interval; ICER, incremental cost-effectiveness ratio; QALY, quality-adjusted life-year.

Cost–utility analysis (ICERs) related to cost per QALY (health-care costs and indirect sick leave cost at £59.85 per diem) comparing below knee cast with Aircast brace

	Below knee cast	Aircast brace
Effect, mean	0.3351	0.4297
Effect, SD	0.2642	0.2491
Effect, SE	0.0299	0.0292
Cost, mean	£628.24	£740.42
Cost, SD	£1543.73	£1688.57
Cost, SE	£174.79	£197.63
Difference (effect), mean		0.0946
Difference (effect), SE		0.0418
Difference (effect), lower 95% CI		0.0127
Difference (effect), upper 95% CI		0.1765
Difference (cost), mean		£112.19
Difference (cost), SE		£263.84
Difference (cost), lower 95% CI		–£404.93
Difference (cost), upper 95% CI		£629.30
ICER		£1186

CI, confidence interval; ICER, incremental cost-effectiveness ratio; QALY, quality-adjusted life-year.

Sensitivity analysis: cost–utility analysis (ICERs) related to cost per QALY (health-care costs and indirect sick leave cost capped at 30 days)

	Tubular bandage	Below knee cast	Aircast brace	Bledsoe boot
Effect, mean	0.3254	0.4299	0.4297	0.4341
Effect, SD	0.2678	0.2802	0.2491	0.2902
Effect, SE	0.0298	0.0317	0.0292	0.0340
Cost, mean	£746.89	£725.92	£928.99	£1028.92
Cost, SD	£1256.61	£1264.99	£1326.03	£1279.08
Cost, SE	£139.62	£143.23	£155.20	£149.70
Difference (effect), mean		0.1044	0.1043	0.1086
Difference (effect), SE		0.0435	0.0417	0.0452
Difference (effect), lower 95% CI		0.0192	0.0227	0.0201
Difference (effect), upper 95% CI		0.1897	0.1859	0.1971
Difference (cost), mean		£6.03	£182.10	£282.03
Difference (cost), SE		£200.02	£208.76	£204.71
Difference (cost), lower 95% CI		–£386.01	–£227.07	–£119.20
Difference (cost), upper 95% CI		£398.07	£591.26	£683.25
ICER		£58	£1746	£2596

CI, confidence interval; ICER, incremental cost-effectiveness ratio; QALY, quality-adjusted life-year.

Sensitivity analysis: cost–utility analysis (ICERs) related to cost per QALY (health-care costs and indirect sick leave cost capped at 30 days) to assess cost-effectiveness of top two performing options

	Below knee cast	Aircast brace
Effect, mean	0.3351	0.4297
Effect, SD	0.2642	0.2491
Effect, SE	0.0299	0.0292
Cost, mean	£752.92	£928.99
Cost, SD	£1264.99	£1326.03
Cost, SE	£143.23	£155.20
Difference (effect), mean		0.0946
Difference (effect), SE		0.0418
Difference (effect), lower 95% CI		0.0127
Difference (effect), upper 95% CI		0.1765
Difference (cost), mean		£176.06
Difference (cost), SE		£211.19
Difference (cost), lower 95% CI		–£237.86
Difference (cost), upper 95% CI		£590.00
ICER		£1861

CI, confidence interval; ICER, incremental cost-effectiveness ratio; QALY, quality-adjusted life-year.

Sensitivity analysis: cost–utility analysis (ICERs) related to cost per QALY (health-care costs at bulk buy discounted prices and indirect sick leave cost) comparing tubular bandage with Aircast brace and with Bledsoe boot

	Tubular bandage	Aircast brace at bulk buy price	Bledsoe boot at bulk buy price
Effect, mean	0.3254	0.4297	0.4341
Effect, SD	0.2678	0.2491	0.2902
Effect, SE	0.0298	0.0292	0.0340
Cost, mean	£940.48	£1298.70	£1033.66
Cost, SD	£1903.39	£3254.27	£1918.34
Cost, SE	£211.49	£380.88	£224.53
Difference (effect), mean		0.1043	0.1086
Difference (effect), SE		0.0417	0.0452
Difference (effect), lower 95% CI		0.0227	0.0201
Difference (effect), upper 95% CI		0.1859	0.1971
Difference (cost), mean		£358.22	£93.18
Difference (cost), SE		£435.66	£308.45
Difference (cost), lower 95% CI		–£495.66	–£511.36
Difference (cost), upper 95% CI		£1212.09	£697.73
ICER		£3435	£858

CI, confidence interval; ICER, incremental cost-effectiveness ratio; QALY, quality-adjusted life-year.

Sensitivity analysis: cost–utility analysis (ICERs) related to cost per QALY (health-care costs and indirect sick leave cost) excluding cases for which imputation necessary

	Tubular bandage	Below knee cast	Aircast brace	Bledsoe boot
Effect, mean	0.3275	0.4225	0.4320	0.4294
Effect, SD	0.2651	0.2798	0.2516	0.2889
Effect, SE	0.0304	0.0321	0.0296	0.0317
Cost, mean	£983.73	£1081.64	£1299.67	£1166.54
Cost, SD	£1955.68	£2872.53	£3285.24	£1942.10
Cost, SE	£224.33	£329.50	£387.17	£227.31
Difference (effect), mean		0.0950	0.1045	0.1019
Difference (effect), SE		0.0442	0.0419	0.0448
Difference (effect), lower 95% CI		0.0083	0.0223	0.0140
Difference (effect), upper 95% CI		0.1817	0.1866	0.1898
Difference (cost), mean		£97.91	£315.93	£182.81
Difference (cost), SE		£398.62	£444.64	£314.46
Difference (cost), lower 95% CI		–£683.37	–£555.55	–£433.53
Difference (cost), upper 95% CI		£879.19	£1187.42	£799.14
ICER		£1031	£3024	£1794

CI, confidence interval; ICER, incremental cost-effectiveness ratio; QALY, quality-adjusted life-year.

Appendix 16

Scattergrams

These illustrate cost-effectiveness for the 1000 trials under the different treatment regimes.

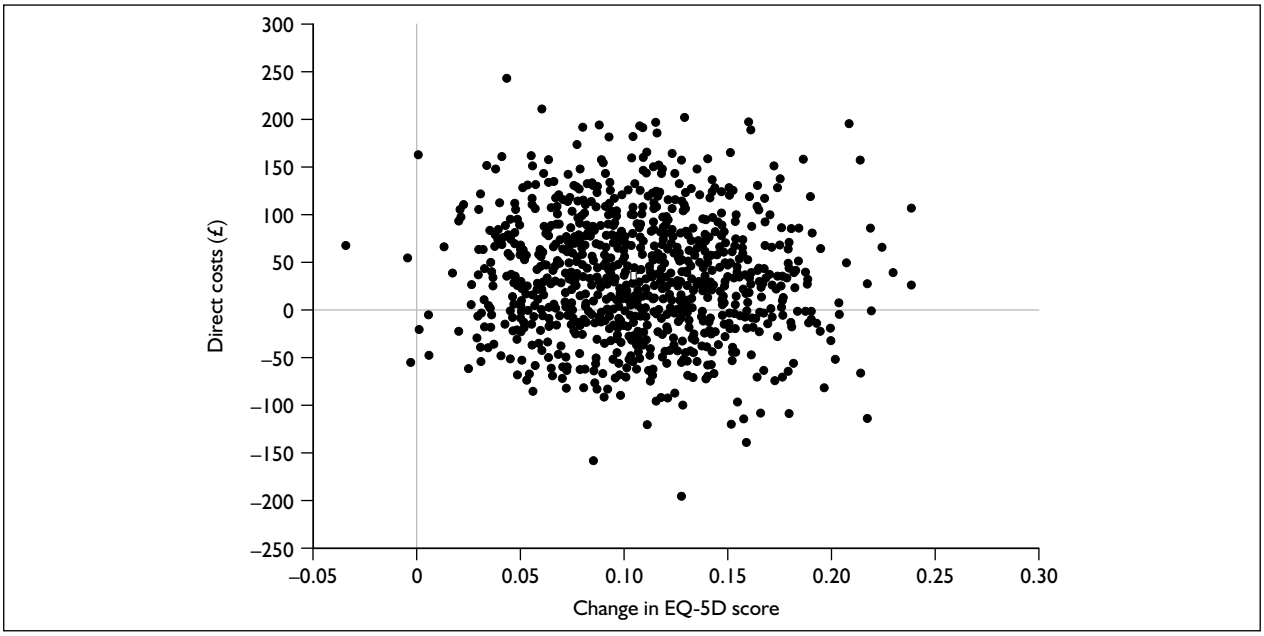


FIGURE 14 *Simulation output (1000 trials) showing the cost-effectiveness of the below knee cast relative to tubular bandage (direct health-care costs).*

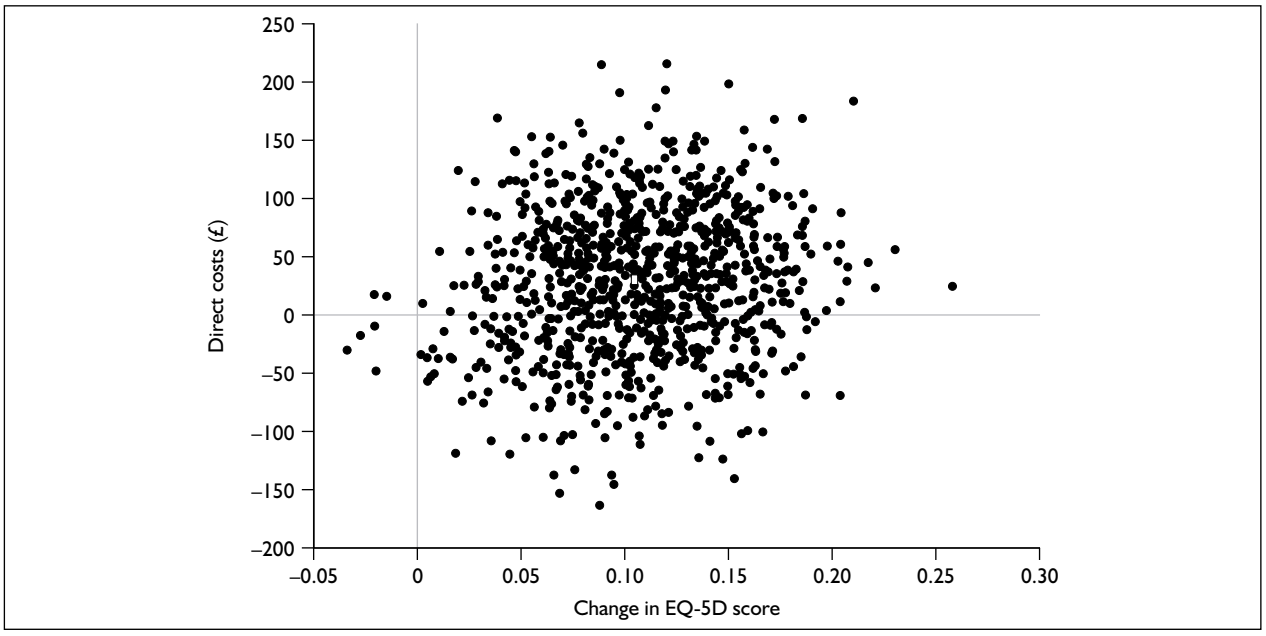


FIGURE 15 *Simulation output (1000 trials) showing the cost-effectiveness of the Aircast brace relative to tubular bandage (direct health-care costs).*

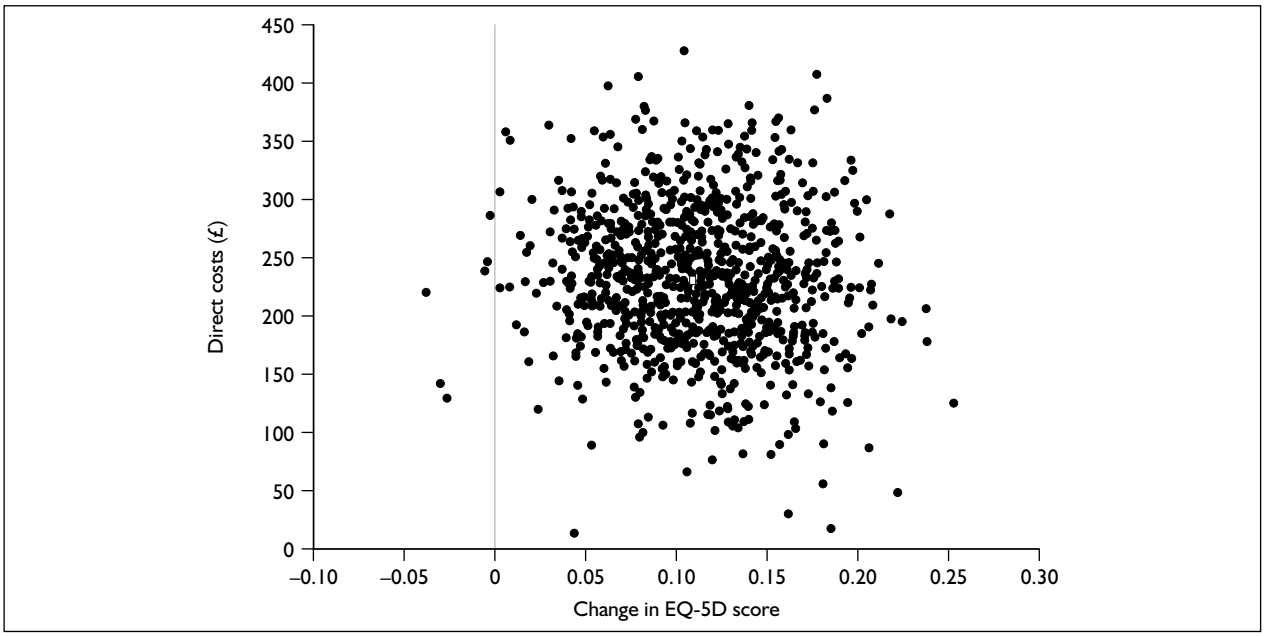


FIGURE 16 *Simulation output (1000 trials) showing the cost-effectiveness of the Bledsoe boot relative to tubular bandage (direct health-care costs).*

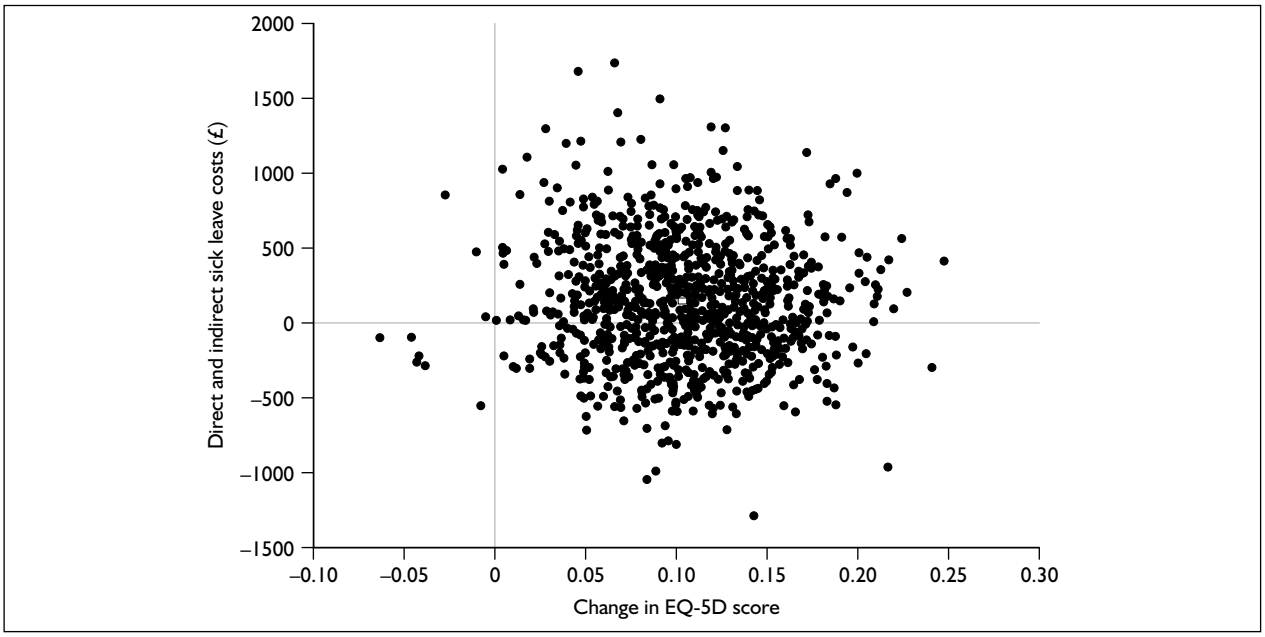


FIGURE 17 *Simulation output (1000 trials) showing the cost-effectiveness of the below knee cast relative to tubular bandage (direct health-care and indirect sick leave costs).*

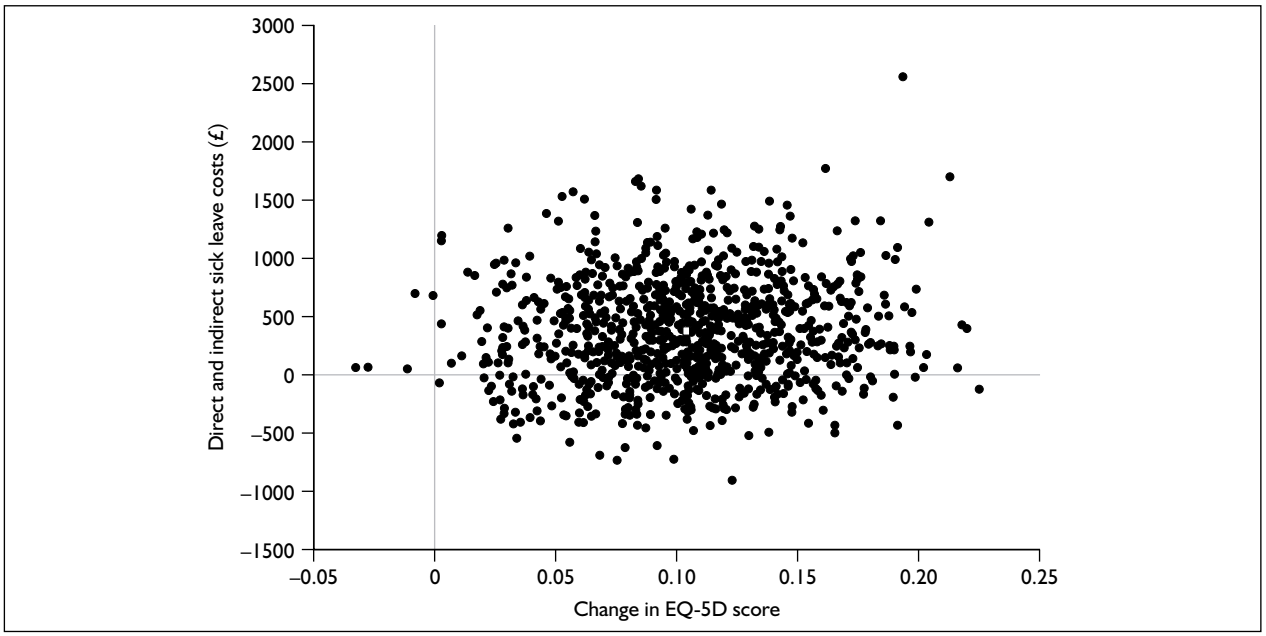


FIGURE 18 *Simulation output (1000 trials) showing the cost-effectiveness of the Aircast brace relative to tubular bandage (direct health-care and indirect sick leave costs).*

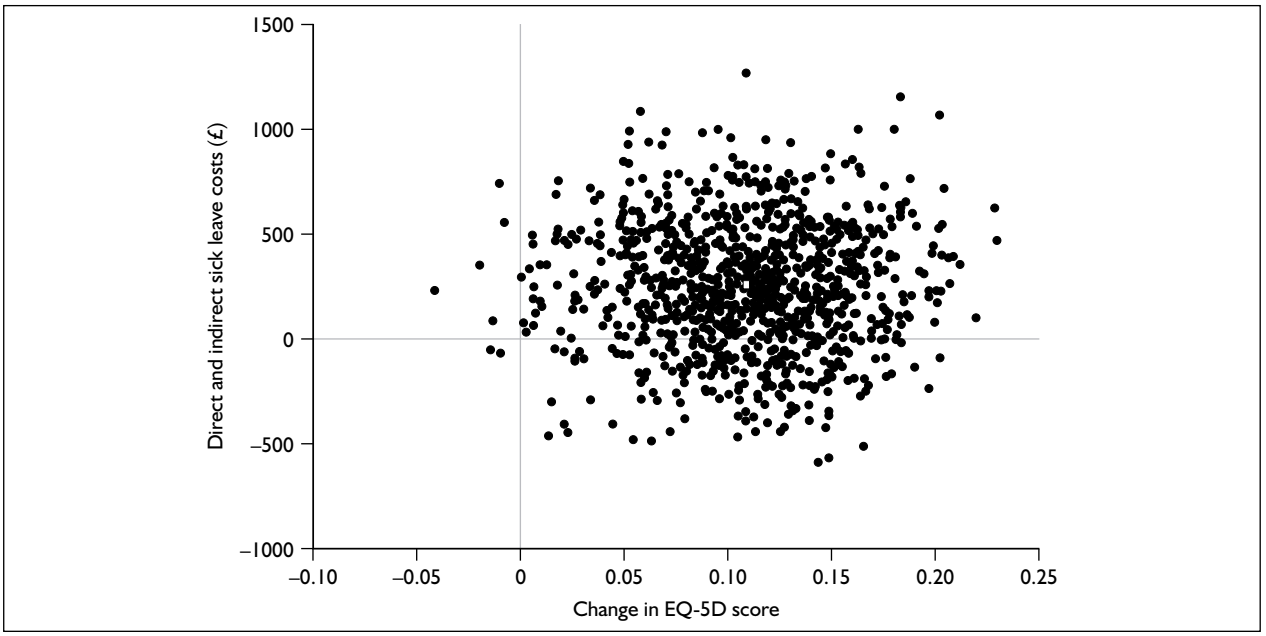


FIGURE 19 *Simulation output (1000 trials) showing the cost-effectiveness of the Bledsoe boot relative to tubular bandage (direct health-care and indirect sick leave costs).*

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We look forward to hearing from you.

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