Biostatistics Research Group,

Population Health Sciences Institute, Newcastle University

Stage 1 - Statistical Analysis Plan

SAP Version number: 1.0

SAP Date: 28/05/2021

This statistical analysis plan is based on protocol version 5.0 [28/10/2020]

IRAS Number: 244715
EudraCT Number: 2018-002633-38
NHS REC Reference: 18/YH/0428
Research Registry & Reference: ISRCTN37815869

RESEARCH SPONSOR
Sponsor Name: The Newcastle upon Tyne Hospitals NHS Foundation Trust
Sponsor Reference: 08781

RESEARCH FUNDER
Funder Name: European Commission: Horizon 2020
Funder Reference: 754825

Prepared by:

Name	Michael Cole	Role	Trial Statistician
Signature		Date	28/05/2021

Authorised by:

Name		Role	Senior Statistician
Signature		Date	
Name		Role	Chief Investigator / Clinical lead
Signature		Date	

This current version of the SAP and all preceding versions will be stored in the Statistical Section of the Trial Master File held by the IHS Biostatistics Research Group.

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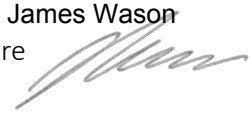
Name	James Wason	Role	Senior Statistician
Signature		Date	28-05-2021
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Name		Role	Trial Statistician
Signature		Date	

Authorised by:

Name		Role	Senior Statistician
Signature		Date	
Name	Michael Wright	Role	Chief Investigator / Clinical lead
Signature	*Michael Wright*	Date	21/06/2021

This current version of the SAP and all preceding versions will be stored in the Statistical Section of the Trial Master File held by the IHS Biostatistics Research Group.

This statistical analysis plan (SAP) provides a framework and guidelines for the statistical analysis and reporting of the *MCDS-Therapy* trial. **This SAP applies to Stage 1 of the *MCDS-Therapy* trial only.**

The SAP applies to a clean and validated dataset. Detailed information on data collection tools, data validation, consistency and accuracy checks and data storage and archiving can be found in the current version of the Data Management Plan (version 1.0 [29/03/2019]).

Any deviation from the methods outlined in this SAP will be documented in the statistical end of trial report. Example Tables, Figures and Listings are for illustrative purposes only and are subject to change.

This SAP, along with all other documents relating to the analysis of this trial, will be stored in the 'Statistical Section' of the Trial Master File (TMF) held and maintained by the PHSI Biostatistics Research Group. The final signed SAP will also be stored in section 16 of the main TMF (16. Statistics / 16.1 Final signed Statistical Analysis Plan).

Revision history

Version	Date	Changes made	Justification for change	Timing of change
1.0	28/05/2021	First version	NA	NA

Abbreviations

ABBREVIATION	DEFINITION
ADR	Adverse Drug Reaction
AE	Adverse Event
AR	Adverse Reaction
CNS	Central Nervous System
CBZ	Carbamazepine
CDMS	Clinical data management system
CI	Chief Investigator
COL10A1	Collagen Type X Alpha 1 Chain - Schmid Metaphyseal Chondrodysplasia
CRF	Case Report Form
CRL	Crown-rump length
CTA	Clinical Trial Authorisation
CTCAE	Common Terminology Criteria for Adverse Events
CTIMP	Clinical Trial of an Investigational Medicinal Product
DLT	Dose Limiting Toxicity
eCRF	Electronic Case Report Form
EMA	European Medicines Agency
EQ-5D-Y	EuroQoL 5 Dimension Youth Questionnaire
ER	Endoplasmic Reticulum
EudraCT	European Clinical Trials Database
GCP	Good Clinical Practice
GDPR	General Data Protection Regulation
GP	General Practitioner
HRQOL	Health Related Quality of Life
HRA	Health Research Authority
HTA	Human Tissue Authority
IB	Investigator Brochure
ICF	Informed Consent Form
ICH	International Conference on Harmonisation of technical requirements for
IDMC	Independent Data Monitoring Committee
IMP	Investigational Medicinal Product
ISF	Investigator Site File
ISRCTN	International Standard Randomised Controlled Trials Number
LPLV	Last Patient Last Visit
MCDS	Metaphyseal chondrodysplasia type Schmid
MedRA	Medical Dictionary for Regulatory Activities
MHRA	Medicines and Healthcare products Regulatory Agency
MTD	Maximum Tolerated Dose
NCTU	Newcastle Clinical Trials Unit
NHS	National Health Service
NIMP	Non-Investigational Medicinal Product
NUTH	The Newcastle upon Tyne Hospitals NHS Foundation Trust
PEDSQL	Paediatric Quality of Life Inventory Pain coping inventory/questionnaire
PI	Principal Investigator
PIC	Participant Identification Centre
PIS	Participant Information Sheet

QA	Quality Assurance
QC	Quality Control
QP	Qualified Person
R&D	Research & Development
REC	Research Ethics Committee
RSI	Reference Safety Information
SAE	Serious Adverse Event
SAR	Serious Adverse Reaction
SDV	Source Data Verification
SOP	Standard Operating Procedure
SmPC	Summary of Product Characteristics
SUSAR	Suspected Unexpected Serious Adverse Reaction
TMG	Trial Management Group
TSC	Trial Steering Committee
TMF	Trial Master File

Contents

1 Introduction

1.1 Background and rationale

The aim of the MCDS therapy trial is to evaluate the effect of carbamazepine (CBZ) on children with a diagnosis of Metaphyseal chondrodysplasia type Schmid (MCDS) with confirmed COL10A1 pathogenic mutation. There is currently no specific treatment for patients with MCDS, and patient care is based only on the management of symptoms.

The trial is based on the results of preclinical studies which support the efficacy of CBZ on cells and in mice with a COL10A1 mutation, both at a molecular level on the pathogenic mechanism reducing endoplasmic reticulum (ER) stress, and on growth and bone alignment in mice.

Carbamazepine is a well-established drug, which has been widely marketed throughout Europe since the 1960s and is routinely used in paediatric care for the treatment of epilepsy and neuropathic pain. It has a well-known safety profile. Based on clinical experience of the MCDS patient population there is no clinical reason to expect a different safety profile of CBZ on patients with MCDS compared to patients of similar ages treated with CBZ for epilepsy. Its effects on patients with MCDS have never been investigated.

The trial includes children with MCDS; to evaluate the effect of CBZ on growth and bone alignment it is necessary to evaluate this on patients who have not reached bone maturity.

MCDS is a very rare disease for which there are no existing natural history studies. Baseline data will be collected in the first year of the trial for all patients before starting administration of CBZ to allow comparison of pre and post treatment characteristics in each individual.

The trial is divided into an initial dose titration and tolerability stage (Stage 1) followed by a treatment stage (Stage 2). The choice of route of administration, dose and dosage regimen have been developed based on the use of CBZ in the treatment of epilepsy in children, for which CBZ is currently licenced.

The optimum dosing will be established during Stage 1. A small cohort of patients will be evaluated through a review of safety and tolerability using laboratory safety assessments, adverse events and physical examination data collected via telephone calls conducted weekly during the initial dose titrations, or clinic visits at week 2 then at 3 months and 6 months.

The efficacy of CBZ in the treatment of children with MCDS will be evaluated in full at the end of Stage 2 based on growth velocity, bone alignment, quality of life and pain using data collected every 3 months for 24 months.

1.2 Stage 1 Objectives

1.2.1 Primary objective

To assess the safety and tolerability of CBZ in the treatment of children with MCDS who are ambulant but have not yet reached skeletal maturity (open epiphyses).

To determine an appropriate dose of CBZ to inform the treatment of children with MCDS, type Schmid in Stage 2 of the MCDS-therapy trial.

1.2.2 Secondary objectives

To evaluate the effect of CBZ on pain in children with MCDS over 12 months.

2 Study Methods

2.1 Trial design

This is a two-stage open label phase I/IIa trial to assess repurposing of CBZ for the treatment of children with MCDS. The trial includes an initial dose determination stage (Stage 1) followed by long-term assessment of efficacy and safety at the chosen dose. The trial was initially designed to have a cohort size of 12 participants in Stage 1 however due to the COVID-19 pandemic and patient withdrawals this has been reduced. The overall sample size for Stages 1 and 2 combined remains the same (N=40).

All participants undergo a 12-month observational phase prior to drug administration during which baseline observation data will be collected at 0, 6- and 12-months post confirmation of eligibility. To allow for a temporary halt of the trial due to COVID -19, the observation period is extended to 18 months for some participants.

Stage 1 consists of a dose titration of CBZ in 5mg/kg increments to a pre-selected maximum dose of 20mg/kg with review of safety and tolerability over a 12-month period. A ***Stage 1 safety review*** will be conducted once the last patient on CBZ in Stage 1 has reached the 6-month time point. If a participant is withdrawn from the trial during Stage 1, they will not be replaced; the additional time that would be required is not compatible with the overall trial timeline. However, an additional participant might be recruited to Stage 2 if a participant is withdrawn during Stage 1. An ***interim safety review*** will be conducted when ***at least six*** patients in Stage 1 have reached their maximum tolerated dose or 20mg/kg, which will allow modification of the regimen if required.

Once a suitable dose is agreed, Stage 1 participants will continue CBZ treatment at this agreed dose until they reach 24 months treatment. Their data will be included in the final analysis following Stage 2, subject to IDMC consultation.

2.2 Study setting and patient population

Stage 1 of MCDS-Therapy is conducted at two centres within the UK: The Newcastle upon Tyne Hospitals NHS Foundation Trust Newcastle upon Tyne UK (NuTH) and Guys and St. Thomas' Hospital London UK (GSTFT).

It is expected that most patients involved in the trial will be identified amongst the patients in the care of the trial sites. Some patients may be referred to the trial sites by selected Participant Identification Centres (PICs), which are secondary or tertiary centres with expertise in rare diseases who might identify newly diagnosed patients not yet known by the trial sites.

2.3 Eligibility criteria

For a full list of inclusion and exclusion criteria see the protocol, version 5.0 (10 October 2020).

2.3.1 Inclusion criteria

Participants will be those with a proven diagnosis of MCDS; a pathogenic mutation in the gene encoding the Collagen Type X Alpha 1 Chain - Schmid Metaphyseal Chondrodysplasia (COL10A1) protein and ambulant at the time of consent/assent, with open epiphyses. Female patients of childbearing potential must have a negative pregnancy test at baseline and agree to regular pregnancy testing during the trial; sexually active female patients of childbearing potential are required to practice true abstinence.

2.3.2 Exclusion criteria

Patients will be excluded if they: have reached skeletal maturity; are known to have atrioventricular block; have had a prior adverse reaction to CBZ or a similar drug; have a history of bone marrow suppression/depression; have evidence of chronic hepatic or renal impairment; have acute intermittent porphyria; have received a monoamine oxidase inhibitor within 14 days of commencing therapy; or have abnormal blood screening results at the time of treatment initiation. Patients of Han Chinese, Thai and other Asian origins who carry the HLA-B*1502 allele are excluded, as are patients who have a planned surgery or planned osteotomy.

2.4 Randomisation and blinding

There is no randomisation or blinding in this trial.

2.5 Definition of outcome measures

2.5.1 Primary endpoints

The primary objectives for Stage 1, establishing the safety and tolerability of CBZ and determining an appropriate dose of CBZ for Stage 2, are assessed through a combination of laboratory safety assessments, adverse events, and physical examinations.

The primary endpoint of Stage 1 is occurrence of dose-limiting toxicity (DLT).

For the purposes of this trial, a DLT will be classed as an adverse event (AE), grade 3 or higher, of the following:

- anaemia
- haemolytic anaemia
- liver function impairment (increased alanine aminotransferase; increased alkaline phosphatase or increased blood total bilirubin)
- kidney function impairment (increased creatinine or chronic kidney disease),

as defined by the Common Terminology Criteria for Adverse Events (CTCAE), Version 5.0, Published: November 27, 2017. See appendix 4 of the protocol for grading details (also copied here in the Appendix, section 8).

Laboratory safety assessments include blood biochemistry - sodium, potassium, urea, creatinine, albumin, total bilirubin, ALP, ALT, AST, LDH, GGT; and a full blood count - haemoglobin, platelets, WBC, neutrophils, lymphocytes.

Physical examinations include assessment for normality of the following body systems:

- head, eyes, ears, nose, throat and neck
- CNS
- respiratory
- cardiovascular
- gastrointestinal
- abdomen
- musculoskeletal
- endocrine/metabolic
- haematopoietic/lymphatic
- neurological
- dermatological
- psychiatric/psychological

2.5.2 Secondary endpoints

Alteration from baseline in pain perception over 12 months as measured by:

- PedsQL Pain Coping Inventory
- PedsQL Pain Questionnaire

PEDSQL Pain Coping Inventory and PEDSQL Pain Questionnaire - to measure pain perception and pain coping strategies. (Varni, J.W., Waldron, S.A., Gragg, R.A., Rapoff, M.A., Bernstein, B.H., Lindsley, C.B., & Newcomb, M.D. (1996). Development of the Waldron/Varni Pediatric Pain Coping Inventory. Pain, 67, 141-150.

https://www.pedsql.org/about_pedsql.html

Separate versions of the PedsQL for completion by the subject (for children aged 5 and over) and for the parent(s)/ legal guardian(s) acting as a proxy for the child are used. When the child is capable of self-completing an age-appropriate version, as assessed by parental and clinician judgement, they will do so. However, if the child is deemed incapable, the proxy version is used alone. It is recommended where possible, the same parent/caregiver should complete the questionnaires at all visits. Thus, two questionnaires, one from the child and one from the parent/guardian, could be available for analysis at each time point.

2.5.2.1 PedsQL Pediatric Pain Coping Inventory

Composed of 41 questions comprising 5 dimensions:

1. Cognitive Self-Instruction
2. Problem-Solving
3. Distraction
4. Seeks Social Support
5. Catastrophizing / Helplessness

A 3-point Likert scale from 0 (Never) to 2 (Often) is used to score each question. Total score is calculated as the sum of all question scores divided by the number of questions answered. If more than 50% of the questions in the scale are missing, the score should not be computed. If 50% or more of the questions are completed: the mean of the completed questions is imputed for those that are missing.

2.5.2.2 PedsQL Pediatric Pain Questionnaire

The Pediatric Pain Questionnaire is composed of 3 items. Questions on "*how you feel now" and "worst pain you had this week"* scored on a VAS and converted to a score of 0 (no pain) to 100 (Severe pain). The third item refers to the localisation of pain and is not scored.

2.5.2.3 PedsQL™ Generic Core Scales Version 4.0 Short Form (SF15)

Used to capture participant QoL. ***This is not a secondary outcome measure for Stage 1.***

Composed of 15 questions comprising 4 dimensions:

1. Physical functioning
2. Emotional functioning
3. Social functioning
4. School functioning

A 5-point Likert scale from 0 (Never) to 4 (Almost always) is used to score each question except for the self-reported version completed by young children (ages 5-7) which uses a 3-point scales: 0 (Not at all), 2 (Sometimes) and 4 (A lot). Questions are reversed scored and linearly transformed to a 0-100 scale as follows: 0=100, 1=75, 2=50, 3=25, 4=0.

Score by Dimensions: If more than 50% of the questions in the scale are missing, the scale scores should not be computed. Mean score is calculated as the sum of the question scores divided by the number of questions answered.

Psychosocial Health Summary Score = Sum of the question scores divided by the number of questions answered in the Emotional, Social, and School Functioning Scales.

Physical Health Summary Score = Sum of the question scores divided by the number of questions answered in the Physical Functioning Scale.

If more than 50% of the questions in the scale are missing, the score should not be computed. If 50% or more of the questions are completed: the mean of the completed questions is imputed for those that are missing.

2.5.3 Study assessments

DLTs are identified through assessment of AEs. Participants are asked at each trial visit or telephone call whether they have experienced any AEs, specifically at the *Baseline observation* visits 1,2 & 3 (0, 6 and 12 months); *Dose titration* visits 1.1, 1.2, 1.3, 1.4, 1.5 & 1.6 (0, 2 weeks and 3, 6, 9 and 12 months); *Dose evaluation telephone calls* (weekly at 1-11 weeks post initiation of CBZ).

Any AEs reported during trial visits, telephone calls or that come to the attention of the trial team by other means, are recorded in the patient's medical notes and the eCRF, within the trial MACRO database. During the trial, participants are instructed to record any AEs in their MCDS-Therapy Patient Diary (Baseline or Dose Titration) diary for use during trial telephone calls and trial visits. AEs also include recording of any incidence of surgical intervention to manage MCDS-related symptoms.

A blood sample for laboratory safety assessments will be taken at *Baseline observation* and *Dose titration* visits as for AE reporting. Physical examinations are performed at the same time points.

Pain questionnaires (PEDSQL Pain Coping Inventory and PEDSQL Pain Questionnaire) will be administered at *Baseline observation* and *Dose titration* visits as for AE reporting.

Baseline observation visits 2 & 3 (6 and 12 months) plus Dose titration visits 1.3, 1.4, 1.5 & 1.6 (3, 6, 9 and 12 months) have a ± 14-day allowable visit window. Dose titration visits 1.2 (at 2 weeks) have a ± 1-day window. Dose evaluation telephone calls are weekly as required.

The PedsQL™ Generic Core Scales Version 4.0 Short Form (SF15) is used to capture participant QoL and is administered at Baseline observation and Dose titration visits. ***This is not a secondary outcome measure for Stage 1.***

To aid with study participant retention due to COVID 19, the 12-month visit window can be up to 12 months plus a further 8 weeks.

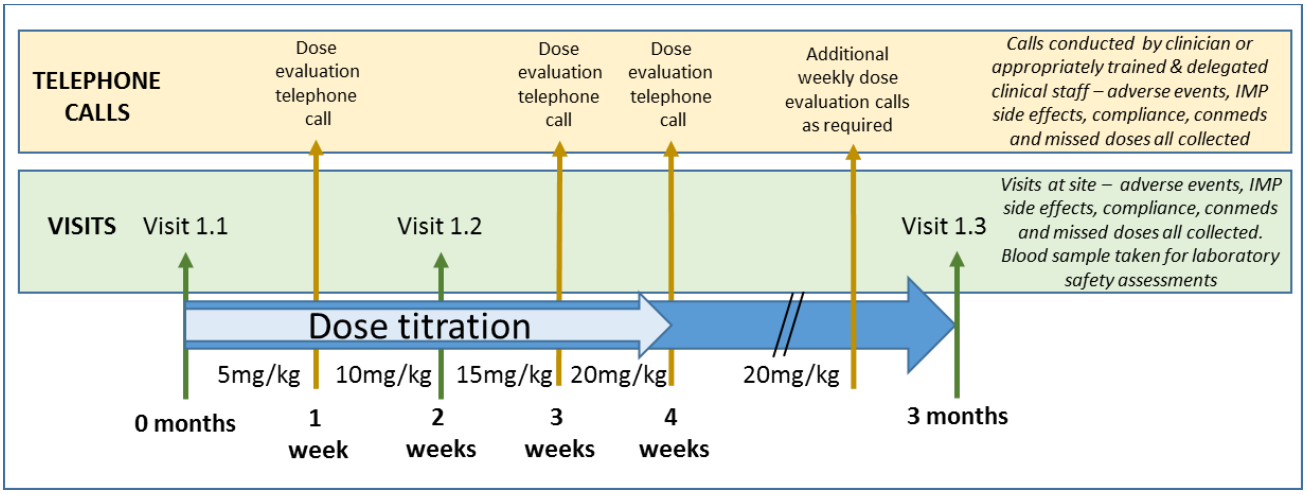
For the purpose of the ***Stage 1 safety review*** and ***interim safety review*** all visits regardless of whether they occurred within the allowable visit window will be used to assess safety and tolerability of treatment.

2.5.4 Sample size and power

The sample size was chosen on the basis of the feasible number of patients that could be recruited to the trial in the specified time period. No statistical criteria were used to choose the sample size.

2.5.5 Study Diagram/Flowchart

Overview of design of dose titration & tolerability period from month 0 to 3



2.6 COVID-19

2.6.1 Additional site lockdowns

If additional local lockdowns occur during the trial, there are several changes that can be implemented (if required) to try and ensure participant safety and compliance with the trial protocol.

2.6.2 Study visits

It is expected that participant visits will take place as per protocol schedule. However, if a face to face visit is not taking place due to COVID-19 restrictions or lockdowns, the PI will contact the patient at the time of the original scheduled visit (3 monthly),and carry out feasible assessments (i.e. SAE check, concomitant medication check, dose evaluation, medication counselling, remote completion of questionnaires and arrange laboratory safety assessments). Follow up calls will take place as per protocol for weeks 1-11.

2.6.3 Participant weight/dose calculation

To ensure participants and families spend the least amount of time in hospital, participants will not be required to have their weight taken at each of the dose titration visits. Participant weight will be mandatory every 6 months and this weight used to calculate the dosage for the next 6 months of study IMP.

2.6.4 Study medication

If required and where possible study medication will be prescribed in 6-month intervals. This will ensure that less time is required for the study visits. It will also be discussed with sites whether the study IMP can be couriered/posted to participants.

2.6.5 Laboratory Safety Assessments

Participant safety bloods will still be required at the 3 monthly intervals. Sites can discuss whether these safety bloods can be taken by the participant's GP or local paediatrician, but only where these results are readily available to the study team. If sites wish to utilise local GPs/ local paediatricians for safety bloods, they must notify the central team in advance, where possible, so the appropriate set up processes can be completed.

Under extenuating circumstance, if safety bloods cannot be completed, it will be considered if it is appropriate for the participant to be withdrawn from IMP. Each case will be reviewed on an individual basis by the CI, Sponsor and the TMG, and it will be decided whether it would be appropriate to restart the participants IMP, once safety bloods become feasible. The IDMC may also be consulted.

2.6.6 COVID-19 Isolation

It is expected that participant visits will take place as per protocol schedule. However, if a participant or someone they live with has symptoms or has tested positive for COVID-19 and is required to self-isolate the study visit window can be extended by 2 weeks.

3 Statistical considerations

3.1.1 Timing of analyses

An ***interim safety review*** will be conducted when ***at least six*** patients in Stage 1 have reached their maximum tolerated dose or 20mg/kg, which will allow modification of the regimen if required. The Stage 1 SAP (this document) will be agreed prior to the IDMC reviewing safety data from the first six patients.

Once the last patient on CBZ in Stage 1 has reached the 6-month time point, a similar safety review, the ***Stage 1 safety review,*** will be conducted to formally agree the IMP dose regimen to be implemented in Stage 2 of the study.

3.1.2 Interim analyses, data monitoring and stopping guidelines

The ***interim safety review*** will be led by the CI, Sponsor will be consulted and agreement from the trial IDMC will be sought. The review will be based on laboratory safety assessments, adverse events, physical examinations and pain questionnaires. Treatment of the remaining Stage 1 participants will not be delayed while this review is ongoing.

Data presented to the IDMC at the ***interim safety review***, and at the ***Stage 1 safety review***, will include the number and reason for any DLTs, laboratory safety assessments, abnormal physical examinations, pain scores and adverse events. The IDMC will recommend, or not, continuation of the trial to the TSC.

There are no formal stopping rules. Participants will be monitored for occurrence of DLTs during the Stage 1 trial visits. If more than one participant experiences a DLT during the Stage 1 dose titration and tolerability, the dose-regimen will be reviewed by the TMG, input from the IDMC will be sought and appropriate modifications made.

3.1.3 Analysis populations

The ***interim safety review*** and the ***Stage 1 safety review*** will include all patients who have completed the baseline observation period and have received at least one dose of CBZ.

Adverse events will be reported for all patients who start their baseline period.

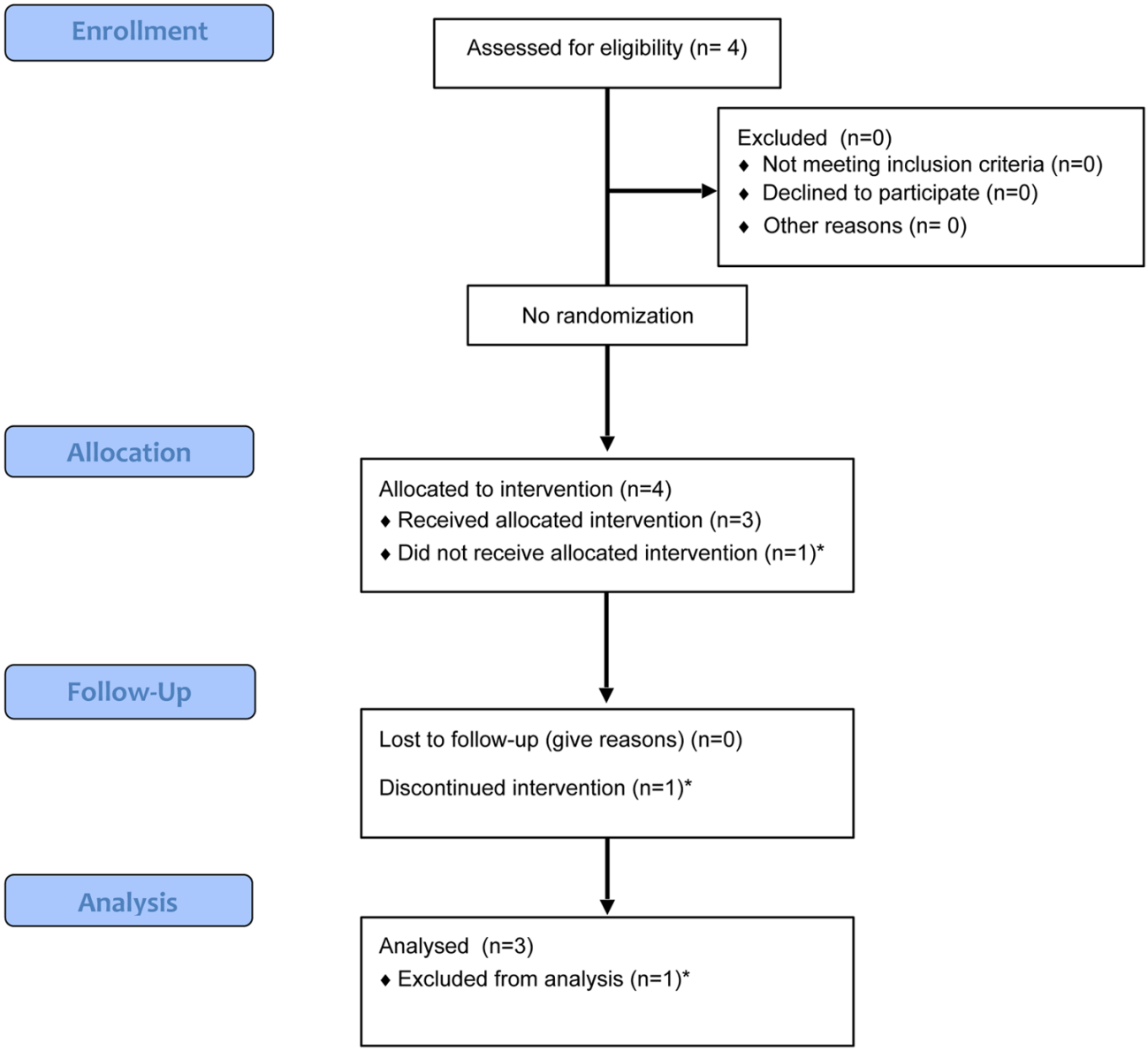
4 Study Population

4.1.1 Participant flow through trial

Patient flow through the trial will be presented using a CONSORT diagram (example below). Information will be provided on numbers and reasons (where appropriate) for: screened patients not being eligible; eligible patients not being consented; patients found to be ineligible after consent; patients deviating from allocated

treatment; patients not evaluable for the primary endpoints; withdrawal from follow-up; withdrawal of consent and all protocol violations.

Example Figure: CONSORT flow diagram



4.1.2 Screening, eligibility and recruitment

Screening data, number assessed for eligibility, number not meeting eligibility criteria (with reasons), number declining participation (with reasons) and any other reasons for not entering the study will be reported.

4.1.3 Protocol deviations

Protocol deviations including missed safety assessments; incorrect dose escalations; missed study assessments; participants not using IMP as prescribed; and, lack of compliance will be reported.

Example Table: Line listing of protocol deviations

Trial ID	Deviation type	Major/minor	Details
	Ineligible/Consent/Treatment not given as per-protocol/Withdrawal from treatment by investigator/Withdrawal from treatment due to participant choice/Use of prohibited concomitant medication/Study procedures/Visit schedule		

4.1.4 Follow-Up

Participants have the right to withdraw from the trial at any time without having to give a reason. If a trial participant withdraws from the trial all data collected to the point of withdrawal will be retained. Consent/assent will be sought to allow this.

The number of patients withdrawing from trial specific follow-up visits, the number withdrawing from any follow-up data to be collected and the number lost to follow up, with timing of withdrawal will be reported.

4.1.5 Baseline characteristics

Demographic, clinical and surgical characteristics recorded at the first visit during the baseline observation period will be summarised. Categorical data will be presented as frequencies and percentages, continuous data will be presented as number of patients, mean, median, standard deviation, minimum, maximum and range.

Demographic characteristics: age, sex, height (or length if <2 years old), sitting height in children >=5 years old, crown-rump length (CRL) in children <5 years old.

Clinical characteristics: age at onset of first symptoms, pain at diagnosis of MCDS (yes/no), current frequency of pain, joints affected with pain, surgical interventions to manage MCDS symptoms (yes/no), bone age, head/neck of femur angle.

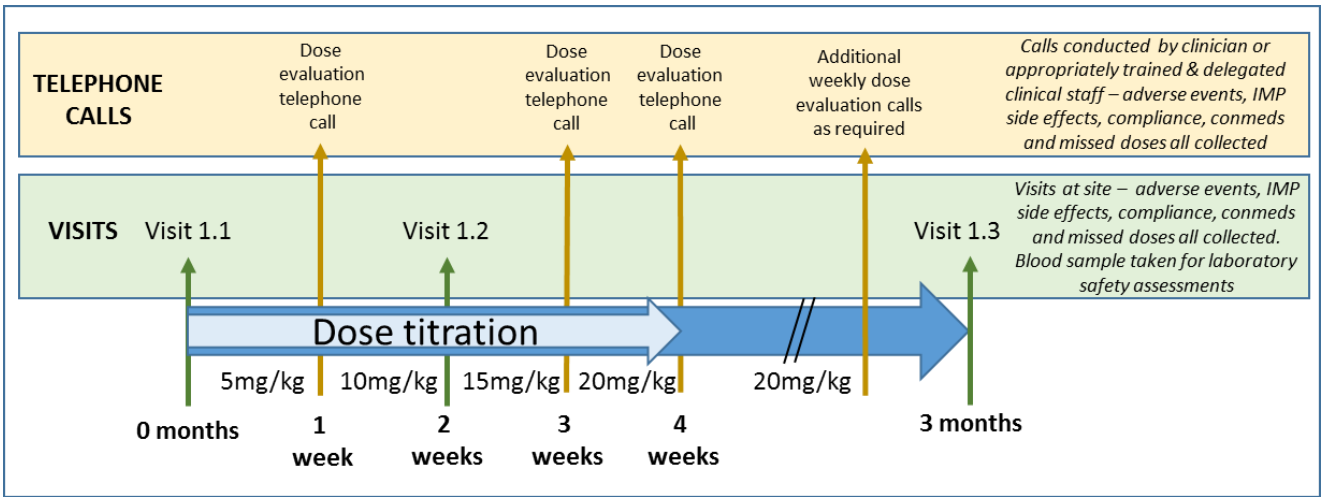
Example Table: Patient demographics at baseline

	n=X	
Sex Male Female		
Age (years) Median Mean		
Median BMI		
Blood pressure (mmHg) Systolic Diastolic		

4.1.6 Treatment received

The trial follows a design that titrates the dose of CBZ to a pre-specified optimum, based on clinical considerations. The trial aims for all Stage 1 participants to reach a dose of 20mg/kg by the end of the 12-month Stage 1 period. Stable dose will be confirmed when a participant reaches a dose of 20mg/kg or the maximum dose at which they are able to tolerate any CBZ-related side effects, their maximum tolerated dose (MTD), and has a period of ***at least 8 weeks*** with no significant IMP related adverse events/side effects.

Overview of design of dose titration & tolerability period from month 0 to 3



Participants will be initiated on a daily CBZ dose of 5mg/kg/day, divided into two separate doses. If the current dose is tolerated following seven days of treatment, the daily dose will be increased by 5mg/kg/day for a further seven days. The dose level will be increased every seven days until a maximum dose of 20mg/kg/day or MTD is achieved.

Participants attend a site trial visit at week 2 at which time blood samples are taken to conduct the laboratory safety assessments. When the laboratory results are available, a follow-up phone call will be made to the participant to discuss any requirement to alter their dose regimen.

In addition to the *week 2* visit, at weekly intervals and until they reach a dose they can tolerate, participants will receive a dose evaluation telephone call to determine if the current dose has been tolerated (additional calls can be conducted if required). Participants are asked to provide information regarding drug side effects, AEs, changes to concomitant medication, drug compliance and details of missed doses; a Diary is provided in which to record this information between calls/visits. All dosage decisions, IMP side effects, AEs and any changes to concomitant medication noted during the dose evaluation calls are recorded in the appropriate eCRF within the trial MACRO database.

If the participant reports side effects/AEs of significant concern to the clinician which are suspected to be related to the IMP, they are invited for further laboratory safety blood assessments and review. If the participant reports severe side effects which prevent adherence to the trial protocol or in the opinion of the clinical investigator deem the participant not suitable to continue participation, then CBZ will be permanently discontinued and the patient withdrawn from the trial. Participants who do not tolerate dosing will be kept on a lower dosing or dosing reduced.

For each participant, the following will be reported:

1. Initial prescribed daily dose (mg/kg) of CBZ and form (tablet/suspension).

2. Daily Dose (mg/kg) and prescribed daily dose (mg or ml, depending on CBZ form) will be shown graphically over the treatment period.

3. Compliance will be reported as the number of missed CBZ doses reported at each visit or dose evaluation phone call together with the percentage of the prescribed daily dose taken.

4. MTD

5 Analysis methods

5.1.1 Primary analysis

The primary objective of Stage 1 is to assess the safety and tolerability of carbamazepine (CBZ) and to determine an appropriate dose of CBZ to inform treatment in Stage 2. The primary endpoint of Stage 1 is occurrence of DLT defined in section 2.5.1.

If there are DLTs we will estimate the probability of DLT as the sample proportion. A confidence interval for this probability will be found using the Clopper-Pearson method.

The number of DLTs will be reported by participant. Details of each DLT will be reported including type of adverse event (anaemia, haemolytic anaemia, liver function impairment or kidney function impairment) and CTCAE grade.

All laboratory safety assessments outside the appropriate local normal reference range will be reported at a participant level.

All abnormal physical examinations will be reported at a participant level together with any further details provided.

For further safety outcome reporting see section 6; for details of CBZ treatment received, see section 4.1.6.

5.1.2 Analysis of secondary outcomes

To evaluate the effect of CBZ on pain in children with MCDS over 12 months. Stage 2 is anticipated to commence before all Stage 1 participants have completed 12 months follow-up, hence the complete pain data will be unavailable at the time of the ***Stage 1 safety review***. Available data at that time will be reported. Full analysis will be completed when 12 months follow-up is available for all participants.

PedsQL Pediatric Pain Coping Inventory total score completed by child/parent will be reported at each visit by participant.

PedsQL Pediatric Pain Questionnaire VAS (0-100) completed by child/parent will be reported at each visit by participant.

6 Safety

All AEs occurring from the point of consent to the end of trial participation are recorded in the trial MACRO database eCRF. AEs are assessed for their relationship to treatment and coded as: Unrelated, Unlikely, Possible, Probable, Definitely or Not assessable. Severity is graded according to the Common Terminology Criteria for Adverse Events (CTCAE), Version 5.0, Published: November 27, 2017.

Grading is based on the following general guideline:

- **Grade 1 Mild**; asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated.
- **Grade 2 Moderate**; minimal, local or non-invasive intervention indicated; limiting age-appropriate instrumental Activities of Daily Living (ADL).
- **Grade 3 Severe** or medically significant but not immediately life-threatening; hospitalization or prolongation of hospitalization indicated; disabling; limiting self-care ADL.
- **Grade 4 Life-threatening** consequences; urgent intervention indicated.
- **Grade 5 Death** related to AE.

AEs are coded using the Medical Dictionary for Regulatory Activities (MedDRA) version 22.0. The Clinical Data Management System (CDMS) auto-codes the majority of AEs to the latest version of the MedDRA dictionary. If this is not possible, AEs are coded from the MedDRA dictionary by the CI.

SARs occurring from the first participant's dose of IMP to the last participant's end of follow-up are recorded on the trial MACRO database eCRF. Following this defined active monitoring period for SARs, investigators are still required to report any SARs or SUSARs which are brought to their attention.

For each SAE the following information is collected:

1. Full details in medical terms and case description
2. Event duration (start and end dates, if applicable)
3. Action taken
4. Outcome
5. Seriousness criteria
6. Causality in the opinion of the investigator
7. Whether the event is considered expected or unexpected in accordance with the approved RSI if a causal relationship is suspected.

6.1.1 Adverse events

The number of adverse events and adverse reactions (those possibly, probably or definitely related to treatment) and the worst grade AE and AR per participant will be summarised descriptively.

Example table: Number of events per participant

	Mean (SD)	Median (Q1, Q3)	Min, Max
All adverse events			
Adverse reactions (possibly, probably, definitely)			

Example table: Worst grade reported per participant (number, %)

	None	Mild	Moderate	Severe
All adverse events				
Adverse reactions (possibly, probably, definitely)				

The number of participants reporting each type of adverse event (by MedDRA System Organ Class) will be tabulated.

Example table: Number and percentage of participants affected by each adverse event, reported by System Organ Class

Event term	Total		Mild		Moderate		Severe	
	N	%	N	%	N	%	N	%
Blood and lymphatic system disorders								
Cardiac disorders								
Endocrine disorders								
Eye disorders								
Gastrointestinal disorders								
General disorders and administration site conditions								
Immune system disorders								
Infections and infestations								
Injury, poisoning and procedural complications								
Investigations								
Metabolism and nutrition disorders								
…..								
…..								

The number and percentage of patients experiencing at least one high grade event (grade 3/4/5).

A line listing of all AEs will be reported, by participant, including severity, seriousness and relationship to study treatment.

EudraCT reporting of AEs requires reporting to be split by serious and non-serious adverse events - number of participants affected and the number of occurrences for each MedDRA System Organ Class (SOC). For serious adverse events, number of occurrences causally related to trial treatment is also required.

6.1.2 Serious adverse events

A chronological listing of serious adverse events (SAEs) will be presented. The number of SAEs and the number of patients reporting at least one SAE will be reported.

Patient ID	Description	MedDRA Preferred Term	Severity	Relationship to treatment	Onset Date	Date of resolution	Duration	Seriousness criteria	Action taken in relation to SAE	Outcome

7 Statistical Software

Data will be output directly from MACRO into a STATA format by the NCTU at time-points agreed by the TMG. Statistical analyses will be carried out by the Trial Statistician at the PHSI BRG using Stata version 14. All programs and output will be stored in the School Statistics folder on the PHSI server.

8 Appendix: CTCAE grading relevant to MCDS-Therapy IMP DLTs

MedDRA Code	MedDRA SOC	CTCAE Term	Grade 1	Grade 2	Grade 3	Grade 4	Grade 5	Definition	
10002272	Blood and lymphatic system disorders	**Anaemia**	Haemoglobin (Hgb) <LLN - 10.0 g/dL; <LLN - 6.2 mmol/L; <LLN - 100 g/L	Hgb <10.0 - 8.0 g/dL; <6.2 - 4.9 mmol/L; <100 - 80g/L	Hgb <8.0 g/dL; <4.9 mmol/L; <80 g/L; transfusion indicated	Life-threatening consequences; urgent intervention indicated	Death	A disorder characterized by a reduction in the amount of haemoglobin in 100 ml of blood. Signs and symptoms of anaemia may include pallor of the skin and mucous membranes, shortness of breath, palpitations of the heart, soft systolic murmurs, lethargy, and fatigability.	
1019491	Blood and lymphatic system disorders	**Haemolysis**	Laboratory evidence of haemolysis only (e.g., direct antiglobulin test; DAT; Coombs'; schistocytes; decreased haptoglobin)	Evidence of hemolysis and >=2 g decrease in haemoglobin	Transfusion or medical intervention indicated (e.g., steroids)	Life-threatening consequences; urgent intervention indicated	Death	A disorder characterized by laboratory test results that indicate widespread erythrocyte cell membrane destruction.	
10001551	Investigations	**Alanine aminotransferase increased**	>ULN - 3.0 x ULN if baseline was normal; 1.5 - 3.0 x baseline if baseline was abnormal	>3.0 - 5.0 x ULN if baseline was normal; >3.0 - 5.0 x baseline if baseline was abnormal	>5.0 - 20.0 x ULN if baseline was normal; >5.0 - 20.0 x baseline if baseline was abnormal	>20.0 x ULN if baseline was normal; >20.0 x baseline if baseline was abnormal	-	A finding based on laboratory test results that indicate an increase in the level of alanine aminotransferase (ALT	Also consider Hepatobiliary disorders: Hepatic failure

								or SGPT) in the blood specimen.	
10001675	Investigations	**Alkaline phosphatase increased**	>ULN - 2.5 x ULN if baseline was normal; 2.0 - 2.5 x baseline if baseline was abnormal	>2.5 - 5.0 x ULN if baseline was normal; >2.5 - 5.0 x baseline if baseline was abnormal	>5.0 - 20.0 x ULN if baseline was normal; >5.0 - 20.0 x baseline if baseline was abnormal	>20.0 x ULN if baseline was normal; >20.0 x baseline if baseline was abnormal	-	A finding based on laboratory test results that indicate an increase in the level of alkaline phosphatase in a blood specimen.	
10005364	Investigations	**Blood bilirubin increased**	>ULN - 1.5 x ULN if baseline was normal; > 1.0 - 1.5 x baseline if baseline was abnormal	>1.5 - 3.0 x ULN if baseline was normal; >1.5 - 3.0 x baseline if baseline was abnormal	>3.0 - 10.0 x ULN if baseline was normal; >3.0 - 10.0 x baseline if baseline was abnormal	>10.0 x ULN if baseline was normal; >10.0 x baseline if baseline was abnormal	-	A finding based on laboratory test results that indicate an abnormally high level of bilirubin in the blood. Excess bilirubin is associated with jaundice.	Also consider Hepatobiliary disorders: Hepatic failure
10011368	Investigations	**Creatinine increased**	>ULN - 1.5 x ULN	>1.5 - 3.0 x baseline; >1.5 - 3.0 x ULN	>3.0 x baseline; >3.0 - 6.0 x ULN	>6.0 x ULN	-	A finding based on laboratory test results that indicate increased levels of creatinine in a biological specimen.	Also consider Renal and urinary disorders: Acute kidney injury
10064848	Renal and urinary disorders	**Chronic kidney disease**	eGFR (estimated Glomerular Filtration Rate) or CrCl (creatinine clearance) <LLN - 60 ml/min/1.73 m2 or proteinuria 2+ present; urine protein/creatinine >0.5	eGFR or CrCl 59 - 30 ml/min/1.73 m2	eGFR or CrCl 29 - 15 ml/min/1.73 m2	eGFR or CrCl <15 ml/min/1.73 m2; dialysis or renal transplant indicated	Death	A disorder characterized by gradual and usually permanent loss of kidney function resulting in renal failure.	