The University Of Sheffield.

Sheffield Children's NHS
NHS Foundation Trust

THE BASIS STUDY

Bracing Adolescent Idiopathic Scoliosis (BASIS) Study – night-time versus full-time bracing in adolescent idiopathic scoliosis

BASIS Study

RESEARCH PROTOCOL
(Version 2.3) 8th February 2022

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Authorised by:	**Mr Ashley Cole (CI)**

Sponsor agreement:
Name: Dr Keith Pugh **Signature:** **Date:** 10/FEB/22

Chief Investigator agreement:

Name: Mr Ashley Cole **Signature:** **Date:** 08/02/2022

Sheffield Clinical Trials Research Unit (CTRU)

BASIS Study Protocol

Night-time versus full-time bracing in adolescent idiopathic scoliosis

This document describes a clinical trial, and provides information about procedures for entering participants. The protocol is not intended for use as a guide to the treatment of other patients. Amendments may be necessary; these will be circulated to known participants in the trial.

Contents

Abbreviations

Definition of terms

AE	Adverse Event
AIS	Adolescent Idiopathic Scoliosis
BSR	British Spine Registry
CCC	Confirmation of Capacity and Capability
CI	Chief Investigator
CRF	Case Report Form
CTU	Clinical Trials Unit
DMEC	Data Monitoring and Ethics Committee
FTB	Full-time bracing (day and night)
GCP	Good Clinical Practice
ICF	Informed Consent Form
ICH	International Conference on Harmonisation
ISF	Investigator Site File (This forms part of the TMF)
ISRCTN	International Standard Randomised Controlled Trials Number
ITT	Intention to Treat Analysis
NHS R&D	National Health Service Research & Development
NTB	Night-time only bracing
Parent	Parent or guardian
PI	Principal Investigator
PIC	Participant Identification Centre
PIS	Participant Information Sheet
PP	Per Protocol Analysis
QA	Quality Assurance
QC	Quality Control
QP	Qualified Person
RAC	Radiographic Adjudication Committee
RCT	Randomised Control Trial
REC	Research Ethics Committee
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SDV	Source Data Verification
SOP	Standard Operating Procedure
SOSORT	International Society on Scoliosis Orthopedic and Rehabilitation Treatment
SSI	Site Specific Information
TLSO	Thoracolumbar Sacral Orthosis
TMF	Trial Master File
TMG	Trial Management Group
TSC	Trial Steering Committee
UKCA	United Kingdom Conformity Assessed

1. General information

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1.4 Role of the Funder

The funder has reviewed the research protocol but will have no role in data collection, analysis, data interpretation, report writing or in the decision to submit the report for publication. The funder has approved the selection of members for oversight committees.

1.5 Protocol amendments

Amendment	Summary of changes
Substantial amendment 1 (v2.0)	Added reference numbers, updates to definition of loss to follow up, corrections to table of assessments, addition of sign-off page for Sponsor and CI, other study management/processes clarified.
Non-substantial amendment 1 (v2.1)	Allow e-consent at a clinic visit rather than by phone if relevant.
Substantial amendment 2 (v2.2)	Clarity added that non-BASIS users of the BSR will see patient name and DOB in patient searches.
Substantial amendment 3 (v2.3)	Administrative changes only

Trial Summary

Study title	Bracing Adolescent Idiopathic Scoliosis (BASIS) Study – night-time versus full-time bracing in adolescent idiopathic scoliosis
Sponsor	Sheffield Children's Hospital
Funder	This study is funded by the National Institute for Health Research (NIHR) Health Technology Assessment (HTA) Programme (NIHR131081).
ISRCTN	63247077
Project start date	1st January 2021
Project end date	28th February 2031
Hypothesis, aims and objectives	**Hypothesis:** The null hypothesis is that NTB is not non-inferior to FTB in preventing curve progression to 50 degrees or more in children with AIS, before skeletal maturity. **Aim:** The aim of the study is to find out whether NTB is non-inferior to FTB in preventing curve progression to 50 degrees or more in children with AIS before skeletal maturity, but superior in terms of patient quality of life and acceptability. **Study Objectives** • To determine if NTB is not inferior to FTB in reducing the risk of curve progression to 50 degrees before skeletal maturity; • To determine if there is a difference in anxiety, depression and quality of life between NTB and FTB; • To determine patient and parent experience and satisfaction of the braces; • To determine the longer-term effects of bracing on quality of life and curve progression up to two years after skeletal maturity.

	• To evaluate the relative cost-effectiveness of NTB compared to FTB.
Trial design	A multicentre, prospective, parallel group, pragmatic, non-blinded, randomised controlled non-inferiority trial. The trial will be conducted in a minimum of 19 hospitals and AIS patients will be recruited through outpatient clinics. Participants will be randomly allocated to either the treatment arm (NTB) or the control arm (FTB) on a 1:1 basis. Randomisation will be completed using minimisation based on site, skeletal maturity (Risser score 0, 1 or 2, and curve size (20-30, 31-40 degrees).
Internal pilot/feasibility criteria	An 18-month internal pilot, with clear progression criteria, will assess feasibility of the RCT. This will include assessment of the following: • Site set up • Participant recruitment • Retention and Cobb angle collection (primary outcome) • Intervention delivery • Minimum wear time in NTB arm • Minimum wear time in FTB arm • Compliance data
Setting	UK NHS hospitals; outpatient clinics
Eligibility criteria	To be eligible for the study, all the following criteria must be met at the point of randomisation: 1. Participants aged 10-15 years inclusive; 2. Clinical diagnosis of adolescent idiopathic scoliosis (AIS); 3. Risser stage 0, 1 or 2;

	4. Curve size (Cobb angle) between 20 and 40 degrees at baseline; 5. Curve apex at or below T7; 6. Have a good level of understanding of the English language, as trial materials are only provided in English. To be eligible for the study, none of the following criteria should be met: 1. Previous bracing or spinal surgery; 2. Child or parent is unable to adhere to trial procedures or complete follow-up.
Intervention & control groups	The intervention group will receive a NTB, worn for 8-12 hours a day, whilst in bed at night. The control group will receive a FTB, worn for 20-24 hours a day. This is the current standard of care.
Primary outcome	The binary primary outcome is Cobb angle progression to 50 degrees or more before skeletal maturity (Risser stage 4 in girls and Risser stage 5 in boys which is treatment failure; or Skeletal maturity without this degree of Cobb angle progression is treatment success.
Secondary outcomes	**Patient-reported outcomes:** 1. Scoliosis Research Society 22 questionnaire; 2. Paediatric health related quality of life, measured using the CHU9D; 3. Bad Sobernheim Stress Questionnaire (BSSQ), a brace specific questionnaire assessing the psychological effects of bracing; 4. Revised Children's Anxiety and Depression Scale (RCADS 25); 5. PROMIS Paediatric Sleep Disturbance Short Form 4a;

	6 PROMIS Paediatric Sleep Related Impairment Short Form 4a 7. Modified Client Satisfaction with Device module of the Orthotics and Prosthetics Users' Survey (CSD-OPUS) 8. Education information assessed using a bespoke questionnaire. **Parent Questionnaires:** 12. Patient Cost Questionnaire, using a bespoke questionnaire 13. Resource Use Questionnaire, using a bespoke questionnaire; 14. School attendance. **Clinical:** 15. Radiological measures: Cobb angle, curve type, curve apex, Risser sign, in-brace Cobb angle, frontal plane balance, apical vertebral rotation, apical vertebral translation; 16. In-brace correction; 17. Menarchial age; 18. Details of any surgery for scoliosis correction; 19. Other treatments prescribed to treat scoliosis, e.g. scoliosis specific exercises; 20. Complications (e.g. skin irritation) and Serious Adverse Events; 21. Brace compliance, assessed using the implantation of a temperature sensor in the FTB or NTB; 22. Treatment switching, including reason for doing so.
Duration of recruitment period and first enrolment date	Planned recruitment start: September 2021.
Duration of follow-up	The primary outcome will be recorded up to the point of skeletal maturity. In a previous study with the same inclusion criteria the mean time to skeletal maturity was

	28 +/- 9 months. Additional outcome data at will be collected at 1 and 2 years after skeletal maturity, or at 8 weeks, 1 year and 2 year post-surgery for those participants who have surgery.
Target sample size	780 participants
Definition of end of trial	The end of the trial is when the last recruited participant reaches their 2 year follow up. Sites will be closed once data cleaning is completed and the ethics committee will be informed.

2. Introduction

2.1 Background

Scoliosis is a lateral curvature of the spine with associated vertebral rotation. It can cause considerable distress primarily because of the appearance (1). The scoliosis curve is measured using an angle called the Cobb angle, which needs to be at least 10 degrees to be classified as scoliosis. 2-3% of the population under 16 years will have a scoliosis more than 10 degrees but only 0.2-0.5% will have a curve greater than 20 degrees (2). The majority begin in early adolescents and have no underlying cause (called adolescent idiopathic scoliosis, or AIS).

Growth is the major factor for worsening of scoliosis. At the end of growth curves less than 50 degrees rarely get worse whilst curves over 50 degrees, have a high chance of progression causing cardiorespiratory morbidity and pain (3). Therefore, surgical treatment is usually reserved for curves of 50 degrees or more and involves insertion of rods to correct the curve and fuse the vertebrae. This procedure has significant risks, including death and paralysis, and is expensive (£27,059, 2019/20 NHS tariff).

The options for reducing the risk of curve progression during growth are [1] 'Scoliosis Specific Exercises' where there is low quality evidence (4); and [2] bracing, where a rigid plastic brace is worn around the torso. These braces seek to "hold" the spine in the current position to prevent the scoliosis worsening. There is strong evidence to support the use of rigid full-time brace (FTB), which emerged from a large, high-quality randomised controlled trial; the BrAIST Trial (5). The BrAIST Trial involved children with curves of 20-40 degrees using a FTB Thoracolumbar Sacral Orthosis (TLSO), compared with observation alone. The primary outcome was progression to a curve of 50 degrees or more before skeletal maturity (treatment failure), considered a surrogate marker of surgical treatment. Skeletal maturity without this degree of Cobb angle progression is treatment success. The study found 72% of the braced patients had a successful outcome compared with only 48% of the observation group, and was stopped early due to overwhelming evidence to support the efficacy of bracing.

Whilst the efficacy of bracing is established, the acceptability of the treatment to adolescents remains unclear. Compliance is a major concern, along with the psychological effects and physical restrictions associated with FTB. Whilst the BrAIST study prescribed FTB for 18 hours a day, the mean compliance was only 12.1 hours per day.

Rahimi et al 2019 report a systematic review of brace compliance, noting poor compliance in FTB caused by appearance, comfort and psychological acceptance (6). FTB are worn for an average 46% of prescribed time (range 19-97%) (7).

AIS patients undergoing brace treatment face psychosocial challenges, and there is growing literature to support optimising this aspect of patient care (8,9). A significant proportion of adolescents report a negative psychological impact from the brace, particularly related to the school environment and performing recreational activities (10).

Young AIS patients have never been more exposed to body image influences as a result of social media, which has increased dramatically over the last decade and co tinues at an incline. 69% of 13- to 15-year-olds use Facebook, 66% use Instagram, and 68% use Snapchat in 2019 (11). Teenage girls are also using image-based social media platforms more frequently than their male counterparts. Usage of social media, especially Facebook and Instagram, is associated with body image concerns in young women and men with potential for exposure to bullying (12). Not all social media is negative; there are a number of social media influencers which provide information, support and encouragement for patients with AIS. Involvement of such influencers in this study would both elevate media exposure and even result in a cultural change to have a positive impact on the psychosocial aspect of living with brace for AIS treatment.

An alternative to the FTB, is a brace only worn at night time (a “night-time brace”, or NTB). Such a brace would be ‘hidden’ from daily life and could significantly improve quality of life and other psychological effects of bracing in this population whilst not increasing the need for surgery. This may therefore have better compliance, with a recent study prescribing a NTB for 8 hours per day and observing a mean wear time of 7.2 hours per day (13). Instead of ‘holding’ the spine to prevent deformity, these attempt to apply a force to the spine to ‘over correct’ the deformity. A NTB has several potential advantages over a FTB: (1) curves reduce in size as gravity is eliminated (curves are 10 degrees smaller lying down compared to standing (14)); (2) the brace comes down further over the pelvis than can be achieved for a FTB allowing a longer lever arm and more corrective force applied to the spine, which would make these braces difficult to stand and sit in; (3) the pressure applied to the spine is more constant whilst in bed but tends to reduce over time for braces worn during the day in the upright position (15); and (4) growth occurs mainly at night with higher levels of growth hormone (16).

The NTB was introduced with the Charleston brace in 1978 (17). This brace is made from a plaster cast model or measurements with the patient laterally flexed towards the side of the curve which produces correction in single curves. However, it is biomechanically less suitable for double curves which limits its use (18) and when double curves are treated in a Charleston brace, success is less than for single curves (19). Low quality comparative studies of Charleston NTB with rigid FTB suggest the Charleston brace may be less effective especially in larger curves (15,16). For these reasons, we will not be using the Charleston brace in this study.

Newer NTBs are designed using computer assisted design and/or manufacture, and include the Providence and Corrective Movement Principle (CMP) NTBs. The Providence brace is produced using a model from patient measurements, and measurements taken after correcting the spine using bolsters attached to a 'measurement board'. Multiple case series studies have demonstrated that this brace can slow scoliosis progression (10,22–24). Three case series studies comparing Providence brace with a rigid FTB have suggested that the NTB is as effective as the FTB, in terms of preventing progression of the curve by more than 5 degrees (average 33% patients progressed by more than 5 degrees in FTB arm, 37% in NTB arm) (10,22,25). There is also some evidence that the Providence brace may still be effective in curves up to 40 degrees (26) Other studies of NTB include a CAD/CAM designed brace (27,28) which work on a similar principle to Providence, though using 3D scans of the torso to plan the design.

There is an ongoing three-arm randomised control trial involving night-time bracing. All three arms have 60 minutes of self-directed physical activity daily, with one intervention arm having additional scoliosis specific exercises and the other a NTB (29). The primary outcome is curve progression more than 6 degrees, with 45 patients in each arm. A recent systematic review of NTB in AIS concludes: 'the low methodological quality of the studies examined does not permit us to draw conclusions about the efficacy of night-time braces with respect to their day-time counterparts' (30). This and a similar review call for a prospective randomised controlled trial (31).

2.2 Rationale for current study

Families tell us that they would prefer the NTB over the FTB, but NTB currently is not available on the NHS in the UK due to lack of evidence. The proposed study addresses

four of the top 12 priorities set in 2017 by the James Lind Alliance partnership for scoliosis (priority 1: strategies to avoid surgery, priority 2: how does scoliosis treatment affect quality of life?, priority 5: how likely is the scoliosis to get worse over time priority 7: what type of brace (e.g. rigid or dynamic) is most effective?) (32).

The US Preventive Services Task Force recommendation statement on screening for adolescent idiopathic scoliosis (33) concluded that bracing reduces curve progression but found inadequate evidence of how this improves long term health outcomes - therefore, a long-term high quality trial is required. There is now enough low quality evidence from the existing studies of NTB to suggest that it may be as good or almost as good as FTB - but this is to be confirmed within a high quality multi-centre randomised controlled trial (RCT).

In the UK, instrumented scoliosis corrections for AIS in England have increased over the past 3 years (unpublished HES data - 906 in 2016/17 to 954 in 2018/19), whilst in Scotland, the incidence of surgery for AIS has increased from 4.4 to 9.8 per 100,000 individuals between 2005 and 2018, $p<0.001$ (34). Given the complications of surgery in this population (35), it is imperative that acceptable and efficacious bracing techniques are identified in order to prevent the progression of scoliosis to levels that require surgical intervention.

The coronavirus pandemic has resulted in long waiting lists for elective surgery in the UK and it is more important than ever to prevent the need for scoliosis surgery wherever possible.

We hypothesise that a major benefit to using the NTB will be the considerable improvement in wellbeing and mental health of not having to wear the brace during the day. These include reduced anxiety, depression, pain and improved perception of physical appearance. Such effects are likely to lead to improved academic success at school and other longer-term benefits.

3. Aims and objectives

3.1 Hypothesis

The null hypothesis is that NTB is not non-inferior to FTB in preventing curve progression to 50 degrees or more in children with AIS, before skeletal maturity.

The binary primary outcome is curve progression to 50 degrees or more (treatment failure) before skeletal maturity and skeletal maturity without this degree of curve progression (treatment success).

3.2 Aims

The aim of the study is to find out whether NTB is non-inferior to FTB in preventing curve progression to 50 degrees or more in children with AIS before skeletal maturity, but superior in terms of patient quality of life and acceptability.

3.3 Objectives

Feasibility objectives

An internal pilot study to determine the feasibility of a full-scale trial, in terms of:

- Site set up
- Participant recruitment
- Retention and Cobb angle collection (primary outcome)
- Intervention delivery
- Minimum wear time in NTB arm
- Minimum wear time in FTB arm
- Compliance data

Study Objectives

- To determine if NTB is not inferior to FTB in reducing the risk of curve progression to 50 degrees before skeletal maturity;
- To determine if there is a difference in anxiety, depression and quality of life between NTB and FTB;
- To determine the patient's and parents' experience and satisfaction of the braces;
- To determine the longer-term effects of bracing on quality of life and curve progression up to two years after skeletal maturity.
- To evaluate the relative cost-effectiveness of NTB compared to FTB.

4. Trial Design

A multicentre, prospective, parallel group, pragmatic, non-blinded, randomised controlled non-inferiority trial.

The trial will be conducted in a minimum of 19 hospitals. Patients with AIS will be identified within the clinic setting - these will either be new patients or those already seeking treatment for AIS, but haven't yet met the threshold for bracing. Eligibility will be confirmed by the site researcher and information given. Participants will be given time to consider the interventions following receipt of information on both the FTB and NTB. Written consent will be taken online via a remote pathway, after all questions have been addressed. Randomisation will then ensue. Consenting participants will be randomised to receive either FTB or NTB. Follow up will be undertaken in three phases - phase 1 (pre-skeletal maturity), phase 2 (post skeletal maturity) and phase 3 (10 year long-term follow-up, to be covered under different project approvals).

An 18-month internal pilot, with clear progression criteria, will follow the recommendations of Avery et al (36) and assess feasibility of the RCT.

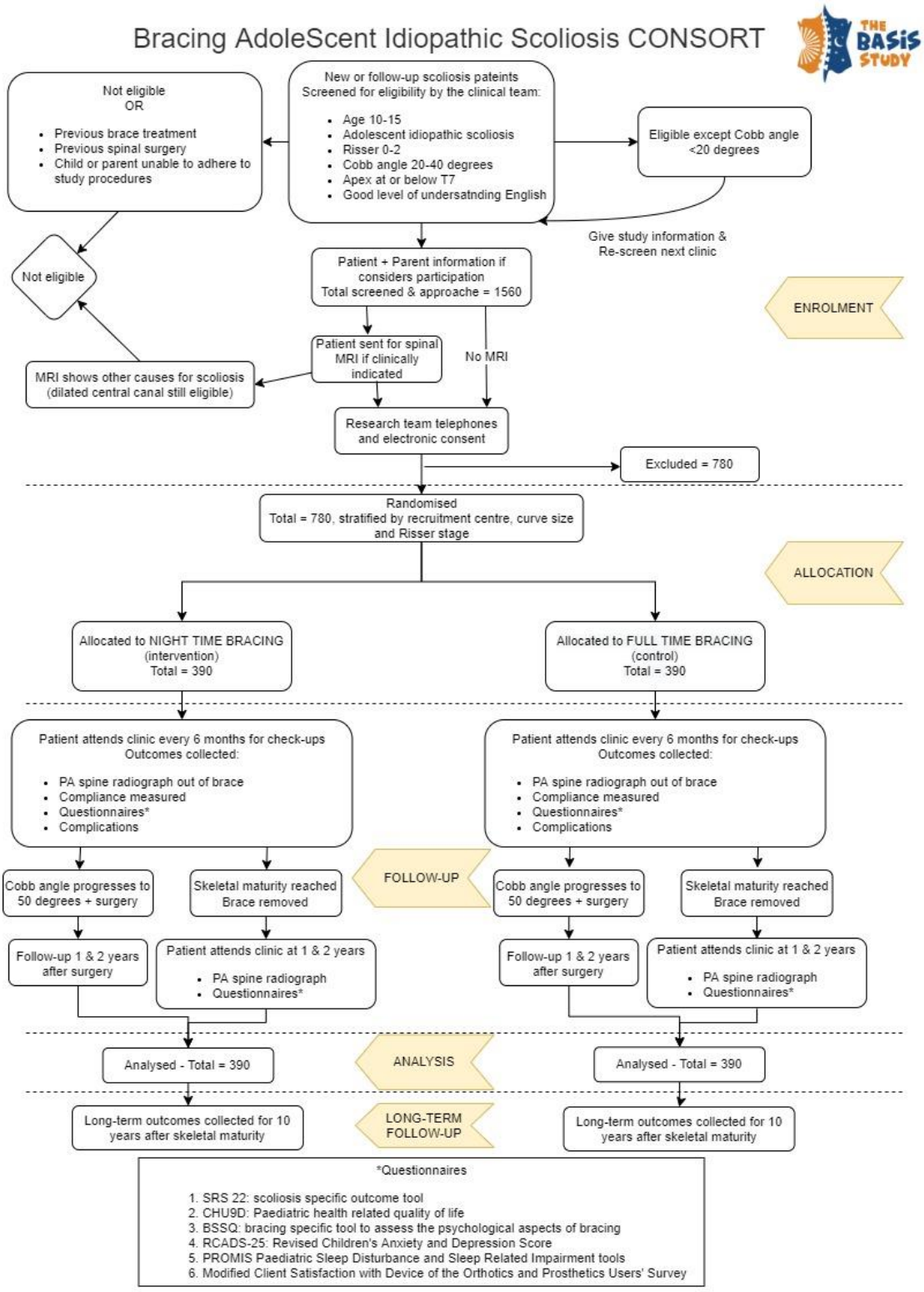
The internal pilot trial will run at all sites planned to participate in the main trial. The progression criteria will be applied to data collected 18 months after the first site is opened. To allow time for collation of recruitment, primary outcome and compliance data, the progression criteria will be assessed by the Trial Steering Committee at the end of the following month. Clinical and patient-reported outcome data from the internal pilot will be included in the final analysis.

4.1 Blinding

In view of the nature of the intervention, patients, their parents and their treating clinicians will not be blinded to the treatment allocation. The Radiographic Adjudication Committee (RAC) will assess the primary outcome: skeletal maturity (Risser stage) and Cobb angle. They will be blinded to treatment allocation.

The trial statistician(s) will remain blinded throughout the study, but will be unblinded at database freeze, for analysis.

5. Selection of participants



5.1 Inclusion criteria

In order to be eligible for the study, all the following criteria must be met at the point of randomisation:

1. Participants aged 10-15 years inclusive;
2. Diagnosis of adolescent idiopathic scoliosis (AIS) based on:
    a. No other cause of scoliosis from the patient history; and
    b. A normal neurological examination (no MRI scan required) or normal MRI scan (dilated central canal not considered to be a syringomyelia is acceptable);
3. Risser stage 0, 1 or 2;
4. Curve size (Cobb angle) between 20 and 40 degrees at baseline;
5. Curve apex at or below T7;
6. Have a good level of understanding of the English language, as trial materials are only provided in English.

Where radiological criteria are close to eligibility limits, confirmation from another consultant is advised.

5.2 Exclusion criteria

In order to be eligible for the study, none of the following criteria should be met:

1. Previous bracing or spinal surgery;
2. Child or parent is unable to adhere to trial procedures or complete follow-up

5.3 Participant identification

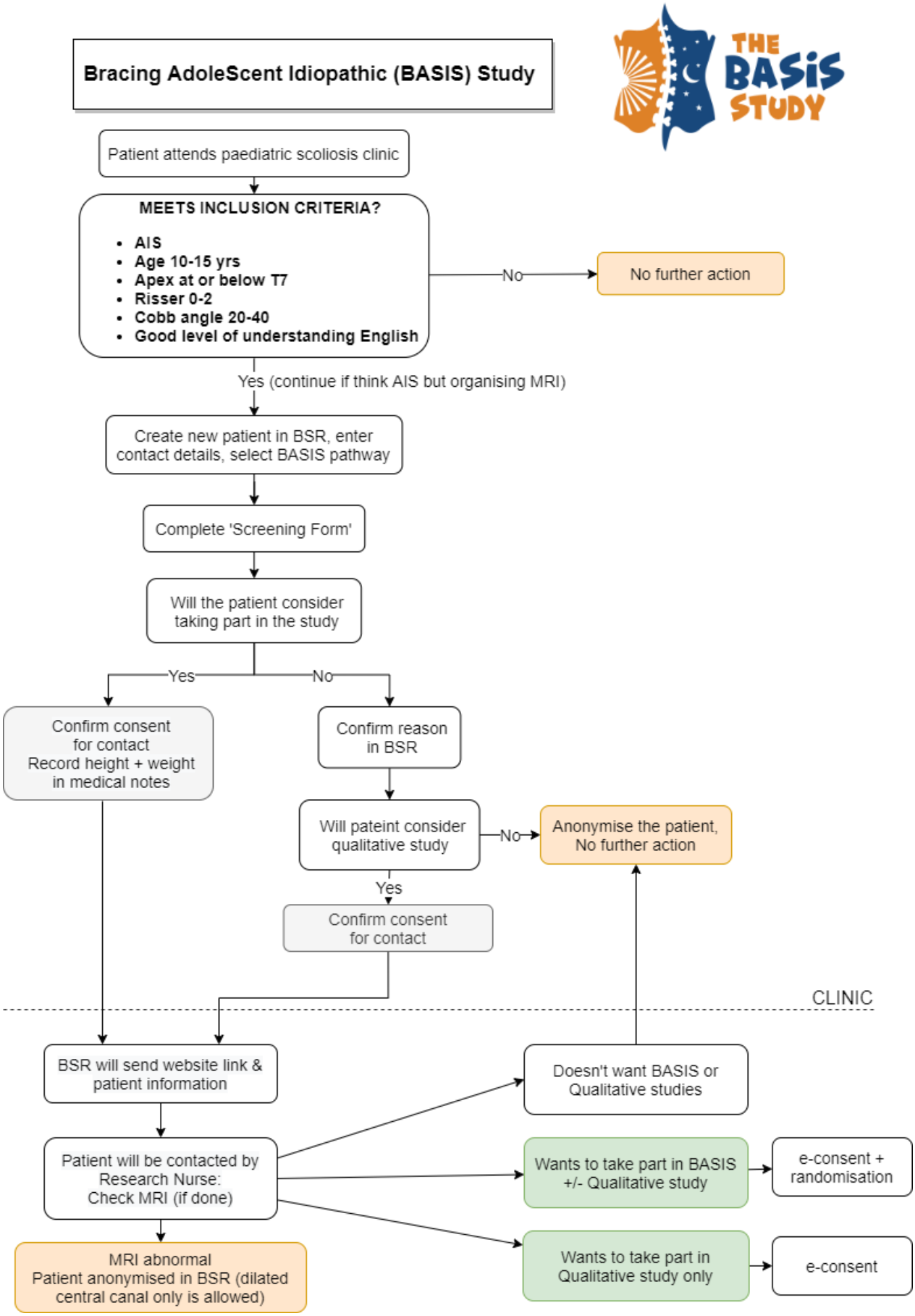
Patients will be recruited from paediatric spinal clinics.

Potential study participants will be either new patients attending the clinic after referral with suspected scoliosis or patients being followed up for potential curve progression who previously had a minor curve (less than 20 degrees). The clinician will screen the patient for eligibility by completing a form on the BASIS Pathway of the British Spine Registry (BSR). Once eligibility is confirmed and if the patient agrees to bracing, the parent/guardian will be asked for their verbal consent to retain screening information (including NHS/CHI number and date of birth) and contact details in the database. The BSR will then send the patient and parent information about the study and a link to the study website.

Patients who are not eligible only because their curve is less than 20 degrees will also be added to the BSR, but as an anonymised patient. They will be sent the study information and will be re-screened for eligibility at their next clinic appointment following a new spinal radiograph (this is usual follow-up). If the new radiograph shows progression of the curve meeting the inclusion criteria, agreement to participate in the study will be sought and consent obtained from the parent/guardian with assent from the patient, and the patient record in the BSR will be de-anonymised at that point.

Patients who do not wish to participate in the study, will be asked if they are prepared to indicate whether they: (1) Just don't want to participate/give a reason; (2) Don't want a brace; (3) Only want a full-time brace. They may also be asked if they would like to participate in the qualitative sub-study.

Clinicians will use their normal clinical practice to determine which patients will be sent for an MRI scan. This is usually boys or girls with an abnormal neurological examination. This is estimated at 10% in this group and an abnormal scan would be found in 10% of those scanned. Recruiting centres will try to get the MRI and report within 3 weeks. The MRI report must be checked by a spinal consultant to confirm that there is no significant MRI abnormality which would exclude them from the study before the patient is consented and randomised. If the MRI scan is not done before the brace is due to be measured, the Research Nurse will find out the approximate date for the MRI scan. The clinician will have already indicated on the screening form if they are prepared to accept delayed application of the brace. The Research Nurse will contact the patient and parents to see if they want to delay brace application for the MRI scan so they can be still considered for the study or proceed with bracing outside the study.


Bracing AdoleScent Idiopathic (BASIS) Study
THE BASIS STUDY
Patient attends paediatric scoliosis clinic
MEETS INCLUSION CRITERIA?
AIS
Age 10-15 yrs
Apex at or below T7
Risser 0-2
Cobb angle 20-40
Good level of understanding English
No
No further action
Yes (continue if think AIS but organising MRI)
Create new patient in BSR, enter contact details, select BASIS pathway
Complete 'Screening Form'
Will the patient consider taking part in the study
Yes
No
Confirm consent for contact Record height + weight in medical notes
Confirm reason in BSR
Will pateint consider qualitative study
No
Anonymise the patient, No further action
Yes
Confirm consent for contact
CLINIC
BSR will send website link & patient information
Patient will be contacted by Research Nurse: Check MRI (if done)
MRI abnormal Patient anonymised in BSR (dilated central canal only is allowed)
Doesn't want BASIS or Qualitative studies
Wants to take part in BASIS +/- Qualitative study
e-consent + randomisation
Wants to take part in Qualitative study only
e-consent

5.4 Informed consent/assent process

The patient's parents will be invited to consent remotely during a telephone call with the site research team. At the time of consent, the patient will also be invited to give assent. They will have already been provided with the patient information materials, and will have had time to consider their potential participation. They will have the opportunity to ask any questions, before providing consent/assent. If they are happy to proceed, consent will be recorded electronically. Parental consent and participant assent must be obtained for the patient to be able to take part in the trial. If the patient and parent are keen to provide consent at a clinic visit, and they have been provided with the study information, e-consent may be taken directly onto an iPad/computer in person at the hospital.

For the qualitative study consent will be sought from the parent, and assent from the child (see section 12). Consent for long-term patient reported follow-up will be sought to collect data at 10 years after skeletal maturity. Once a patient reaches age 16 years old, they will be re-consented at the next clinic appointment or remotely (as above).

6. Trial treatment

A FTB corrects the spinal curve(s) as much as possible within the limitations for prolonged wear during the day and at night. The force that these braces can apply to the spine is less than for a NTB as: (1) the lever arm is less as the brace cannot extend over the hips as this makes it difficult to stand and sit; and (2) the brace needs to be comfortable in a standing position where the curve is larger than when lying down due to the introduction of gravity; (3) Pressure applied by the brace to the trunk reduces over time in a standing position.

FTBs and NTBs are produced using the same 4 steps:

1. Measurement, where the patient has physical measurements and/or optical scanning measurements taken.
2. Design, where the measurements and the spinal radiograph are used to design the brace, often using computer aided design (CAD).
3. Manufacture, where the design is used to produce a plastic brace usually with a foam inner lining, often using computer aided manufacture (CAM).

4. Fitting, where the brace is fitted to the patient and additional padding inserted or alterations made to ensure comfort with optimal curve correction.

FTB s and NTBs are made of the same plastic material with a foam lining and are CE marked on manufacture.

Before randomisation, patients will be given standard care information about the braces including pictures, a description of the process of measurement and fitting, protocol for wearing the brace and details of the follow-up.

6.1 Patients randomised to receive NTB

All NTBs work on the same principles of action with no reason to suspect they differ in effectiveness. Individual centres will select which NTB they will use within the trial. The NTB must meet two key criteria: 1) CAD/CAM designed, as these braces are replacing older measurement and design techniques (37,38) and 2) logistically feasible to be used in the UK. Practically, orthotists will be given initial training in measurement, design, manufacture and fitting of the Providence brace, CMP brace (a CAD/CAM designed brace available in the UK) and training to help them produce their own CAD/CAM NTB if they have the equipment and skills locally to enable this. The Providence brace is the only brace manufactured outside the UK but does have a UK distributer.

The NTB will be prescribed for recumbent use at night-time only (8-12hrs each day) as recommended by the International Society on Scoliosis Orthopedic and Rehabilitation Treatment (SOSORT) Guidelines (39). A supine in-brace radiograph will be obtained to allow comparison with the standing radiograph. The correction of the curve supine, in brace measured as a percentage of the standing curve size is an important measure of brace quality and curve flexibility.

The Orthotist will be trained in the provision of their preferred NTB. There will be a training session or online training for NTBs with certification.

6.2 Patients randomised to FTB

There are many different FTB designs being used in the UK. There is no evidence to show that one brace is better than another. There are 2 basic types of FTB: (1) Sym-

metrical thoracolumbosacral orthosis (TLSO) as used in the BrAIST study; (2) Asymmetrical braces which are designed using digital scanning and CAD/CAM +/- finite element modelling. Although asymmetrical braces compared with symmetrical FTBs produce better in-brace correction and are lighter but more expensive, there is no high-quality evidence that they reduce the risk of curve progression to a surrogate marker of surgical treatment. The measurement and design of the FTB will be chosen by the Orthotist and spinal surgeon based on current practice, recording the method for measurement, the design process, and the brace type.

The FTB will be prescribed for 20-24 hours each day as recommended by the SOSORT Guidelines (39). A standing in-brace radiograph will be obtained to allow comparison with the standing out-of-brace radiograph. The correction of the curve in brace measured as a percentage of the standing curve size is an important measure of brace quality and curve flexibility.

6.3 Both braces

Sites should aim to have patients in brace within 8 weeks of consultant referral to reduce the risk of curve progression before bracing.

Following randomisation, the patient will attend a first clinic appointment with the Orthotist where they will be measured for their allocated brace. From these measurements, the brace will be designed and manufactured. The patient will return for a brace fitting appointment where the brace will be 'fine-tuned' (with pads if required). Once the brace is fitted, an in brace spinal radiograph either at the initial fitting or within the first 6 weeks in brace is obtained to ensure good curve correction. This will be done standing for the FTB and supine for the NTB. Further adjustments are permissible as required. The patient will be followed up as per local protocol, including regular brace check, adjustment, download of compliance data as required, and complications noted. A standing spine x-ray out of brace will be performed with an in-brace x-ray if required to guide brace adjustment. The patient will be reviewed by the spinal team to evaluate Cobb angle and skeletal maturity (Risser sign). All patients will have contact details for the spinal team, research team and orthotist for advice or concerns.

Braces will be renewed when required due to growth of the child. When a brace is renewed, the same protocol described above will be followed. Bracing will continue

until the patient reaches skeletal maturity (Risser 4 (girls) or Risser 5 (boys)), or until surgery is required. At this point, the brace can be discontinued.

6.3 Compliance monitoring

Adherence will be measured using a heat sensor inserted into each brace. Data will be downloaded and will allow monitoring of adherence for the whole duration of bracing. The monitor will be fitted to the FTB or NTB. Participants and their parents will be aware the monitor is there, but will not be given the adherence data.

6.4 Cross-over

Some scoliosis curves will progress despite brace treatment. The spinal team and orthotist in each centre will be aware that this is monitored by the DMEC for each brace type. Cross-over from NTB to FTB will be discouraged and monitored.

The risk of curve progression reduces after peak height velocity (40) and most patients will be beyond this before progression is noted. Instead, high compliance with the NTB will be encouraged.

Switching will not be permitted from FTB to NTB as this treatment is not currently available on the NHS. If patients wish to switch from NTB to FTB, they will be asked for their reasons why.

6.5 Other Treatments

Patients will we allowed to have other care such as physiotherapy but this will be recorded. Surgical treatment will not be offered unless the curve gets to 50 degrees as determined by the Radiographic Adjudication Committee (RAC).

7. Randomisation and enrolment

Once eligibility has been confirmed, consent acquired and baseline data taken the participant will be randomly allocated to either the treatment arm (NTB) or the control arm (FTB) on a 1:1 basis, using a web-based system provided by the Sheffield Clinical

Trials Research Unit (CTRU). Patient details (ID, date of birth and stratification information) will be entered into the randomisation system and the treatment allocation will be returned. Randomisation will be completed using minimisation based on site, skeletal maturity (Risser score 0, 1 or 2, and curve size (20-30, 31-40 degrees). Randomisation will be done by site staff. Patients and their parents will be informed of their trial allocation, confirmed by SMS or email, followed by a letter. Their GP will also be informed of their participation in the trial, and their treatment allocation.

8. Outcomes

8.1 Primary outcome/endpoint

The binary primary outcome is curve progression to 50 degrees or more (treatment failure) before skeletal maturity (Risser stage 4 in girls and Risser stage 5 in boys and skeletal maturity without this degree of curve progression (treatment success).

A Radiographic Adjudication Committee (RAC) will review patients considered to have reached or come close to reaching the primary outcome:

1. If the Spinal Team measures the Cobb angle over 45 degrees:
    a. The patient is informed that the curve has reached a point where RAC assessment is needed. The patient is advised to continue wearing the brace and a provisional plan is made if the RAC reports an angle of 50 degrees or more.
    b. The image is sent by Image Exchange Portal (IEP) and measured by the RAC and the angle is reported back to the clinical team who will inform the patient. The RAC will be blinded to treatment allocation
2. If the Spinal Team suspects the patient may have reached Risser stage 4 in girls and Risser stage 5 in boys:
    a. The patient is informed that they may have reached skeletal maturity and RAC assessment is needed. The patient is advised to continue wearing the brace and a provisional plan is made if the RAC reports skeletal maturity.
    b. The image is sent by IEP and assessed by the RAC and the Risser stage is reported back to the clinical team who will inform the patient. If in doubt, it will be concluded that the primary outcome has not been reached and the patient remains in brace for a further 6 months. The RAC will be blinded to treatment allocation.

If a curve measures 50 degrees or more at the same visit that skeletal maturity is reached, the patient will be recorded as having progressed to 50 degrees or more before skeletal maturity.

In order to coordinate RAC review and centralized measurement of spinal x-rays, images will be transferred from each site to the lead site (Sheffield Children's Hospital) via IEP transfer. Trial participants will be added to the Sheffield Children's Hospital patient records system, with the minimum information required (name, NHS number and date of birth), so that once the images arrive, they can be assigned to the patient's record. No other medical information will be added to their patient record. A member of the research team at Sheffield Children's Hospital will then download images for RAC review, and anonymise these, so that they are only identifiable by the study ID number.

8.2 Secondary outcomes/endpoints

Patient-reported outcomes (collected throughout the study unless stated otherwise):

1. Scoliosis Research Society 22 questionnaire (41);
2. Paediatric health related quality of life, measured using the CHU9D (42);
3. Bad Sobernheim Stress Questionnaire (BSSQ) (43), a brace specific questionnaire assessing the psychological effects of bracing;
4. Revised Children's Anxiety and Depression Scale (RCADS 25) (44);
5. PROMIS Paediatric Sleep Disturbance Short Form 4a (45);
6. PROMIS Paediatric Sleep Related Impairment Short Form 4a
7. Modified Client Satisfaction with Device module of the Orthotics and Prosthetics Users' Survey (CSD-OPUS) (46)
8. Educational information assessed using a bespoke questionnaire after GCSE results;

Parent Questionnaires (collected throughout the study unless stated otherwise):

9. Patient Cost Questionnaire, using a bespoke questionnaire
10. Resource Use Questionnaire, using a bespoke questionnaire;
11. School attendance (only during bracing).

Clinical (collected throughout the study unless stated otherwise):

12. Radiological measures from out-of-brace spinal radiographs (with correction of any leg length inequality): Cobb angle, curve type, curve apex, Risser sign, in-brace

Cobb angle, frontal plane balance, apical vertebral rotation, apical vertebral translation;

13. In-brace correction, measured for all new braces as the percentage Cobb angle correction in-brace compared with out-of-brace. The in-brace x-ray will be performed standing for FTB and supine for NTB. This reflects brace quality and curve flexibility. Bracing is more likely to fail when there is a lower initial in-brace correction of the curve (47,48). In-brace correction will be monitored during the trial by the DMEC for the new intervention of the NTB and will feedback any training suggestions to the Trial Management Group (TMG);
14. Menarchial age;
15. Details of any surgery for scoliosis correction;
16. Other treatments prescribed to treat scoliosis, e.g. scoliosis specific exercises;
17. Complications (e.g. skin irritation) and Serious Adverse Events;
18. Brace compliance, assessed using the implantation of a temperature sensor in the FTB or NTB (collected only during bracing);
19. Treatment switching, including reason for doing so (bespoke questionnaire).

Before randomisation, patients will be asked if they have a preference for which brace they would want. This question will be asked by the site research team and documented on the study database, rather than a specific questionnaire.

All SAEs occurring up to 2 years post skeletal maturity (end of involvement in the trial) will be reported to the CTRU/Sponsor on learning of their occurrence. Delegated site trial staff will be responsible for recording all adverse events and making them known to the Principal Investigator (see Section 10).

8.3 Internal pilot outcomes

Criteria are provided below to ensure feasibility of the RCT. Sheffield CTRU will aggregate study data to assess the feasibility of the research and intervention protocols based on the following feasibility outcomes:

#At least one NTB/FTB designed, manufactured, fitted and provided to patient

Cross-over will not be assessed within the success criteria as too few patients will have reached the point at which cross-over would be considered (i.e. progression of their condition). Crossover will be monitored by the DMEC.

Domain	**Target at end of internal pilot**	**Green**	**Amber**	**Red**
Site set-up	19 centres set-up and recruited first participant	15 centres recruited first participant	12-14 centres recruited first participant	Fewer than 12 centres recruited first participant
Participant recruitment	Average of 1.1 participants recruited per centre, per month	Minimum 80% of target (per centre per month)	70-79% of target (per centre, per month)	Below 70% of target (per centre, per month)
Retention & cobb angle collection (primary outcome)	100% of expected data points those randomised collected on database	Minimum 90% of target	70-89% of target	Below 70% of target
Intervention delivery	100% of participants receive the treatment they are randomised to #	100% of target	85-99% of target	Below 85% of target
Minimum wear time in NTB arm	Participants randomised to do so wear the NTB brace for the prescribed wear time (8-10 hours/day)	Median wear time of at least 7 hours/day	Median wear time of 5-7 hours/day	Median wear time of less than 5 hours/day
Minimum wear time in FTB arm	Participants randomised to do so wear the FTB brace for the prescribed wear time (20-23 hours/day)	Median wear time of at least 12 hours/day	Median wear time of 10-12 hours/day	Median wear time of less than 10 hours/day
Compliance data	Compliance data available for 100% of participants who have received a brace and have attended at least one follow-up appointment	Minimum 80% of target	70-79% of target	Below 70% of target

9. Assessments and procedures

All clinical data will be entered by the research site staff onto the British Spine Registry (BSR); PROMs data will also be entered directly onto this system by the patient, with paper copies available if this is not possible. The BSR is an existing national register

of spinal patients currently used to evaluate surgical patients and is familiar to the clinical staff in each centre, and an efficient means of follow-up in routine use. The central team will ensure data quality and data completeness is optimised.

Data Management (CRF design, data cleaning and validation) will be provided by the CTRU. Project-specific procedures for data management will be detailed in a data management plan.

Data will be collected in three phases:

Phase 1: Pre-skeletal maturity

Whilst in brace, patients will be seen routinely every 6-months for clinical monitoring, anchored from the date of randomisation. Routinely collected out-of-brace spinal radiographs will be taken at each visit in order to measure the Cobb angle (primary outcome). This is accepted as best practice guidelines for bracing in AIS (49). Such radiographs will be sent through the Image Exchange Portal and clinical data entered onto the BSR by research staff. Before the 6 month visit, parents and/or patients will be emailed a link to the questionnaires in the BSR which would be labelled for either 'patient' or 'parent' completion. If not completed, they will use a computer or tablet in the clinic to complete the questionnaires, with paper forms available as a back-up. Questionnaire completion will be checked and chased by mail or telephone as required.

There are a few scenarios:

- If the primary outcome is reached (progression to 50 degrees) before skeletal maturity, follow up will continue via email link to the BSR which will collect PROMs every 6 months
- If the patient has surgery, radiographs and questionnaires will be collected at routine post-operative clinic follow-up at 6-8 weeks, 1 year and 2 years after surgery.
- If the patient changes from NTB to FTB (cross-over), the reason will be recorded. Cross-over in the other direction is not allowed. Follow-up will continue unchanged.
- If the patient stops bracing altogether, follow-up will be continued.
- Rarely, during follow-up, patients will develop symptoms that prompt a spinal MRI scan. If this shows spinal dysraphism (dilated central canal is not defined as spinal dysraphism) as the cause for their scoliosis, the patient will continue in the trial for analysis on 'intention to treat' (ITT) but will be excluded from the per protocol (PP) analysis.

Phase 2: Post-skeletal maturity

Phase 2 follow-up will commence, in all patients who have not had surgery, once skeletal maturity is reached (Risser 4 in girls, Risser 5 in boys). It is important to follow-up patients with AIS after skeletal maturity as some curves will continue to progress (50,51).

If the patient reaches skeletal maturity with a curve below 50 degrees, follow-up will involve a spinal radiograph at 12 and 24 months to assess any curve progression. This is part of routine follow-up as recommended by the Scoliosis Research Society (52). Questionnaires will be administered by the BSR at 12 and 24 months after skeletal maturity collected by the email link or in the clinic. Again, data will be checked and chased by email or telephone as required.

If the curve progresses to 50 degrees or more, the patient may or may not have surgical treatment. If they don't have surgical treatment, follow-up with spinal radiographs and questionnaires will be done at 12 and 24 months as above. If the patient has surgery, radiographs and questionnaires will be completed at routine post-operative clinic follow-up at 6-8 weeks and 1 year after surgery.

Phase 3: Long-term follow up

If consent is obtained from the patient, follow-up will continue for 10 years after skeletal maturity (i.e. up to 8 years after the end of the trial).

The timing of data collection will be anchored to randomisation as "time zero", until the participant reaches skeletal maturity or the curve progresses beyond 50 degrees; after which the follow-up outcome data will be collected according to routine clinical practice. Access to the data will be given to CTRU staff in order to undertake data monitoring and validation.

A window of +/- 2 months will be permitted for the collection of follow-up data.

9.1 Study assessments schedule

Data collection will follow the following schedule to the point of surgery (for those patients who have surgery):

	Phase 1 (pre-skeletal maturity)			**Phase 2 (2 years post skeletal maturity)**		**Phase 3 (long term)**
	Screening	**Baseline/ randomisation**	**Every 6 months, until skeletal maturity**	**12 months post skeletal maturity**	**24 monthly post skeletal maturity**	**10 years post skeletal maturity**
Clinical						
Screening form/log (baseline visit)	MN/IP	-	-	-	-	-
Eligibility form	MN	-	-	-	-	-
Informed consent form	E	-	-	-	-	-
Demographics (age, sex, diagnosis, medical history, medication)	MN	-	-	-	-	-
Height, weight	IP	-	IP	IP	IP	-
Cobb angle, Risser stage	MN (pre randomisation)		CT/RAC	CT/RAC	CT/RAC	-
Additional radiological measures (curve type, curve apex etc)	CT	-	CT	CT	CT	-
Need for surgery	-	-	MN	MN	MN	E
In-brace correction	-	CT (0-6 weeks after each brace fitting)		-	-	-
Compliance	-	-	SEN	-	-	-
Treatment switching	-	-	MN	-	-	-
Patient reported measures						
SRS-22, CHU9D, RCADS 25, PROMIS sleep x2	-	IP/E	IP/E	IP/E	IP/E	E
BSSQ, OPUS CSD (whilst in brace only)	-	IP/E	IP/E	-	-	-
Educational information (summer of year 11)	-	-	E~	E~	E~	E~
Other treatments prescribed to treat scoliosis	-	IP/E	IP/E	IP/E	IP/E	-
Parent questionnaires						
Ethnicity	-	E	-	-	-	-
Resource Use Questionnaire	-	E	E	E	E	E#
Patient Cost Questionnaire	-	E	-	-	-	-

School attendance	-	E	E	-	-	-
Harms						
Complications and SAEs	-	-	IP/E	E	E	E

MN = medical notes or BSR form, IP = in-person, RAC = radiographic adjudication committee, E = Electronic, online via an email link sent to the patient (may be chased by mail or telephone), CT = central team, SEN = sensor, implanted into brace.
~ collected summer of year 11, age 16, independent of where the patient is in the study
 # completed by the patient at 10 years

NB. The screening log will capture the details of any patient who has had the trial discussed with them. This allows capture of information relating to reasons for non-participation, and also dates of contact for reporting in line with CONSORT.

X-rays are intended to be in line with the frequency in standard care, however, it may be that at some centres, a maximum of 4 additional x-rays are undertaken in some patients if their usual care differs.

Before randomisation, patients will be asked if they have a preference for which brace they would want. This question will be asked by the site research team and documented on the study database, rather than a specific questionnaire.

If patients choose to switch from NTB to FTB, or to stop bracing altogether, a questionnaire will be sent to them to ask for their reasons why. Patients who have surgery will be managed as above whilst on the waiting list but will be followed up with radiographs and questionnaires (SRS-22, CHU9D, RCADS 25, PROMIS sleep x2, resource use questionnaire and school attendance) at 6-8 weeks, 1 year and 2 years after surgery, with a plan for 10 year follow-up. Educational information, other treatments, complications and SAEs will be recorded. Patients having surgery after skeletal maturity will only have follow-up to 1 year.

9.2 Patient Timeline from Eligibility to first 6 month appointment

- Day 0: Screening visit: Seen in clinic and X-rayed to determine eligibility and given information

- Week 0-7: Telephone call from Research Team+ e-consent + randomisation (may be in person if patient prefers at clinic visit). This may be delayed if the patient is sent for a spinal MRI
- Week 2-6: Brace measurement (after randomisation)
- Week 4-8: Brace fitting
- In brace XR within 6 weeks of brace fitting
- Week 26: First follow-up 6 months after randomisation.

9.3 Unscheduled visits

Participants may be seen at additional visits outside those scheduled for the study, but these visits would be part of usual care. Any complication identified at additional usual care visits, will be documented in the CRF. Patients will be asked at each follow up visit if they have experienced any AEs since their previous study visit.

9.4 Procedures for assessing efficacy

Efficacy is assessed by measuring the percentage correction of Cobb angle in brace compared with the most recent standing radiograph taken at the appointment before randomisation. This is determined by curve flexibility and the type of brace used (NTB will have a higher correction in brace as the radiograph is taken supine). The DMEC will review this efficacy data at each meeting for the new intervention of the NTB and will feedback any training suggestions to the Trial Management Group (TMG).

9.5 Procedure for assessing safety

Adverse events and serious adverse events are discussed in Section 10. If the site research team have any concerns about a participant's wellbeing or safety during the course of the trial, this will be flagged to the patient's usual clinical team.

9.6 Participant withdrawals

Excessive participant withdrawal from follow-up is likely to have a negative impact on the study. Centres will explain the importance of remaining on study follow-up to participants, and that changes to planned treatment need not imply withdrawal from the study. Nevertheless, if participants do not wish to remain in the study their decision must be respected and usual clinical care will continue.

Efforts will be made to keep participants engaged in study follow-up. Regular updates will be provided through newsletters, and prize draws will take place to include participants who complete follow up questionnaires. The follow-up visits have been aligned to the timescales of usual clinical follow-up to minimize the additional burden on participants. Most follow ups involve routine measures, with the addition of some patient completed questionnaires.

Participants may wish to withdraw from study treatment, or there may be a clinical need to withdraw the participant, such as development of a medical comorbidity which prevents further brace treatment.
Participants may withdraw their consent for the study at any time, without providing a reason for this. If this occurs, this will be documented on a study completion/discontinuation form and the patient notes, and no further data will be collected for this participant for the study. Although the participant is not required to give a reason for discontinuing their study treatment, a reasonable effort will be made to establish this reason while fully respecting the participants' rights. Any data collected up to the point of the participant's withdrawal will be retained, and used in the final analysis, and this is made clear to the patient at the time of consent. If a patient chooses to withdraw from the study, they will be asked if they are happy for the study team to use their routinely collected data in order to inform the primary outcome. This will be optional, but if the patient agrees, it will help to maintain the statistical power when assessing trial outcomes.

Guidance on cross-over can be found in section 6.4.

9.7 Loss to follow-up

Participants may be considered lost to follow up if they fail both to attend for a study visit and complete the corresponding visit questionnaires, and all reasonable efforts to contact the participant by different methods, including contact on different days/at different times, have been unsuccessful. If this occurs, the study team may liaise with the participant's clinical team to see whether they have also stopped attending clinical appointments. If a patient is still attending clinical appointments, this study visit will be marked as missing, and attempts will be made to contact the participant for the next study visit. If a participant fails to attend 2 study visits in a row, including non-completion of the corresponding questionnaires, they will be considered lost to follow up and this will be recorded on the study discontinuation form.

10. Safety Reporting

ICH-GCP requires that both investigators and sponsors follow specific procedures when reporting adverse events in clinical studies. These procedures are described in this section.

10.1 Definitions

Term	Definition
Adverse Event (AE)	Any untoward medical occurrence in a study participant which is considered to be possibly related to brace treatment, or complications arising from spinal surgery.
Unexpected AE/SAE	An adverse event or serious adverse event which has not been pre-specified as expected.
Serious Adverse Event (SAE)	An AE which is serious, defined as any untoward medical occurrence or effect that: • Results in death • Is life-threatening* • Requires hospitalisation or prolongation of existing inpatients' hospitalisation** • Results in persistent or significant disability or incapacity • Is a congenital anomaly/birth defect • Is otherwise considered medically significant by the investigator***
Related AE/SAE	An AE or SAE which is related to a research procedure
Notable Event	An event of particular interest that does not necessarily meet the criteria for seriousness but requires expedited reporting as per the protocol.

*The term life-threatening in the definition of a serious event refers to an event in which the patient is at risk of death at the time of the event; it does not refer to an event that hypothetically might cause death if it were more severe, for example, a silent myocardial infarction.

**Hospitalisation is defined as an inpatient admission, regardless of length of stay, even if the hospitalisation is a precautionary measure for continued observation. Hospitalisations for a pre-existing condition, that has not worsened or for an elective procedure do not constitute an SAE.

***Other important medical events that may not result in death, be life-threatening, or require hospitalisation may be considered a serious adverse event/experience when, based upon appropriate medical judgement, they may jeopardise the patient and may require medical or surgical intervention to prevent one of the outcomes listed in this definition.

10.2 Recording and reporting

AEs and SAEs are defined as an event that occurs after the patient has provided written informed consent for trial entry and prior to their completion of the trial.

AEs will be recorded on the adverse event report form, where these are considered to be possibly related to brace treatment, or complications arising from spinal surgery, within the participant CRF, including those that fulfil the criteria for being serious (see

section 10.1). Sites are asked to enter all available information onto the study database as soon as possible after the site becomes aware of the event.

SAEs will require more detailed information to be recorded. In such cases, the event must also be reported to the Sheffield CTRU within 24 hours of the site becoming aware of the event. The CTRU will coordinate ongoing monthly reporting to the Sponsor, or as soon as possible if unexpected SAE. All SAEs will be reported, not just those related to brace treatment, or complications arising from spinal surgery.

10.3 Study specific exemptions

Scoliosis surgery is an expected outcome for this patient group. This will not be recorded as an SAE, and will be collected elsewhere on the CRF.

Adverse events which are expected with brace treatment, are listed below. If any of these occur during the trial, and also meet the criteria for being an SAE, they will be exempt from reporting within 24 hours. Such AEs and SAEs will still be reported, but removing this expedited timeframe will reduce the burden on sites.

- Severe pain from the brace requiring brace adjustment or re-design.
- Medical Device Related Pressure Ulcer (Injury)(53). We will follow the European Pressure Ulcer Advisory Panel definition but dividing Stage 2 into two commonly seen categories with spinal brace treatment. The following should be recorded as an AE but if it meets the criteria for an SAE, will not be reported within 24 hours:
    - Stage 1: Skin erythema which is non-blanching with pressure
    - Stage 2a: Superficial abrasions

  AEs/SAEs meeting the following definitions **will be reported** in line with requirements in section 10.4.
    - Stage 2b: Partial thickness skin loss
    - Stage 3: Full thickness skin loss (dermis and epidermis) (SAE)
    - Stage 4: Full thickness tissue loss (SAE)

10.4 SAE notification procedure

CTRU should be notified of all SAEs (unless exempt), within 24 hours of the investigator becoming aware of the event.

The SAE form must be completed by the investigator or delegated member of the research team. All SAE forms must be sent by email to ctru-saes-group@sheffield.ac.uk. Receipt of the initial report should be confirmed within one working day. The site research team should contact the study team at CTRU if confirmation of receipt is not received within one working day.

Initial SAE reports must be followed by detailed reports when further information becomes available. Participants must be followed up until clinical recovery is complete and laboratory results have returned to normal or baseline, or until the event has stabilized. Follow up information will be provided on an SAE report marked as such.

10.5 CTRU responsibilities

The Sponsor usually delegates CTRU responsibility for the reporting of SAEs to the regulatory authorities and the research ethics committee, as appropriate. CTRU will also keep all investigators informed of any safety issues that arise during the course of the study.

10.6 SAE additional reporting

The DMEC and TSC will also receive information on all AEs and SAEs, at a frequency agreed with each committee and documented in the appropriate charter/terms of reference. Should these committees require any further information on any AEs or SAEs, this will be communicated to the site by CTRU.

11. Statistics

11.1 Sample size

In the BrAIST trial 28% of braced patients progressed to 50 degrees or more before skeletal maturity, which was the primary endpoint (5), so assuming this for the FTB group, with a non-inferiority margin of 11%, 90% power, 2.5% one-sided significance level and 10% attrition, the study will require 780 participants (390 per group).

This margin was chosen based on participants and parents. They have stated there is considerable functional and psychological benefit from not wearing braces during the daytime. During both PPI focus groups patients have expressed mixed views about FTB, which some were being treated with, and the concept of NTB. Approximately 50% of the group expressed a preference for a NTB. In our SAUK survey, 60% said

they would prefer a NTB compared to 27% for a FTB (and 7% no brace, 6% no answer).

11.2 Statistical Analysis

The trial will be analysed and reported according to CONSORT guidelines for non-inferiority designs (54).

The ITT population (and safety) populations will consist of all participants who consent and are randomised to receive FTB or NTB.

The per protocol (PP) will be defined for participants in the FTB group, as
1) receiving the FTB treatment as documented in the study protocol (see Section 6)
2) Complying and adhering to the treatment they were assigned to. Compliance with FTB would mean wearing the brace for average of >12.9hrs/day (= >65% of the minimum prescribed time) over the post-randomisation follow-up period.

For the NTB group, the PP population will be defined as
1) receiving the NTB treatment as documented in the study protocol
2) Complying and adhering to the treatment they were assigned to. Compliance with NTB would mean wearing the brace for average of >5.2hrs/day (= >65% of the minimum prescribed time) over the post-randomisation follow-up period.

Patients who cross-over from NTB to FTB will be removed from the PP population for the analysis of the primary outcome.

The binary primary outcome is curve progression to 50 degrees or more (treatment failure) before skeletal maturity and skeletal maturity without this degree of curve progression (treatment success). Non-inferiority for the primary outcome will be declared if the two-sided 95% confidence interval (equivalent to a one-sided 97.5%) for the risk difference in the event rate of progression to 50 degrees between the NTB group and the FTB group does not exceed 11%. The analysis will be completed using a Generalized Linear Model (GLM) with binomially distributed response and identity link (55) adjusted for baseline covariates (site, skeletal maturity Risser score 0, 1 or 2, and Cobb angle). This will be conducted on both an intention-to-treat (ITT) population and per protocol (PP) basis. The adjusted differences in failure rates, along with 95% confidence intervals will be calculated and presented.

Missing data

For the primary outcome, curve progression to 50 degrees or more (treatment failure) and skeletal maturity without this degree of curve progression (treatment success) any missing outcome data will be imputed through a default “worst” case scenario (i.e. assume treatment failure) and “best” case scenario (i.e. assume treatment success) and the results compared with the available data analysis.

Time to event analysis will also be completed on the primary outcome data. This will also be considered on an ITT and PP basis. For the PP analysis non-adherers will be censored at the time at which they begin to non-adhere - what is defined as non-adherence will be pre-specified after discussion with clinical experts, including the DMEC and TSC. To account for potential time dependent confounding an inverse probability weighting (IPW) approach will be used to estimate the PP treatment effect (56). This is important because non-adherence might be related to prognosis, and therefore censoring non-adherers may represent informative censoring and induce selection bias. In addition, an analysis that adjusts specifically for any treatment crossover that occurs will be undertaken. The IPW approach will again be used for this analysis, as will a rank preserving structural failure time model (RPSFTM), in line with recommendations made by the National Institute for Health and Care Excellence (NICE) Decision Support Unit for adjusting (when relevant) for treatment switching in randomised controlled trials (57).

For the secondary outcome of Cobb angle, a longitudinal analysis of all time points will be used to assess the difference on a non-inferiority basis between the two groups. This analysis will use a linear mixed-model including the all available time points, other important potential baseline confounders (such as Risser score 0, 1 or 2, and baseline Cobb angle) and site as a random effect.

Patient reported repeated outcome measures will be assessed over time using summary measures such as Area Under the Curve on a superiority basis (58).

Data on adverse events and serious adverse events will be tabulated at the end of the trial and presented by treatment arm. This will include the number and percentage of participants reported as having any adverse event.

Detailed statistical methods for all outcomes and scenarios will be described in a related trial Statistical Analysis Plan written before the data is analysed according to the Sheffield CTRU standard operating procedures approved by the TSC and DMEC (both of which have independent statistical members).

Economic evaluation

Different bracing options are likely to result in different costs, whether due to intervention costs, other related healthcare costs, or subsequent surgery costs. Also, it is conceivable that different bracing options will result in different health-related quality of life; even if NTB results in poorer control of scoliosis, there could be offsetting improvements in quality of life due to not having to wear a FTB (conversely, there could be reductions in quality of life if control of scoliosis is poor). Therefore, it is highly relevant to conduct an economic evaluation alongside this trial. We will estimate the relative cost-effectiveness (CE) of NTB compared to FTB and will present results for two key outcome measures: cost-per quality adjusted life years (QALYs) gained, and cost-per surgery avoided. Usually only cost per QALY results are presented for economic evaluations, but in this case, where a critical outcome is the avoidance of surgery, we consider it relevant to also present cost per surgery avoided – particularly because the patient population is children and so cost per QALY results will require considerable extrapolation beyond the end of the trial. It will be assumed that scoliosis of 50 degrees or greater will result in surgery.

The primary CE analyses will take an NHS and personal social services perspective in accordance with NICE (59), and the primary cost per QALY analysis will take a lifetime perspective, with proportions of patients who do and do not progress to surgery estimated based upon scoliosis degrees. A secondary analysis will present cost per QALY results restricted to the trial follow-up period. Intervention costs will be based upon information collected using CRFs, to include the type of brace and the resource use associated with fitting it. Wider resource use will include any other health care costs incurred (such as primary care appointments, and hospital admissions or appointments) that are related to the brace or scoliosis. Information on these will be collected via a bespoke resource use questionnaire. Unit costs will be derived from national sources (60,61). Health related quality of life (HRQL) will be estimated using the CHU9D questionnaire (42), specifically developed for children aged between 7 and 17. Both measures can be used to estimate preference-based utility scores, allowing QALYs to be derived.

For the evaluation that takes a lifetime perspective we will extrapolate beyond adolescence using utility scores based on a search of the literature. A supplementary analysis from a broader perspective, incorporating societal costs associated with parents' time taken off work and travel costs associated with hospital visits related to the brace or scoliosis, will be included. Information on these costs including on private health care costs associated with the brace or scoliosis will be collected via a patient cost questionnaire.

The primary CE analyses will be based on ITT-based estimates of effectiveness. However, analyses that incorporate findings from the PP analysis and/or analyses that adjust for treatment crossover will be undertaken, if these are deemed relevant given the protocol violations and treatment switches that are observed in the trial, and given the decision problem defined for the economic evaluation; that is, whether initiating treatment with NTB represents a cost-effective use of NHS resources compared to initiating treatment with FTB. Results will allow for uncertainty using bootstrapping and probabilistic sensitivity analysis. Incremental CE ratios will be presented.

12. Ancillary sub-studies

12.1 BASIS Communication Study

During the internal pilot, a qualitative study will be undertaken to explore patients' and parents' views of the trial recruitment processes and perspectives on the two treatments. This will identify ways to enhance participant recruitment and experience of the remainder of the trial (e.g. via improvements to communication and information materials about the trial). The qualitative findings will also be important to inform ways to support patients in wearing the braces as advised, and assist interpretation of the quantitative findings at the end of the trial. Few previous studies have explored patients' experiences of bracing for AIS despite the challenges this treatment presents for patients, and no such research has been conducted with UK patients (62–65).

Recruiters at NHS sites will request consent from families who are approached about the main BASIS study to forward their contact details to the qualitative study researcher. The qualitative study researcher will contact the family to send participant information sheet(s), offer more information about doing an interview and provisionally arrange an interview. In-depth semi-structured interviews will be conducted with a purposive sample of 20-25 patient-parent dyads at 3-9 months into bracing treatment.

Purposive sampling will be operationalised via a matrix to encompass diversity in key characteristics including: treatment allocation (night-time versus full-time braces); high versus low bracing adherence; patient demographics and trial site. A small sub-set of patients and parents who decline the trial will also be interviewed in order to seek insights into reasons for non-recruitment. Sampling will aim for data saturation and be reviewed in the light of the developing analysis.

Interviewing will be topic-guided, yet conversational and exploratory. Topic guides will be developed collaboratively with our PPI group, the starting point will be other qualitative evaluations in this area (62,64–66), although we anticipate interviews will explore: perceptions of the trial, the recruitment processes/information materials and suggestions for improving these; views and experiences of deciding whether to participate in the trial, treatment preferences and influences on these; lived experience of the two treatments and influences on bracing adherence (including issues such as pain, sleep quality, psychological difficulties, concerns about appearance, engagement in physical/social activities and concerns about future treatment and well-being); suggestions for enhancing support for patients/parents with tolerating the two types of bracing and for facilitating continued participation in the trial. Topic guides will be adapted as appropriate to patients and parents and periodically revised in the light of the developing analysis to ensure exploration of important but unanticipated issues. Interviewing will be conducted by FS, an experienced qualitative researcher, under the supervision of BY.

Participatory techniques will be used to ensure interviews are engaging for participants. We anticipate that most interviews will be face-to-face in their homes or another suitable place, provided social distancing restrictions are lifted by the time interviews commence. If restrictions are still in place, or if participants prefer, they will be interviewed via video-conference/telephone. For all interviews, informed consent will be individually sought from the child and parent(s) by the qualitative researcher. If a parent consents to interview but the patient does not, the parent will be interviewed, and vice versa. For face-to-face interviews, written consent will be sought. For video-conference/telephone interviews, consent will be sought verbally – this will involve the researcher reading each aspect of the consent form to participants. The researcher will initial next to each box on the consent form when the participant provides verbal consent, will add the participant name, date and “telephone interview” where the signature is required and will post/email a copy of the form to the participant (based on participant

preference). Informed consent discussions will be audio recorded for auditing purposes and as with written consent, will be stored for up to 10 years at the University of Liverpool. All patients will also be offered the choice of being interviewed alone or with their parent/guardian present.

Interviews will be audio-recorded, transcribed, checked and pseudo-anonymised before being analysed. Data analysis will be interpretive and draw on reflexive thematic approaches (67,68), and be informed by writings on quality in qualitative research (69) and its use to inform trials (70). Coding of transcripts will be assisted by QSR NVivo software. FS will lead the analysis, meeting regularly with BY to review a proportion of transcripts and compare coding and interpretations. Discussions with the wider team members will help to ground the analysis and ensure that the findings are fed back to sites to enhance recruitment, retention and communication in the main trial.

12.2 BAPQ (Brace Adherence Prediction Questionnaire)

A de-novo questionnaire is to be developed, focusing on psychological factors that predict brace adherence – a key determinant of bracing success. This will be the first theory-based Brace Adherence Prediction Questionnaire (BAPQ) involving patients and parents in its development. This questionnaire will be similar to, but superior to the existing questionnaire created by Morton et al, the Brace Beliefs Questionnaire (BBQ), which was developed with consultation exclusively with health professionals (71).

Qualitative analysis of semi-structured interviews with patients and parents will be done, to explore beliefs and experiences of brace adherence. Interview questions will be developed around Rogers' (1983) Protection Motivation Theory (PMT) (72) to explore threat appraisals about the condition (perceptions of severity and vulnerability) and coping appraisals about brace treatment (response efficacy, self-efficacy, and response costs). Interviews will be recorded and transcribed for analysis.

This sub-study will aim to interview 20-30 patient-parent dyads using online interviews of AIS patients currently undergoing brace treatment (i.e. not BASIS study participants). The themes emerging from these interviews will be used to develop the BAPQ which will be given to patients recruited to BASIS, between randomization and starting bracing treatment, and at subsequent trial follow up appointments. This will validate the BAPQ and examine longitudinal change pre- and post-treatment exposure. Find-

ings will help guide patient communication to optimise adherence behaviour (e.g. patient materials, physician-patient interactions) and shared decision-making around brace treatment.

The BAPQ will be reviewed by a PPI group for acceptability. This will be submitted for NHS REC approval at a later date, prior to recruitment commencing for the BASIS study.

13. Trial supervision

The BASIS study will be led by the Chief Investigator working in coordination with the co-applicants and Sheffield CTRU. The Sponsor will be Sheffield Children's NHS Foundation Trust. Sheffield CTRU will take responsibility for project management and have set up a collaborator agreement for governance and safety reporting with the Sponsor. There is a dedicated study manager who is supervised by the CI and senior staff in the CTRU, meeting regularly, and will liaise with the whole study team. Robin Chatters and Dan Hind will provide oversight for the delivery of all CTRU support including trial management, data management, QA, randomization, statistics, health economics, analysis reporting and dissemination. Health Research Authority (HRA) approval will be sought prior to commencement of the trial at participating centres.

Three committees will govern study conduct, deliver the trial, monitor study performance and ensure its safety; TSC, DMEC and Trial Management Group (TMG). The committees will function in accordance with Sheffield CTRU standard operating procedures.

13.1 Trial Steering Committee

The TSC will consist of an independent chair, clinicians with relevant clinical expertise, statistician, health economist and a patient representative. The role of the TSC is to provide supervision of the protocol, and statistical analysis plan, to provide advice on and monitor the study, to review information from other sources and consider recommendations from the DMEC. The TSC will meet at regular intervals, as defined in the TSC terms of reference. The TSC can prematurely close the trial, should this be recommended by the DMEC.

13.2 Data Monitoring and Ethics Committee

The DMEC will consist of an independent statistician, clinician and trial methodologist.

The DMEC will review reports provided by the CTRU to assess the progress of the study, the safety data and the critical endpoint data as required. The DMEC will meet at regular intervals, as defined by the DMEC charter, and meetings will comprise an open session to which members of the study team may attend, followed by a closed session with independent members only and to which unblinded data will be available. The DMEC may recommend the trial is stopped or modified on the basis of the data, in writing, to the chair of the TSC.

13.3 Trial Management Group

The Trial Management Group (TMG) consists of the CI, co-applicants and staff from CTRU, with site PIs and other site staff attending depending on need at each stage of the study. The CI will chair meetings to discuss the day-to-day running of the trial, including any implementation issues. The TMG will receive reports from the TSC and DMEC to manage trial progress.

14. Data handling and record keeping

Participant confidentiality will be respected at all times and the principles of GDPR will be followed. The investigator will ensure that identifiable data is kept securely and protected from unauthorised parties. As with other clinical registries, non-BASIS users of the registry will be able to see BASIS patient names and dates of birth within a patient search, but will not have access to any other details if they are not involved in that patient's clinical care or research participation.

Data management will be provided by the University of Sheffield CTRU who adhere to their own Standard Operating Procedures (SOPs), relating to all aspects of data management, including data protection and archiving. As the study will use a database provided by Amplitude, which will be modified to support the study requirements by the addition of a new pathway, CTRU will assess whether compliance with the principles of the relevant SOPs can be met; any deviations required will be documented. A separate data management plan (DMP) will detail data management activities for the study in accordance with SOP (Shef/CTRU/DM009).

The investigator or delegate at each site will maintain comprehensive and accurate source documents to record all relevant study information regarding each participant, in all instances where the database does not form the source data.

The sites will use eCRFs with task reminders produced by the database.

As the Amplitude database, which is a clinical database, is being used to collect study data, patient identifiable information will be available. However, in all communication between sites and CTRU, participants will be referred to by their allocated study ID number, and identifiable information will only be accessed by those with the need and authority to do so. Research staff will only have access to the BASIS pathway of the database, and therefore only data collected for the study, with no access to any previous clinical data already stored within different pathways in the registry. The only exception is that BASIS patient names and dates of birth will appear in searches of the registry by non-BASIS users. These users will not be able to see any further details about BASIS patients if they are not involved in their clinical care or research participation.

In order to comply with CE (and UKCA) marking regulations, participant names and other identifiable information will need to be passed onto the brace manufacturer, as is the case in standard clinical care. This is made clear in the parent information sheet.

14.1 Archiving

At the initial consent parents will be asked to consent to their child being contacted when they are aged 16 to give consent to the study and to retain their data in the BSR. The patient will be contacted when they are aged 16 to consent to long-term data storage in the BSR. As a Registry, the BSR usually stores patient data long-term.

In addition, external study records, including source data, will be stored for 15 years after the completion of the study by participating sites, before being destroyed. Data in the BSR will be extracted and archived at the end of the study. Each investigator is responsible for ensuring records are retained and securely archived during the retention period and information supplied to the Chief Investigator and Sponsor. Where trial related information is documented in the medical records, those records will be retained for at least 15 years after the last patient last visit. Access will be restricted to authorised individuals.

Data held by the CTRU will be stored in accordance with the archiving Standard Operating Procedure (CTRU SOP PM012) for 15 years following completion. Archived

documents will be logged on a register which will also record items retrieved, by named individuals, from the archive. Electronic data will be stored in an 'archive' area of the secure CTRU server for a minimum of 15 years to ensure that access is future-proofed against changes in technology.

15. Data access and quality assurance

BASIS will use a study specific pathway within the BSR, provided by Amplitude for the capture and storage of study-specific participant data. Access to Amplitude, and the study specific pathway is controlled by usernames and salted hashed passwords, and a comprehensive access management feature will be used to ensure that users have access to only the minimum amount of data required to complete tasks relevant to their study role. This feature can also be used to restrict access to personal identifiable data.

Study staff at each site will enter data from clinical assessments into the database when available. Participants will complete questionnaire data directly into the database via the BSR patient portal, using the link provided. Consent will also be captured in the same way both by the participant/their parent, and the staff member taking consent.

After data is entered, validation rules will be applied to the study data on a regular basis to query missing follow ups, and potentially erroneous data, so that this can be checked with the site staff.

Participant confidentiality will be respected at all times. Research data will be identified using the participant's study ID number, with access to personal data only by those who need it. Directly identifiable data will not be transferred to the statisticians.

Participating investigators shall agree to allow study-related monitoring, including audits, ethics committee review and regulatory inspections, by providing direct access to source data, and documents, as required. Participants' consent for this will be obtained as part of the consent process.

15.1 Site assessment

Throughout this protocol, the trial 'site' refers to the hospital at which trial-related activities are conducted. Participating sites must be able to comply with:

- Trial treatments, imaging, clinical care, follow up schedules and all requirements of the trial protocol;
- Requirements of the UK Policy Framework for Health and Social Care Research;
- Data collection requirements.

All site staff, including research staff, must be appropriately qualified by education, training and experience to perform the trial related duties allocated to them, which must be recorded on the site delegation log. CVs for all staff must be kept up to date, and copies held in the Investigator Site File (ISF), and the Trial Master File (TMF).

Before each site is activated, capability to conduct the trial will be assessed and documented. The CTRU will arrange a remote site initiation “visit” with each site. Site staff will be trained in the day-to-day management of the trial and essential documentation required for the trial will be checked. Once all the required documentation is in order and site staff have been trained, CTRU will formally activate the site to start recruitment. Sites should not open to recruitment until CTRU have provided this confirmation of activation.

15.2 Risk assessment

A risk assessment has been performed by the CTRU, in accordance with Sheffield CTRU Standard Operating Procedures.

Central and/or on-site monitoring will be undertaken at a level appropriate to the detailed risk assessment, and will be documented in the Trial Monitoring Plan.

15.3 Reporting serious breaches and non-compliances

A “serious breach” is a breach of the conditions and principles of GCP in connection with the trial, or of the protocol relating to the trial, which is likely to affect to a significant degree –

- the safety or physical or mental integrity of the participants of the trial; or
- the scientific value of the trial

The sponsor will be notified immediately of any case where the above definition may apply during the trial conduct phase. The sponsor of a clinical trial will notify the REC within 7 days of becoming aware of a serious breach.

All serious breaches and protocol non-compliances should be reported to CTRU within 24 hours of site staff becoming aware.

15.4 On-site monitoring

On-site or remote monitoring will be performed according to the monitoring plan and in line with the Sheffield CTRU Site Monitoring SOP.

A site initiation visit will be carried out remotely for each participating site before each site recruits their first participant. During this remote contact, the Monitor will review with site staff the protocol, study requirements and their responsibilities to satisfy regulatory, ethical and Sponsor requirements.

Regular site monitoring will occur throughout the study (likely remotely) as specified in the Site Monitoring Plan and additional visits will be undertaken where required. At these visits, the Monitor will review activity to verify that the:

1. Data are authentic, accurate and complete.
2. Safety and rights of the patient are being protected and
3. Study is conducted in accordance with the approved protocol and study agreements, GCP and all applicable regulatory requirements.

Accurate and reliable data collection will be assured by verification and cross-check of the eCRF against Investigator's records by the Study Monitor, for data points where the source data is not the database (source document verification) (see section 13 for further details on data collection). Study Monitor will contact sites regularly to inspect CRFs throughout the study, to verify adherence to the protocol and completeness, consistency and accuracy of the data being entered on the CRFs.

Site close-out will be performed after the last patient last visit at each site. Further close-out activities may be carried out remotely after this time, up to database freeze.

15.5 Central monitoring

CTRU staff will review entered data for possible errors and missing data points. A central review of consent forms will also be completed remotely due to consent being taken electronically. This will be made clear to the participant prior to their consent to the trial.

16. Publication

Results of the study will be disseminated through peer reviewed scientific journals and at clinical and academic conferences, as well as submission of a final report to the funder, which will be made available online.

Details of the study will also be made available on the Sheffield CTRU website. Summaries of the research will be updated periodically to inform readers of ongoing progress.

The results will be published on a freely accessible database within one year of completion of the trial.

Full details, including guidance on authorship, are documented in the Publication and Dissemination Plan.

17. Finance

BASIS is funded by the National Institute for Health Research (NIHR) Health Technology Assessment (HTA) Programme (NIHR131081). The views expressed are those of the author(s) and not necessarily those of the NIHR or the Department of Health and Social Care.
There is a prize draw every 2 months, in which participants who have completed follow up questionnaires are entered to win a £20 shopping voucher. As follow up visits have been timed to coincide with the timing of routine follow up visits, participant travel expenses will not be provided.

18. Ethics approval & regulatory compliance

Before initiation of the study at participating site, the protocol, informed consent forms and information materials to be given to the participants will be submitted to an NHS Research Ethics Committee. Any further amendments will be submitted and approved by the HRA and ethics committee.

The study will be submitted to local participating Trusts to confirm Capacity and Capability before any research activity takes place.

Any amendments, including protocol modifications will be notified to all sites and collaborating parties to confirm ongoing Confirmation of Capacity and Capability (CCC) in light of the new information. Participants will be notified and reconsented if appropriate to the change.

19. Sponsor and site approval

Before initiation of the study at participating sites, the protocol, informed consent forms, and information materials to be given to the participants will require sponsor approval.

A site agreement between the Sponsor, participating sites and Sheffield CTRU outlines responsibilities of all parties and is to be signed prior to commencement of recruitment at sites.

Recruitment of study participants will not commence at a site until a letter of Confirmation of Capacity and Capability (CCC) has been issued.

20. Trial Organisation and Responsibilities

20.1 Principal Investigators

Each site will have a local Principal Investigator (PI) who will be delegated responsibility for the conduct of research at their centre and must sign a declaration to acknowledge these responsibilities. The local PI should ensure that all relevant staff involved are well informed about the trial and trained in study procedures, including obtaining informed consent and conduct of the trial according to GCP. The local PI will liaise with the Trial Manager on logistic and administrative matters connected with the trial.

20.2 Sheffield Clinical Trials Research Unit (CTRU)

The Sheffield CTRU at Sheffield University will provide set-up and monitoring of the trial conduct to CTRU SOPs and the GCP conditions and principles as detailed in the UK Policy Framework for Health and Social Care Research 2017. CTRU responsibilities include randomisation design and service, protocol development, CRF design, trial design, source data verification, monitoring schedule and statistical analysis for the

trial. In addition, the CTRU will support the main REC, HRA and site-specific submissions, clinical set-up, on-going management including training, monitoring reports and promotion of the trial.

The CTRU Study Manager will be responsible for supplying investigator site files to each collaborating centre after relevant ethics committee approval and local R&D Confirmation of Capacity and Capability (CCC) has been obtained. The CTRU will be responsible for the day-to-day running of the trial including trial administration, database administrative functions, data management, safety reporting and all statistical analyses. The CTRU will develop the site monitoring plan and data management plan (in conjunction with Amplitude) and will assist the CI to resolve any local problems that may be encountered during the trial including any issues of noncompliance.

21. Patient & Public Involvement (PPI)

We have established the Sheffield Scoliosis Group, comprising of 11 children with AIS and their parents. The group have met twice in the development of this study and will continue to meet regularly (at least annually, but more regularly during set-up) throughout the trial. PPI members will be invited to attend TMG and TSC meetings to input into the running of the trial, and will contribute during the write-up period to ensure the needs of a service-user audience are met.

The PPI group have suggested key improvements to the design of the trial including 1) incentivising questionnaire completion by undertaking a regular prize draw, 2) creating videos describing the experience of patients undergoing FTB and NTB in order for patients to make an informed choice to participate in the trial, and (3) The use of electronic questionnaires, their frequency and length. The group tested how long it would take to complete the PROMs – this averaged between 7 and 9 minutes.

We also continue to seek the views of patients and their parents through Scoliosis Association UK (SAUK).

22. Indemnity / Compensation / Insurance

The University of Sheffield has in place clinical trials insurance against liabilities for which it may be legally liable and this cover includes any such liabilities arising out of this clinical study.

Standard NHS indemnity operates in respect of the clinical treatment that is provided.

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