Management of ANkle fractures in CHildren: the feasibility Of a Randomised controlled trial

ANCHOR Trial protocol v3.2 date 28-02-2022

Full title	Management of ANkle fractures in CHildren: the feasibility Of a Randomised controlled trial
Short title	ANCHOR: Ankle fractures in children
Acronym	ANCHOR
Trial Registration	ISRCTN reference
IRAS Project ID	277534
Trial sponsor	Nottingham University Hospitals NHS Trust
Sponsor reference	20OR002
Funding source	NIHR RFPB NIHR200580

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SIGNATURE PAGE

The undersigned confirm that the following protocol has been agreed and accepted and that the Chief Investigator agrees to conduct the study in compliance with the approved protocol and will adhere to the principles outlined in the Declaration of Helsinki, the Sponsor's SOPs, and other regulatory requirement.

I agree to ensure that the confidential information contained in this document will not be used for any other purpose other than the evaluation or conduct of the investigation without the prior written consent of the Sponsor

I also confirm that I will make the findings of the study publicly available through publication or other dissemination tools without any unnecessary delay and that an honest accurate and transparent account of the study will be given; and that any discrepancies from the study as planned in this protocol will be explained.

For and on behalf of the Study Sponsor:

Signature:

.....

Date:

...../...../.....

Name (please print):

.....

Position:

.....

Chief Investigator:

Signature: ....

Date:

.2./.12./..2020..

Name: (please print):

Mr Ben Ollivere

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STUDY SUMMARY

Study Title	Management of ANkle fractures in CHildren: the feasibility Of a Randomised controlled trial
Internal ref. no. (or short title)	ANCHOR: Ankle fractures in children
Study Design	Parallel group, 3-arm, multicentre, feasibility, randomised trial
Planned Size of Sample (if applicable)	126 in trial 24 parent-child dyads in interviews (18 dyads who were randomised and 6 dyads who declined to participate in the main trial) A total 174 participants will be recruited

Eligibility criteria	**Inclusion criteria**
	
	Children (aged 5-15 years inclusive) will be suitable for inclusion in the study if they have either:
	• A proven low-risk ankle fracture on x-ray
	  ○ minimally displaced or undisplaced fibular fracture
	• A clinical undisplaced fracture which fulfils the Ottawa criteria:
	  ○ A history of trauma
	  ○ Tenderness at the posterior edge of the lateral malleolus
	  ○ Unable to weight bear for more than 4 steps
	  ○ No alternative cause of pain identified on x-ray
	Exclusion criteria
	
	Children will be excluded if
	• The injury is more than 7 days old at randomisation
	• They in conjunction with their parents are unable to complete the outcome measures chosen in English
	• The child is on the Child Protection Register or where there is any concern about the cause of the injury.

Follow up duration (if applicable)	12 weeks
Planned Study Period	Time from first recruitment to final follow up: 28 months (1/10/2020 – 1/02/2023)
Research Question/Aim(s)	To establish the feasibility of performing a randomised trial to identify the best treatment for low-risk ankle fractures in children
Outcome Measures	Electronic, web-based randomisation. Assessors blinded but participants cannot be blinded.
Statistical Methods	Feasibility of randomised trial including patient feasibility, outcomes feasibility and site and clinician feasibility

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ABBREVIATIONS

AE	Adverse Event
CI	Chief Investigator overall
CRF	Case Report Form
DMC	Data Monitoring Committee
GCP	Good Clinical Practice
ICF	Informed Consent Form
NHS	National Health Service
P/GIS	Parent / Guardian Information Sheet
PI	Principal Investigator at a local centre
PIS	Participant Information Sheet
REC	Research Ethics Committee
R&D	Research and Development department
SAE	Serious Adverse Event

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FUNDING AND SUPPORT IN KIND

FUNDER(S) (Names and contact details of ALL organisations providing funding and/or support in kind for this study)	FINANCIAL AND NON FINANCIALSUPPORT GIVEN
National Institute for Health Research Research For Patient Benefit	Full funding for this study

ROLE OF STUDY SPONSOR AND FUNDER

Nottingham University Hospitals NHS Trust are the sponsor for this study. This study is funded by the National Institute for Health Research (NIHR) Research For Patient Benefit (project reference NIHR200580). The views expressed are those of the author(s) and not necessarily those of the NIHR or the Department of Health and Social Care.

The study sponsor will monitor the study conduct against nationally agreed standards. The study sponsor and study funder will have no role in the design, data analysis, interpretation, manuscript writing and dissemination of the results. The sponsor and funders will be consulted for the final decision/s regarding any aspects of this study. The Sponsor reserves the right to discontinue this trial at any time for failure to meet expected enrolment goals, for safety or any other administrative reasons. The Sponsor shall take advice from the Trial Steering Committee and Data Monitoring Committee as appropriate in making this decision.

ROLES AND RESPONSIBILITIES OF STUDY MANAGEMENT COMMITTEES/GROUPS & INDIVIDUALS

Study Steering Groups

The Chief Investigator has overall responsibility for the study and shall oversee all study management. The Chief Investigator will provide supervision for students involved in the research.

The trial management group will meet every 4 weeks to review study progress, any AEs and review study analysis. The trial management group will include the Chief investigator, the deputy chief investigator, qualitative expert and clinical expert

The trial steering committee will meet every 6 months to review progress against the primary endpoints during the study and review all adverse events. This will be composed of the Chief investigator, deputy chief investigator and all co-applicants, including PPI representative.

The data management committee will meet every 6 months ahead of the trial steering committee to review data returns from all sites and monitor key targets such as recruitment and missing data. This will compromise of the study coordinator and study statistician.

Key Words

Fractures, Bone; Child; Ankle; Randomized Controlled Trial; Casts, Surgical; Splints

Contents

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STUDY FLOW CHART

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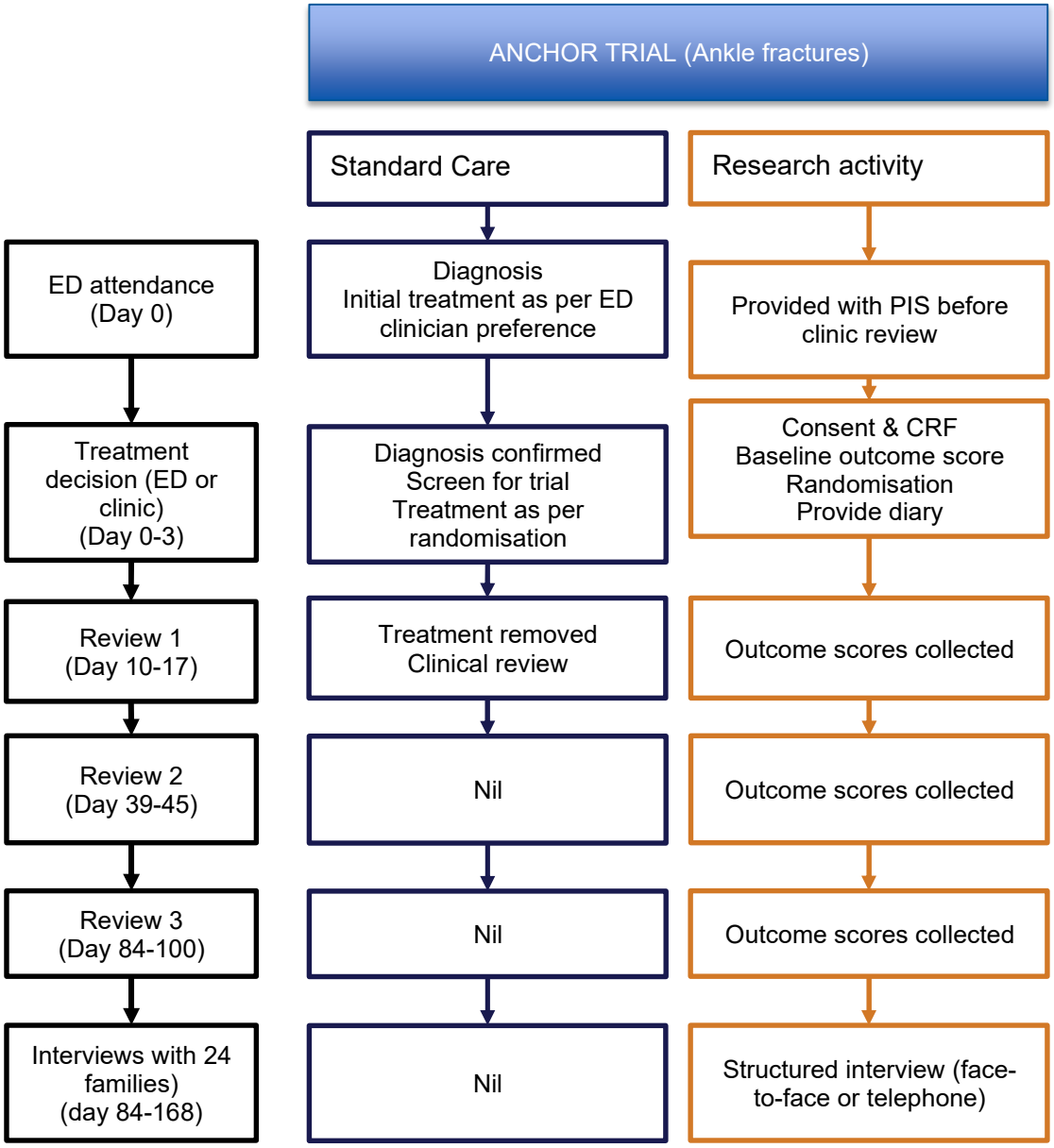

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1. BACKGROUND

1.1. SCALE OF THE PROBLEM

Epidemiology of childhood fractures: Incidence and prevalence

There are 12.47 Million children aged 0-16 living in the United Kingdom[1]. A third of these children will sustain a fracture by their 17th birthday[2]. Many of these children will be treated in the community, with 55,000 children requiring a hospital admission to U.K. hospitals each year for fractures[3].

In epidemiological studies from Europe and the United States, the annual incidence of fractures in children is reported to be 20.1-36.1 per 1,000 children. Within these studies, there is discrepancy with the upper limit of 'childhood', ranging from 14-19 years of age. Despite this, the distribution of bone fractures is similar from Germany, Scotland, Sweden, USA and Wales with ankle fractures forming 4-7% of all childhood fractures.

Outcomes following childhood injuries

The impact on recovery and quality of life of injuries and fractures has been evaluated in the U.K. Burden of injury survey. This was a longitudinal survey of 298 children (164 who completed 12-month questionnaires) who attended the Emergency departments of 4 U.K. hospitals that covered a catchment generally representative of the overall U.K. population.

The survey identified that 9% of children who attended the emergency department did not make a full recovery at 12 months on a self-reported questionnaire. Children with a 'mild' injury had a higher chance of making a full recovery[4].

The findings from this survey were replicated in British Colombia, Canada where children who attended the Emergency Department with an injury were surveyed at one year. A significant decrease in quality of life as measured by a decrease of more than 1 standard deviation from baseline PedsQL score was observed for 8% of injured children, independent of injury severity[5].

While these surveys are useful for gaining an understanding of the overall trends of recovery following injury, it remains unclear as to why a significant proportion do not make a full recovery from their injuries. In addition, the World Health Organisation have observed that there are additional impacts to families with children with broken bones including loss of work, schooling and participation with play, parents and peers[6], however there is little published work to evaluate these broader outcomes or to identify if these are relevant to families and clinicians when deciding on treatment strategies.

1.2. CURRENT STATE OF THE EVIDENCE TO MANAGE CHILDHOOD FRACTURES

Cochrane reviews

There are six Cochrane reviews that have evaluated the literature supporting the management of childhood fractures[7]–[12]. These are summarised in Table 1. The reviews have identified 45 trials with sufficient quality to inform practice, with most trials relating to the management of wrist fractures.

The review of interventions for the management of ankle fractures was published in 2016, with searches completed in September 2015. In this review, a higher functional score was identified in children treated with brace or bandage when compared to children treated in a plaster cast.

Despite this evidence that was available at the time of the Cochrane review, only 22% of 558 American paediatric orthopaedic surgeons report using a removable splint in routine practice for low-risk ankle fractures (distal fibular avulsion fractures)[13].

The current clinical practice for managing ankle fractures in children is unclear, despite the suggestion that functional treatments may be superior to cast treatments. This uncertainty has led to the development of the research question for this study.

Table 1 Cochrane reviews for childhood fractures

Authors	Year	Topic	Number of trials	Conclusions
Abraham et al[7]	2011	Surgery for forearm fractures	0	Lack of RCT evidence to inform if surgery is required
Madhuri et al[8]	2013	Conservative techniques for treating forearm fractures	0	Lack of RCT evidence to identify best treatment
Handoll et al[9]	2018	Wrist fractures	30	Low quality RCT evidence. Evidence for good outcome following any treatment for buckle fractures
Capstick & Giele[10]	2014	Fingertip injuries	2	Lack of RCT evidence to identify best treatment
Yeung et al[11]	2016	Stable ankle fracture	3	Low quality evidence of improved recovery with an ankle brace vs plaster
Madhuri et al[12]	2014	Femur	10	Insufficient long-term evidence to compare surgery and traction. Nails may reduce recovery time.

What is a low-risk ankle fracture?

A low-risk ankle fracture is a break to the ankle joint where the patient can safely weight bear. Low-risk fractures include a variety of injuries; avulsion fractures, undisplaced fractures and fractures that cannot be seen on x-ray (**Error! Reference source not found.**). Fractures in children behave differently to those in adults due to their thick periosteum that provides additional stability.

Diagnosis of these injuries can be challenging as occult or growth plate injuries can be very subtle on x-ray images. The Ottawa ankle rules provide a basis for risk stratification of ankle injuries[14], with a sensitivity of 97.9 and specificity of 21% for diagnosis of fracture[15].

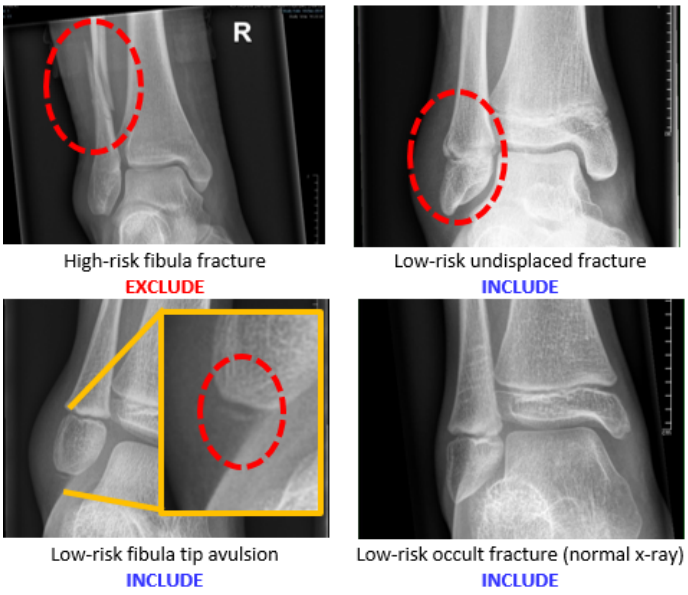

Figure 1 Types of ankle fractures categorised as high-risk and low-risk [25]

The Ottawa ankle rule includes:

- A history of trauma
- Tenderness at the posterior edge of the lateral malleolus
- Unable to weight bear for more than 4 steps
- No alternative cause of pain identified on x-ray

What are the treatment options?

Treatment options for these injuries can be regarded as mobile (where the ankle joint is free to move) or rigid (where the ankle joint is fixed). Techniques to achieve this that have been reported in previous trials are summarised in Table 2:

Table 2 Interventions reported in previous trials. *PPI workshop views

	Potential advantages	Potential harms
Tubigrip, elasticated bandage[16], [17]	Early movement of the ankle	Some families think it would be less protective*
Removable brace or splint (e.g. Air-stirrup brace)[18], [19]	Early motion with some protection Can be removed for bathing	Higher number of pressure related complications than cast[19]
Below knee cast[16]–[18]	Likely most protective*	No movement at ankle joint, cannot be removed, may result in bone thinning

Which is the best treatment?

In a recent systematic review, children prescribed removable treatments have a more rapid return to activities, have a higher functional outcome at four weeks and do not seem to suffer any additional pain[20].

However, there were some significant issues when completing this analysis. There was heterogeneity in study design and conduct. The biggest issue is that all the trials used a different primary outcome measure, with inconsistent reporting of secondary outcomes and statistical techniques. Two studies used variations on the Activity Scale for Kids score (ASK-P) which evaluates function over the preceding two weeks. It would therefore be expected, that if a child remains in a cast then their ASK-p score will be lower as it is difficult to mobilise in a cast even as a healthy volunteer[21].

2. RATIONALE

In order to understand what the ideal treatment for childhood ankle fractures is, we need to establish

1. Is it feasible to conduct a randomised trial in the U.K. to answer this question?
2. What are the most important outcomes to measure and contrast treatments?
3. What is the validity of the instruments available to measure these outcomes?

Work is in progress to identify the outcome domains for a core outcome set in childhood fractures. In a recent systematic review, no patient reported outcome measures have been designed explicitly for childhood fractures, and the quality of evidence available to assess measurement properties is poor.

The ANCHOR study will address these uncertainties with a feasibility randomised trial to provide feasibility data and additional validation of outcome measures.

3. RESEARCH QUESTION AND AIMS

3.1. TRIAL PURPOSE

To establish the feasibility of performing a randomised trial to identify the best treatment for low-risk ankle fractures in school aged children

Objectives

Evaluation of the feasibility of a definitive randomised trial through:

1. Patient feasibility
    a. Compliance with treatment and other outcome scores
    b. Are there any complications with treatments?
2. Outcome feasibility
    a. Determine the ideal outcome measure for this trial.
    b. Determine the effect sizes of the interventions for a sample size calculation of a definitive trial
3. Site and clinician feasibility
    a. Numbers of eligible patients
    b. Recruitment and retention rates for this trial
    c. Fidelity assessment of inclusion criteria and interventions

3.2. OUTCOMES

Feasibility outcomes

Feasibility outcomes will determine if a future main trial is possible and desirable. The following feasibility outcomes will be assessed:

- Recruitment rates compared to site screening logs;
- Retention rates, drop out and crossovers;
- Adherence to treatments through a 14-day patient diary;
- Trial experience and qualitative feedback from participants.

Clinical outcomes

Clinical outcomes will be collected to assess the relevance and acceptability of these outcomes for use in a future definitive RCT and to validate the tools to measure outcomes for childhood fractures through:

1. Calculation of minimally important clinical difference for outcome tools;
2. Validation of PROMIS Mobility for ankle fractures in children.

The following clinical outcomes will be assessed:

- Physical function as measured by PROMIS Mobility;
- Quality of life as measured by EQ-5D-Y;
- Global rating of change score;

- Daily pain scores through a 14-day patient diary;
- Re-injury rates;
- Complications.

Safety endpoints

No significant safety issues are expected related to this trial. Spontaneous adverse events will be monitored during the trial, in particular at the 6-week follow up requiring additional treatment or physiotherapy.

Stopping rules and discontinuation

No specific stopping or discontinuation rules have been identified for this study. As this is a feasibility study, if the accumulating evidence shows that the study is not feasible then at the advice of the TSC, the sponsor reserves the right to stop the study at any time

3.3. Compliance

Study compliance is one of the primary objectives to be measured as part of the feasibility trial. The study will quantify:

1. Self-reported treatment compliance: patient diaries will be completed with an option to complete usage time, in hours, of the treatment device. This diary will be returned for analysis at the two week follow up visit
2. Outcomes compliance: completion of outcome tools will be monitored with an expected completion of instrument items of 95%. Patients will be provided with a reminder to complete outcomes and provided with options for returning the 12 week follow up as electronic, postal or by telephone
3. Clinic attendance: clinic attendance will be monitored particularly the completion of 6 week follow up outcomes assessment.

3.4. Progression criteria

The trial will progress to a full trial if all the following are fulfilled:

1. A suitable outcome measure can be determined using the feasibility data and the effect size of the three interventions estimated along with the standard deviations in order to properly power a definitive trial;
2. None of the interventions have an unacceptable complication rate as agreed by the trial steering committee;
3. Recruitment rates are greater than 50% anticipated allowing a full trial to be completed within a 3-year time frame within the U.K. Trauma Trials Network;
4. Study retention is greater than 60% at the 6-week follow up in all groups;
5. The effect size and standard deviation produces a sample size calculation that can be achieved across the trauma trials network within a reasonable time frame and within scope of an NIHR HTA funding;

4. STUDY DESIGN AND METHODS OF DATA COLLECTION AND DATA ANALYSIS

4.1. TRIAL CONFIGURATION

A prospective three-arm, parallel, multicentre, feasibility randomised trial with an embedded interview study exploring attitudes and experience of participating in a trial

4.2. DETAILS OF PRODUCT(S)

The ANCHOR Trial is a randomised, feasibility trial. This design will permit evaluation of trial feasibility and deliver validation data for outcome instruments used in childhood lower limb fractures.

Products will be prescribed for the ANCHOR Trial population. Participants will be randomised to receive a supportive bandage, removable brace or walking cast.

Product Description

1. Supportive bandage. An elastic bandage (e.g. tubigrip) will be provided for the child to wear for two weeks. The bandage will be sized according to manufacturer instructions.
2. Semi-rigid, removable brace (including splints or custom orthoses). A removable ankle brace (e.g. Aircast Air-Stirrup Ankle Brace, removable weightbearing backslab Walker boot or Aircast boot) will be prescribed at the discretion of the local treating physician. The device will be sized and fitted according to manufacturer instructions.
3. Below knee walking cast. A non-removable, below knee walking cast will be applied according to local protocols. The cast may be synthetic or resin based and will be applied over standard padding. The cast will be circumferential or a backslab but must be constructed to bear weight and will be applied and removed by a trained member of staff.

Manufacture

Local NHS supply chain approved devices will be prescribed in each centre and used according to manufacturer guidelines.

Known Side Effects

Previously reported side effects of treatments include:

Pressure related injuries e.g. marks and blisters – This is more common in the removable brace group than cast group and is associated with patients not wearing the supplied protective sock [22]. This will be mitigated by reminding this group to wear the sock and by ensuring patients in brace or cast have adequate padding.

Plaster saw injuries – removal of a below knee walking cast requires the use of an electronic oscillating plaster saw which may cause injury. Injury is typically caused through thermal damage to the skin. This will be reduced by requiring casts to be applied and removed by trained and experienced personnel. This is in line with the 2015 British Orthopaedic Association Casting Standards (https://www.boa.ac.uk/uploads/assets/uploaded/83dcfe25-307e-4e82-abf362976f08a3ae.pdf)

4.3. RANDOMIZATION AND BLINDING

Participants will be individually allocated in a 1:1:1 ratio to one of the three treatment groups using a minimisation algorithm by the Nottingham Clinical Database Support Service (CDSS) and held on a secure server. The minimisation variables will comprise age, injury type and study site. The investigator or authorised designee will use the remote, internet-based randomisation system to obtain the treatment allocation for each participant. Other than the allocated treatment, all groups will be followed up in the same way to exclude bias.

It will not be possible to blind participants to treatment allocation. Assessor blinding will be achieved by removal of the treatment device by nursing staff independent to the trial on arrival to follow up clinic for those children who require an appointment to remove a cast. Follow up will be performed remotely by the central trial team. Non-response will be minimised through the use of electronic and telephone reminders.

Maintenance of randomisation codes and procedures for breaking code

Access to the randomisation system will be confined to the CDSS IT staff.

In most cases, the un-blinding will be part of managing an SAE, and will be reported with the SAE, however, in cases where un-blinding was not associated with an SAE, such actions should be reported in a timely manner. The default will be to use the same timeline requirements for investigator reporting of SAEs (notification of Sponsor immediately as practicable by phone or email, followed by a written narrative of the event within 48 hours).

No interim analysis is planned during this study. At the end of the study, anonymous linked records of outcomes and treatment allocation will be provided for analysis.

4.4. STATISTICS

Feasibility outcomes

All analyses will be documented in a Statistical Analysis Plan which will be finalised prior to database lock. Descriptive statistics (with 95% confidence intervals (CI) where appropriate) will address feasibility objectives (e.g. recruitment and follow-up rates, missing clinical outcome data, intervention adherence, standard deviations for clinical outcomes). Demographic and baseline clinical characteristics will be descriptively compared by study arm.

Assessment of efficacy

As this is a feasibility study, no formal assessment of efficacy will be undertaken. The potential primary clinical outcome for the future main trial will be analysed descriptively per arm, with confidence intervals generated using appropriate regression model to estimate the likely range of intervention effects. Secondary clinical outcomes will be descriptively summarised by treatment arm.

There is no consensus yet on the outcomes that should be measured in childhood fractures. In our preparatory work for this proposal families have identified ‘return to normal activities’ and ‘pain’ as the two most important outcomes.

Initial findings from the CORE-KIDS lower limb fracture study have suggested that the EQ-5D-Y and PROMIS Mobility outcome sets should be used as the primary outcome measures, as they assess a broad range of function and mobility domains.

A formal minimally important clinical difference (MCID) in this patient group has not been calculated, and previous trialists have used a range between 5 and 7%[9,10] to represent an important difference.

Assessment of safety

No significant safety issues are expected related to this trial. Spontaneous adverse events will be monitored during the trial, in particular at the 6-week follow up requiring additional treatment or physiotherapy.

All adverse events will be discussed at the trial management group meetings. Significant adverse events will be escalated to the trial steering committee and study sponsor.

Procedures for missing, unused and spurious data

Proportions and patterns of missing data will be summarised by arm but there will be no imputation for missing data at follow-up assessments nor any model-based adjustment for missing data.

Baseline and outcome data will be summarised by allocated group, regardless of adherence with the intervention. Safety will be evaluated using the Safety set: All randomised participants who receive at least one treatment.

4.5. QUALITATIVE ANALYSIS

A qualitative evaluation of interview transcripts will be performed to identify themes in

1. Treatment compliance
2. Attitudes to randomisation
3. Treatment experience

Interviews will be transcribed and anonymised. A framework analysis will be performed based on the SWIFFT analytic framework[23]. Initial coding of data will be led by one researcher. Verification of lower-level coding will be performed by the senior qualitative researcher with any disagreements resolved by consensus. Higher level themes and, if required, revision of the framework will be discussed and agreed by the trial steering committee.

5. STUDY SETTING

This is a multi-centre trial. The setting for this study will be hospitals that provide care for children aged 5-15 with low-risk ankle fractures or clinically undisplaced ankle fractures. The design of this study is to minimise the additional research burden on participants and NHS teams.

5.1. STUDY ACTIVITIES FOR THE TRIAL

At time of diagnosis (typically in the Emergency Department), potential participants may be identified and provided with a patient information sheet by the usual care team. Screening of participants may also be performed by the usual care team in face-to-face or virtual fracture clinics and information sheets provided.

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Where eligible participants wish to join the study, a member of the research team will obtain informed consent and undertake randomisation to a product at the point in the local care pathway where a definitive treatment is being offered. This may be in the Emergency Department, Emergency clinics or fracture clinic depending on the local pathways.

Following completion of pre-injury baseline scores and CRF, the patient will be randomised using a web-based electronic randomisation with 1:1:1 allocation with stratification for fracture type (occult and visible fracture line) and child age (5-10, 11-15) with block sizes of 3, 6 & 9.

Treatment will be provided according to random allocation by a trained member of the clinic staff according to the manufacturer's guidelines. As described in section 4.2, the available treatments are:

1. Supportive bandage.
2. Semi-rigid, removable brace (including splints or custom orthoses).
3. Below knee walking cast

Routine follow up will be provided according to local protocols and decided by the usual care team. Patients who have a below knee walking cast are likely to require a clinic review to remove the device. Other patients may be discharged with instructions to remove their own device at home.

A patient diary is provided to participants at time treatment is provided. The diary is returned after two weeks.

Outcome assessment will be completed by the central research team using an electronic interface through the Redcap system. Outcomes will be collected at 2 weeks, 6 weeks and 12 weeks. Telephone, SMS text messages (Esendex, Nottingham) and e-mail reminders will be used to encourage completion of outcome scores.

Table 3 Schedule of outcome assessment. Demographic included: age; gender; side of injury; mechanism of injury; dominant side; location of injury; type of fracture. GROC: Global rating of change score

	Baseline (pre-injury) score	Review 1 (Day 7-23)	Review 2 (Day 35-52)	Review 3 (Day 84-100)
Demographics	X			
Physical function (PROMIS Mobility)	X	X	X	X
Quality of life (EQ-5D-Y)	X	X	X	X
Daily pain (faces pain or VAS)	X	X		
Re-injuries			X	X
Complications		X	X	X
Parent satisfaction			X	X
Child satisfaction			X	X
GROC		X	X	X

Study activities for interviews

A subgroup of participants recruited to the ANCHOR trial will be invited to complete structured interviews regarding the study experience. 4-6 participant dyads who declined to be randomised to the

trial will also be recruited. A target of 24 parent-child dyads will be interviewed after the 12-week follow up and before 24 weeks have elapsed since randomisation.

Purposeful sampling will be undertaken to conduct interviews with a balance of families:

- From different recruiting sites
- With different treatments
- With different ages of child (5-10, 11-15)

As advocated in the child health literature, a pragmatic and participant-centred approach (based on choice, participation, and flexibility) to collecting qualitative data will be employed[24]. Interviews will be conducted with children and parents/legal guardians either collectively or separately. Interviews will take place at the participants' preferred time and method (e.g. face-to-face, telephone)[24]. This interview will follow a standard interview schedule including questions for both the person with parental responsibility and children. This schedule will be piloted with our PPI group to confirm acceptability and validity of the tool.

The interviews will explore the experience of participation in a trial, acceptability of treatments, barriers to participation and adherence to the study protocols and strategies to promote recruitment and retention to a future full trial.

It is anticipated that most interviews will be performed by members of the research team working at the lead site (Nottingham University Hospitals NHS Trust). However, members of local research teams with adequate qualitative research experience (as judged by the Chief Investigator and as indicated on the delegation log) may also perform interviews using the standard interview schedule. Audio files will be transferred to the lead site using secure NHS email servers.

6. SAMPLE AND RECRUITMENT

6.1. Eligibility Criteria

Inclusion criteria

Children (aged 5-15 years inclusive) will be suitable for inclusion in the study if they have:

- A proven low-risk ankle fracture on x-ray
  - minimally displaced or undisplaced fibular fracture
- A clinical undisplaced fracture which fulfils the Ottawa criteria:
  - A history of trauma
  - Tenderness at the posterior edge of the lateral malleolus
  - Unable to weight bear for more than 4 steps
  - No alternative cause of pain identified on x-ray

Exclusion criteria

Children will be excluded if

- The injury is more than 7 days old at randomisation
- They in conjunction with their parents are unable to complete the outcome measures chosen in English.

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- The child is on the Child Protection Register or where there is any concern about the cause of the injury.

Expected duration of participant participation

Study participants will be participating in the study for 12 weeks

Removal of participants from therapy or assessments/Participant Withdrawal

Participants may be withdrawn from the trial either at their own request or at the discretion of the Investigator. The participants will be made aware that this will not affect their future care. Participants will be made aware (via the information sheet and consent form) that should they withdraw the data collected to date cannot be erased and may still be used in the final analysis. Enrolled participants in the ANCHOR TRIAL who are not yet randomised can be replaced (though keeping their trial ID), but participants who withdraw after randomisation will not be replaced.

6.2. SIZE OF SAMPLE

No formal sample size calculation is required for the feasibility trial. An estimate for the sample size of the full trial requires 969 patients for 90% power with a MCID for ASK-P of 5 and standard deviation of 16.5[9]. Assuming a 30% loss to follow up, for feasibility this requires 42 patients to be recruited into each group of the feasibility study.

6.3. RECRUITMENT

Participants will be recruited from the Emergency Department, acute fracture or injury clinics. The initial approach will be from a member of the patient's usual care team (which may include the investigator), and information about the trial will be on display in the relevant clinical areas in the form of posters and information leaflets. Only members of the patient's existing clinical care team will have access to patient records without explicit consent in order to identify potential participants, check whether they meet the inclusion criteria or make the initial approach to patients.

The investigator or their nominee, e.g. from the research team or a member of the participant's usual care team, will inform the participant or their nominated representative (other individual or other body with appropriate jurisdiction), of all aspects pertaining to participation in the study.

If needed, the usual hospital interpreter and translator services will be available to assist with discussion of the trial, the participant information sheets, and consent forms, but the consent forms and information sheets will not be available printed in other languages.

It will be explained to the potential participant that entry into the trial is entirely voluntary and that their treatment and care will not be affected by their decision. It will also be explained that they can withdraw at any time, but attempts will be made to avoid this occurrence. In the event of their withdrawal it will be explained that their data collected so far cannot be erased and we will seek consent to use the data in the final analyses where appropriate.

Participants who are eligible for the study and are approached by the research team but decline to participate will be invited to provide their contact details so they may be invited to join an interview with the research team at the end of their child's treatment.

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6.4. CONSENT

Written informed consent will be obtained before any participant enters the main study. All participants will require a written consent form completed by a person with parental responsibility. If a child wishes to assent, this may be documented on the consent form. Where a child and the person with parental responsibility disagree, then the child will not be recruited. Separate consent forms will be used for children entering the ANCHOR Trial and those participating in interviews. Participants consenting for the ANCHOR Trial will be asked to provide additional, optional consent to be contacted for a qualitative interview. A written information sheet about the interview will be provided to parent/child dyads who decline the main study but consent to interview. The researcher will go through the information sheet and answer any questions prior to the provision of a written informed consent form for trial participants, or verbal informed consent in the case of non-trial participants who have declined the main study. The consent forms for the interview study are separate to the main consent form for the trial to allow participants to consent to either half of the study dependent on their individual preferences. Individuals taking part in the RCT do not have to participate in the interview study, and individuals who decline participation in the RCT should be offered the opportunity to participate in the interview study.

The Informed Consent Form will be signed and dated by the participant's parent or legal guardian before they enter the study. The Investigator will explain the details of the trial and provide a Participant Information Sheet, ensuring that the participant has sufficient time to consider participating or not. The Investigator will answer any questions that the participant has concerning study participation.

As all participants will be children under the age of 16, the Participant Information Sheets include a child-friendly study summary that has been piloted with children aged 5-15. No child will enter the study without parental or legal guardian consent and, where appropriate, will give assent that will be documented on the same consent form. Where Consent is given, and assent is refused the child will not be recruited to the study.

Informed consent will be collected from each participant before they undergo any interventions (including physical examination and history taking) related to the study. One copy of this will be kept by the participant, one will be kept by the Investigator, and a third will be retained in the patient's hospital records.

Should there be any subsequent amendment to the final protocol, which might affect a participant's participation in the trial, continuing consent will be obtained using an amended Consent form which will be signed by the participant.

6.5. DURATION OF PARTICIPANT INVOLVEMENT

The study duration from first recruitment to final follow up: 18 months (1/10/2020 – 1/4/2022). Participants in the trial will be involved in the study for 12 weeks. Patients contributing to the interviews will be involved for a total of 24 weeks. The end of the study will be the last postal return (12-week follow up) of the last participant.

7. ETHICAL AND REGULATORY CONSIDERATIONS

7.1. ASSESSMENT AND MANAGEMENT OF RISK

Trial participants

Trial participants will be monitored for adverse events as detailed below. Where researchers become aware of any suspected or alleged abuse of children or vulnerable adults in the course of this research then the local NHS safeguarding policy will be followed. Specifically, if a researcher:

a) suspects that a child or adult at risk has been, or is at risk of being abused;
b) has had a disclosure of abuse made to them;
c) receives a complaint relating to young person or adult at risk safeguarding issues at the hospital;
d) is contacted by a local authority as part of its enquires about a child that might be suffering or at risk of suffering significant harm

Then the researcher will report the matter with the Chief Investigator who will seek advice from the Lead Safeguarding Officer for the NHS site. This will be escalated and documented in line with the local policy.

Interviews

It is not anticipated that the conduct of interviews with parents/carers and children within this study will generate major ethical issues. The content of the interviews is unlikely to uncover particularly sensitive issues to the child or their family, but where participants are becoming upset or distressed the interviewer will be empowered to amend the questions recommended in the interview schedule or postpone or terminate the interview if required.

Researchers will be subject to the local fieldwork policy where researchers are conducting interviews at the participant's homes or outside of the hospital or university premises. This requires a risk assessment to be completed and authorised by the relevant safety officer prior to any fieldwork being initiated.

7.2. RESEARCH ETHICS COMMITTEE (REC) REVIEW & REPORTS

Before the start of the study, approval will be sought from a REC for the study protocol, informed consent forms and other relevant documents e.g. advertisements.

Substantial amendments that require review by REC will not be implemented until all the appropriate regulatory bodies grant a favourable opinion for the study (note that amendments may also need to be reviewed and accepted by R&D departments, or through other research governance mechanisms, before they can be implemented in practice at sites).

All correspondence with the REC will be retained.

It is the Chief Investigator's responsibility to produce the annual reports as required. The Chief Investigator will notify the REC of the end of the study.

An annual progress report (APR) will be submitted to the REC within 30 days of the anniversary date on which the favourable opinion was given, and annually until the study is declared ended. If the study is ended prematurely, the Chief Investigator will notify the REC, including the reasons for the premature termination. Within one year after the end of the study, the Chief Investigator will submit a final report with the results, including any publications/abstracts, to the REC.

7.3. PEER REVIEW

The study protocol was peer-reviewed as part of the NIHR RfPB funding award.

7.4. PATIENT & PUBLIC INVOLVEMENT

This research plan will maintain the parent and public involvement throughout the study period. A sequence of face-to-face parent involvement focus groups will be used to develop the study design, delivery and dissemination. These will be supplemented with the use of virtual parent and patient involvement activities with parental representation on the study management panel.

Following feedback regarding hosting parent involvement groups at the Nottingham University Hospital Site where parking is difficult, and childcare is limited we have decided to host parent and patient involvement groups at suitable family friendly venues such as Twycross Zoo. Four focus group sessions are planned over the two-year study period to coincide with school holidays. The programme for the focus groups is flexible to accommodate for any unseen issues with the study delivery. It is anticipated to include: screening of the description of outcomes for inclusion in the Delphi survey, face validity and acceptability of secondary outcomes for inclusion in the trial, retention strategies for the trial and dissemination of findings.

In order to maintain collaboration with our international PPI panel, further electronic communication will be sent to the virtual PPI group. This group will be sent out regular newsletters documenting study progress and will be consulted using electronic survey for wording of questions for the Delphi survey. The virtual PPI group will be an important avenue for dissemination of study findings.

The study has a parent co-applicant who has experience in managing children with injuries both as a mother and as a schoolteacher. She will be an important member of the study management panel ensuring study acceptability, deliverability and in the dissemination of research findings. PPI training will be provided from the University of Nottingham.

Expenses for all PPI participants is being provided in line with INVOLVE guidelines

7.5. REGULATORY COMPLIANCE

Before any site can enrol patients into the study, the Chief Investigator will apply for and receive HRA approval for the study

Prior to commencing recruitment, sites must confirm their capacity and capability to conduct the study, as per the HRA approval letter.

Any amendment to the protocol should be considered that it may potentially affect a site's capacity to continue in the study, the Chief Investigator/ Principal Investigator or designee will inform the Sponsor of the proposed amendment. The amendment will be submitted as per Section 8.7.

7.6. Protocol compliance

Accidental protocol deviations can happen at any time. They must be adequately documented on the relevant forms and reported to the Chief Investigator and Sponsor immediately.

Deviations from the protocol which are found to frequently recur are not acceptable, will require immediate action and could potentially be classified as a serious breach.

7.7. Amendments

It is the sponsor's responsibility to decide whether an amendment is substantial or non-substantial for the purposes of submission to the REC. If the sponsor wishes to make a substantial amendment to the REC application or the supporting documents, the sponsor must submit a valid notice of amendment to the REC for consideration. The REC will provide a response regarding the amendment within 35 days of receipt of the notice, informing the HRA of the amendment. Site R&D departments will also need to be provided with the information on the amendment. Their level of review will be dictated by the category as assessed by the REC or HRA (A, B or C).

Non-substantial amendments also need to be notified to the HRA as well as the relevant R&D departments of participating sites to assess whether the amendment affects the continued capacity for that site. Note that some amendments that may be considered to be non-substantial for the purposes of REC and/or MHRA, may still need to be notified to REC and/or MHRA (e.g. a change to the funding arrangements).

7.8. Adverse Event

Potential adverse events

Table 4 lists adverse events reported in previous trials of childhood low-risk ankle fractures.

Children participating in the ANCHOR Trial will be screened at clinical follow up for the following potential adverse events:

- Pressure related issues
  - Heel pain
  - Blisters
  - Sores
- Skin irritation or rashes
- Persistent swelling
- Persistent bruising
- Additional visits to healthcare providers (e.g. physiotherapy, fracture clinic etc)

Table 4 Adverse events reported in previous trials of "low-risk" ankle fractures

Trial	Adverse events
Boutis et al 2007[18]¤	Unscheduled visits to healthcare provider Skin irritation / rash
Barnett et al 2012[19]	Additional visits to healthcare provider Pressure related complications
Gleeson et al 1996[16]	No adverse events reported
Launay et al 2008[17]	Persistent swelling and bruising

Reporting Procedures

Proportionate to the type of study and participant involvement, all adverse events should be reported. Depending on the nature of the event the reporting procedures below should be followed. Any questions concerning adverse event reporting should be directed to the Chief Investigator in the first instance.

Non serious AEs

All such events, whether expected or not, should be recorded.

Serious AEs

An SAE form should be completed and sent to the Chief Investigator within 24 hours. Hospitalisations for elective treatment of a pre-existing condition do not need reporting as SAEs.

All SAEs should be reported to the Derby REC where in the opinion of the Chief Investigator, the event was:

'related', ie resulted from the administration of any of the research procedures; and

'unexpected', ie an event that is not listed in the protocol as an expected occurrence

Reports of related and unexpected SAEs should be submitted within 15 days of the Chief Investigator becoming aware of the event, using the NUH SAE form for non-CTIMP studies.

Local investigators should report any SAEs as required by their Local Research Ethics Committee and/or Research & Development Office.

The Sponsor Contact Details for SAEs *are*:

- Email (RDSAE@nuh.nhs.uk)
- Hand delivered not mailed (R&I, NHSP, C Floor, South Block, QMC)
- Telephone (0115 9709049) if written report not immediately possible

Any queries please contact a member of staff in the Nottingham University Hospitals Research & Innovations department:

- Telephone: 0115 9709049
- Email: researchsponsor@nuh.nhs.uk

Participant removal from the study due to adverse events

Any participant who experiences an adverse event may be withdrawn from the study at the discretion of the Investigator.

7.9. DATA PROTECTION AND PATIENT CONFIDENTIALITY

Case Report Forms

Each participant will be assigned a trial identity code number for use on CRFs, other trial documents and the electronic database

CRFs will be treated as confidential documents and held securely in accordance with regulations. The investigator will make a separate confidential record of the participant's name, date of birth, local hospital number or NHS number, and Participant Trial Number (the Trial Recruitment Log), to permit identification of all participants enrolled in the trial, in accordance with regulatory requirements and for follow-up as required

CRFs shall be restricted to those personnel approved by the Chief or local Principal Investigator and recorded on the 'Trial Delegation Log.'

All paper forms shall be filled in using black ballpoint pen. Errors shall be lined out but not obliterated by using correction fluid and the correction inserted, initialled and dated.

The Chief or local Principal Investigator shall sign a declaration ensuring accuracy of data recorded in the CRF.

Source documents

Source documents shall be filed at the investigator's site and may include but are not limited to, consent forms, current medical records, laboratory results and records. A CRF may also completely serve as its own source data. Only trial staff as listed on the Delegation Log shall have access to trial documentation other than the regulatory requirements listed below.

Direct access to source data / documents

The CRF and all source documents, including progress notes and copies of laboratory and medical test results shall made be available at all times for review by the Chief Investigator, Sponsor's designee and inspection by relevant regulatory authorities (e.g. DH).

Data protection

All trial staff and investigators will endeavour to protect the rights of the trial's participants to privacy and informed consent, and will adhere to the Data Protection Act, 2018. The CRF will only collect the minimum required information for the purposes of the trial. CRFs will be held securely in a locked cupboard or cabinet, in a locked room. Access to the information will be limited to the trial staff and investigators and relevant regulatory authorities (see above). Computer held data including the trial database will be held securely and password protected. All data will be stored on a secure dedicated web server. Access will be restricted by user identifiers and passwords (encrypted using a one way encryption method).

Information about the trial in the participant's medical records / hospital notes will be treated confidentially in the same way as all other confidential medical information.

Electronic data will be backed up every 24 hours to both local and remote media in encrypted format.

7.10. INDEMNITY

As Nottingham University Hospitals NHS Trust is acting as sponsor for this study, NHS indemnity applies. NHS bodies are legally liable for the negligent acts and omissions of their employees. Non-negligent harm is not covered by the NHS indemnity scheme. The Nottingham University Hospitals NHS Trust, therefore, cannot agree in advance to pay compensation in these circumstances. In exceptional circumstances an ex-gratia payment may be offered

7.11. ACCESS TO THE FINAL STUDY DATASET

Trial data

Monitoring of trial data shall include confirmation of informed consent; source data verification; data storage and data transfer procedures; local quality control checks and procedures, back-up and disaster recovery of any local databases and validation of data manipulation. The research sponsor will ensure arrangements and systems are in place for the management and monitoring of research, taking a risk based approach. The monitoring and auditing of the conduct of the study will reflect that set out in the UK Framework for Health and Social Care 2017 and Sponsor SOP RES-013 and SOP QMS-004

Entries on CRFs will be verified by inspection against the source data. A sample of CRFs (10% or as per the study risk assessment) will be checked on a regular basis for verification of all entries made. In addition, the subsequent capture of the data on the trial database will be checked. Where corrections are required these will carry a full audit trail and justification.

Trial conduct

Trial conduct may be subject to systems audit of the Trial Master File for inclusion of essential documents; permissions to conduct the trial; Trial Delegation Log; CVs of trial staff and training received; local document control procedures; consent procedures and recruitment logs; adherence to procedures defined in the protocol (e.g. inclusion / exclusion criteria, correct randomisation, timeliness of visits); adverse event recording and reporting; accountability of trial materials and equipment calibration logs.

The Academic Supervisor, or where required, a nominated designee of the Sponsor, shall carry out a site system audit at least yearly and an audit report shall be made to the Trial Steering Committee.

Trial data and evidence of monitoring and systems audits will be made available for inspection by REC as required.

Authorised individuals

Analysis of the final dataset in accordance with the statistical plan will be performed by the research team at Nottingham University Hospitals and the University of Nottingham as documented in the delegation log.

7.12. RECORD RETENTION AND ARCHIVING

In compliance with the ICH/GCP guidelines, the Chief or local Principal Investigator will maintain all records and documents regarding the conduct of the study. These will be retained for at least 5 years or for longer if required. If the responsible investigator is no longer able to maintain the study records, a second person will be nominated to take over this responsibility.

The Trial Master File and trial documents held by the Chief Investigator on behalf of the Sponsor shall be finally archived at secure archive facilities at the Nottingham University Hospitals NHS Trust. This archive shall include all trial databases and associated meta-data encryption codes.

7.13. STATEMENT OF CONFIDENTIALITY

Individual participant medical information obtained as a result of this study are considered confidential and disclosure to third parties is prohibited with the exceptions noted above.

Participant confidentiality will be further ensured by utilising identification code numbers to correspond to treatment data in the computer files.

Such medical information may be given to the participant's medical team and all appropriate medical personnel responsible for the participant's welfare.

If information is disclosed during the study that could pose a risk of harm to the participant or others, the researcher will discuss this with the CI and where appropriate report accordingly.

Data generated as a result of this trial will be available for inspection on request by the participating physicians, the Nottingham University Hospitals representatives, the REC, local R&D Departments and the regulatory authorities.

8. DISSEMINATION POLICY

8.1. DISSEMINATION POLICY

Study results will be presented at national and international meetings and disseminated via peer reviewed journals. Participants will be provided with a plain English summary of results and a statement will be placed on the group's website.

8.2. AUTHORSHIP ELIGIBILITY GUIDELINES AND ANY INTENDED USE OF PROFESSIONAL WRITERS

The study report will be compiled without the use of any professional writers. Authorship will comply with ICMJE guidelines, namely all authors will comply with the following four criteria:

1. Substantial contributions to the conception or design of the work; or the acquisition, analysis, or interpretation of data for the work; AND
2. Drafting the work or revising it critically for important intellectual content; AND
3. Final approval of the version to be published; AND
4. Agreement to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

The study report will be drafted by the trial steering group and revised by the trial steering group. The trial steering group will be the primary authors of the paper.

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10. APPENDICIES

10.1. APPENDIX 1- REQUIRED DOCUMENTATION

Research sites will be required to provide documentation of the following prior to initiating recruitment

1. Complete delegation log
2. PIS on local headed paper
3. Consent forms on local headed paper
4. CV of PI
5. CV of research team
6. GCP Confirmation for all members of the research team

10.2. APPENDIX 2 – SCHEDULE OF PROCEDURES

Procedures	Visits (insert visit numbers as appropriate)				
	Screening	Recruitment	2 weeks	6 weeks	12 weeks (online)
Screening for eligibility	X				
Provision of PIS	X				
Informed Consent		X			
Baseline Scores		X			
Completion of CRF		X			
Provision of diary		X			
Collection of diary			X		
Removal of device			X		
Follow up scores			X	X	X

10.3. APPENDIX 3 – AMENDMENT HISTORY

Amendment No.	Protocol version no.	Date issued	Author(s) of changes	Details of changes made

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