Effect of creatine monohydrate on functional muscle strength and muscle mass in children with FSHD: a multi-centre, randomised, double-blind placebo-controlled crossover trial.

Statistical Analysis Plan

Version 1
9 March 2023

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Authors:
Ian Woodcock[1,2,3]

Investigators:
Principal Investigator: Dr Ian Woodcock[1,2,3]

1. Department of Paediatrics, University of Melbourne, Parkville, Victoria, Australia
2. Department of Neurology, The Royal Children's Hospital, Parkville, Victoria Australia
3. Murdoch Children's Research Institute, Parkville, Victoria, Australia

Signature Page

This statistical analysis plan is approved by:

9 March 2023

Dr Ian R Woodcock
Principle Investigator
Author of Statistical Analysis Plan v1

CONTENTS

List of Abbreviations

AE	Adverse Event
CI	Confidence Interval
CRF	Case Report Form
DSMC	Data Safety Monitoring Committee
FSHD	Facioscapulohumeral muscular dystrophy
FSH-COM	FSHD Composite Outcome Measure
FSH-HI	FSHD Health Index
GCP	Good Clinical Practice
ITT	Intent-To-Treat
MFM	Motor Function Measure for Neuromuscular Diseases
NMD	Neuromuscular Disease/s
PUL	Performance of the Upper Limb Score
SAE	Serious Adverse Event
SD	Standard Deviation
SE	Standard Error
SSI	Significant Safety Issue
SUSAR	Suspected Unexpected Serious Adverse Reaction

1. ADMINISTRATIVE INFORMATION

Protocol: Version 8 dated 8 April 2021
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1.1 Document Version History

Version Date	Version	Author	Signature	Change Description	Reason/Comment
	1.0			Initial release.	Not applicable.

2. STUDY SYNOPSIS

This will be a randomised multicenter placebo-controlled, cross-over double-blind trial. ParticipantParticipants will include children with genetically confirmed FSHD aged 5-18 years. All eligible patients consenting to be enrolled into the trial will undergo baseline testing then will be randomised into two treatment groups. Group 1 will receive creatine monohydrate (100mg/kg, to a maximum of 10g daily) for three months. They will then have a six week wash-out period, followed by a second three month treatment period with placebo. Group 2 will receive placebo for three months followed by a six week washout period followed by creatine monohydrate for 3 months. Each patient will undergo clinical assessments and study safety assessments at the beginning and end of each treatment period. Each participant will therefore act as his/her own control.

Study assessments will include the Motor Function Measure for neuromuscular diseases (MFM), quantitative muscle strength testing of muscle groups typically affected in FSHD, assessment of functional tasks (including the Performance of the Upper Limb Score (PUL) and six-minute walk test (6MWT)), activities of daily living, patient-reported outcome measures, body composition assessments and muscle MRI and ultrasound. Safety data will also be collected at each visit.

2.1. Primary Objective

The primary objective of this trial is to compare in children with FSHD the change in strength-related motor function following treatment with creatine monohydrate to treatment with placebo, as measured by the Motor Function Measure (MFM) for neuromuscular diseases, from baseline to 12 weeks.

2.2. Secondary Objectives

The secondary objectives of this trial are, in children with FSHD:

1. To compare changes in secondary outcome measures of muscle strength, endurance, upper limb function, quality of life and muscle MRI parameters from baseline to 12 weeks following treatment with creatine monohydrate, versus placebo.
2. To assess the safety and tolerability of creatine monohydrate supplementation in children with FSHD over a 12-week period.

Secondary outcome measures are: quantitative muscle strength testing of muscle groups typically affected in FSHD, assessment of functional tasks (including the PUL scale and six-minute walk test), activities of daily living, patient-reported outcome measures, FSHD clinical severity scale, FSH-COM composite assessment tool, and muscle MRI.

2.3. Study Population

2.3.1 Number of Participants

We aim to recruit twenty children aged between 5 and 18 years old with genetically confirmed FSHD.

2.3.2 Eligibility Criteria

Participants will be assigned to a randomised study treatment only if they meet all inclusion criteria and none of the exclusion criteria.

2.3.3 Inclusion criteria

Each participant must meet all of the following criteria to be enrolled in this study:

- Is between the ages of 5 and 18 years inclusive at the time of randomisation
- Has a confirmed genetic diagnosis of Facioscapulohumeral Muscular Dystrophy (FSHD) type 1 or 2 or has a first degree relative with genetically confirmed FSHD and had clinical features in keeping with this diagnosis as determined by an expert in the field. *(In Australia all genetic testing for FSHD occurs in one of three testing laboratories. If genetic testing for an individual participant was not carried out at one of these recognised laboratories, then that participants genetic results will be reviewed by the study investigators in consultation with a geneticist and a representative from the recognised testing laboratories. A decision will be made whether repeat testing at one of the recognised testing laboratories is required on a case by case basis.)*
- Has a legally acceptable representative capable of understanding the informed consent document and providing consent on the participant's behalf.
- Participant and parent/guardian are willing and able to comply with scheduled visits, study drug administration plan, and study procedures.

2.3.4 Exclusion criteria

Participants meeting any of the following criteria will be excluded from the study:

- Has clinically significant elevation in plasma creatinine level.
- Unexplained persistent hypertension at screening. *(For this study hypertension is defined as blood pressure >130 mmHg in patients aged 5 to 11 years old and >140 mmHg in patient over 12 years old. If participant's blood pressure at screening is in the above range for hypertension, it should be repeated three times over the course of an hour and the average reading recorded. If the level was still within the above range then the participant should be recalled for a second visit within a week and the above procedure repeated. If the blood pressure is within the normal limits during repeat testing then the participant can remain in the study. If on repeated testing as described above the participant is found to have hypertension as defined above they would be a screening fail and should be excluded from the study. In this instance the participant's treating team should be made aware so that arrangements could be made for investigating the cause of the hypertension.) These ranges are taken from the Victorian Children's Tool for Observation and Response (https://www.victor.org.au/victor-charts/)*
- Has a prior diagnosis of acute or chronic renal failure.
- Has a known hypersensitivity to creatine monohydrate or maltodextrin placebo.
- Patients already taking any medications to increase muscle bulk or strength or concomitant use of regular sodium valproate, corticosteroids or beta agonists such as salbutamol.
- Dairy intolerance or allergy

2.4. Design and Intervention

This study is a multi-centre, randomised placebo-controlled, double-blind, crossover trial comparing creatine monohydrate against placebo. Participants will be randomised to study groups at a 1:1 ratio. As this is a crossover trial, each participant will receive active agent and placebo, in two distinct treatment periods over the course of the study period. Due to the relative rarity of FSHD in the paediatric population and the wide range of clinical severity, the study population is likely to be small and heterogeneous. In order to maximise the study sample size, participants will be recruited from four Australian major centres of excellence for care of children with FSHD. In previous studies a clinical effect from creatine supplementation has been evident within three months, and so the cross-over design was chosen for this study. The cross-over design allows for comparisons to be made between and within participants.

A washout period between treatment periods has been factored into the study design, to negate any potential carry over effects from one treatment period to the other. The study design includes a washout period of six weeks to ensure adequate time for drug clearance. This will be more than adequate given the serum half-life of creatine monohydrate is 20-172 minutes.(3)

Despite the good safety record of creatine monophosphate use, safety data will be collected throughout the study at every study visit and a safety assessment will be performed at the halfway mark of the study. Parents will be educated to contact the study investigators and report any adverse events.

2.5. Randomisation and Blinding

2.5.1 Randomisation Procedures

A randomisation schedule was created by the MCRI Clinical Epidemiology and Biostatistics Unit (CEBU).

2.5.2 Blinding arrangements

The study will be double blinded; however, one sub-investigator will remain unblinded to the study allocation to facilitate necessary processes. This sub-investigator will not be involved in study assessments, or the initial data analysis.

The group allocation will be provided by CEBU via locked data file to the unblinded sub-investigator who will communicate the appropriate recipe to the formula room staff. The recipe will be provided in hardcopy and will remain in a locked filing cabinet at Monash University, Department of Nutrition, Dietetics and Food. Participants will receive individual shake sachets labelled only with their randomisation code and details as listed above.

2.6. Sample Size

FSHD within the paediatric population is a rare and heterogeneous condition. It is estimated that the maximum number of participants eligible to be enrolled into the study across Melbourne, Sydney and Brisbane will be thirty to forty patients. The primary outcome measure (Motor Function Measure for Neuromuscular Disease) does not have a widely accepted published and verified minimal clinically important difference (MCID) or standard deviation, to allow accurate power calculations to be made. However, a single study of a heterogeneous group of patients with different types of NMD found the annual mean change in MFM score to be 2.4 with a standard deviation of 5.5. In seventeen

patients with FSHD the mean score change was 1.5 +/- 3.4.(4) It is difficult to extrapolate this exactly but an estimation would be that twenty participants would power this study to 80% for an effect size of 0.9 of a standard deviation. Therefore, if the standard deviation for the FSHD population of 3.4 is used, then enrolling twenty participants into this study would ensure that it is powered to 80% for a change in the MFM score of 3 or more with the planned intervention.

2.7. Study Procedures

Study Schedule of Visits and Assessments Creatine RCT

	Enrolment	Allocation	Post-allocation				Close-out
Study Visit	**1**	**2**	**3**	**4**	**5**	**6**	**7**
TIME POINT (weeks)	***-4***	**0**	***12***	***18***	***30***	***34***	***38***
ENROLMENT:							
Eligibility screen	X						
Informed consent	X						
Concomitant medication review	X	X	X	X	X	X	
Allocation		X					
INTERVENTIONS:							
Group 1		wk 0 →	wk12 →	wk 18 →	wk 30		
Group 2		wk 0 →	wk12 →	wk 18 →	wk 30		
ASSESSMENTS:							
Medical History	X		X	X		X	
Complete Physical Exam	X						
Vital Signs	X	X	X	X	X		
Brief Physical Exam		X	X	X	X		
Urine pregnancy test	X						
Study drug accountability		X	X	X	X		
Blood tests (LFTs, U&Es, GPX3 level)	X		X	X	X		
Urine tests	X		X	X	X		
Adverse Event Log		X	X	X	X	X	X
Motor Function Measure (MFM)	X	X	X	X	X		
Quantitative strength testing		X	X	X	X		
Performance of the Upper Limb (PUL) Scale		X	X	X	X		
6 minute walk test with GAITRite	X	X	X	X	X		
FSHD clinical severity scale (CSS)	X	X	X	X	X		
FSHD Clinical Score (FCS)	X	X			X		
FSH-COM	X	X	X	X	X		
Global Rating of Change (GRC)		X	X	X	X		

	Enrolment	Allocation	Post-allocation				Close-out
Study Visit	**1**	**2**	**3**	**4**	**5**	**6**	**7**
TIME POINT (weeks)	***-4***	**0**	***12***	***18***	***30***	***34***	***38***
PedsQoL Neuromuscular module (PedsQoL)	X	X	X	X	X		
FSH-Health Index (FSH-HI)	X	X	X	X	X		
StepWatch	X		X		X		
Muscle MRI		X	X		X		
Muscle Ultrasound		X	X		X		
Telephone Consultation and Safety Check						X	

= creatine monohydrate
= placebo
= washout period

Full details of the background to the trial and its design are presented in the protocol.

3 GENERAL STATISTICAL METHODOLOGY

3.1. Objectives of Analysis Plan

This analysis plan covers the analysis of all objectives.

3.2. Analysis Software

Data with be analysed using Stata v16, or later.

3.3. Definition of Baseline

The baseline for each trail period within the crossover design is taken as the measures and assessments recorded at the pre-treatment visit for each time period (visit 2 and visit 6).

3.4. Definition of analysis populations

Data from this study will be analysed as an intention to treat analysis. Data from all participants who are randomised will be included in the intention to treat (ITT) analysis.

3.5. Definitions related to Adverse Events (AEs)

Other than standard adverse effects, the following specific adverse events will be reported on the CRF:

- Gastrointestinal symptoms: diarrhoea, nausea, vomiting, abdominal pain, cramping, flatulence, discomfort on passing faeces
- Neurologic symptoms: headache, dizziness, fatigue, seizure
- Dermatologic: rash, skin discolouration, pruritis, dry mouth, acne, eczema
- Cardiac: chest pain, palpitations, new ECG abnormalities, hypertension, postural hypotension
- Respiratory: shortness of breath, wheeze, chest infections
- Renal: haematuria, urine colour change, cystitis, urinary tract infection, proteinuria, cast nephropathy
- Hematologic: abnormalities in full blood count parameters

- Hepatic: jaundice, hepatomegaly, abnormal liver function tests
- Musculoskeletal: myalgia, cramps, raised creatine kinase, back pain
- Ophthalmologic: blurred vision, double vision, red eyes, itchy eyes
- Genitourinary: epididymitis

3.6. Adjustment for Multiplicity

Given that there is only a single primary outcome measure, there are no plans to adjust for multiplicity.

3.7. Interim Analyses

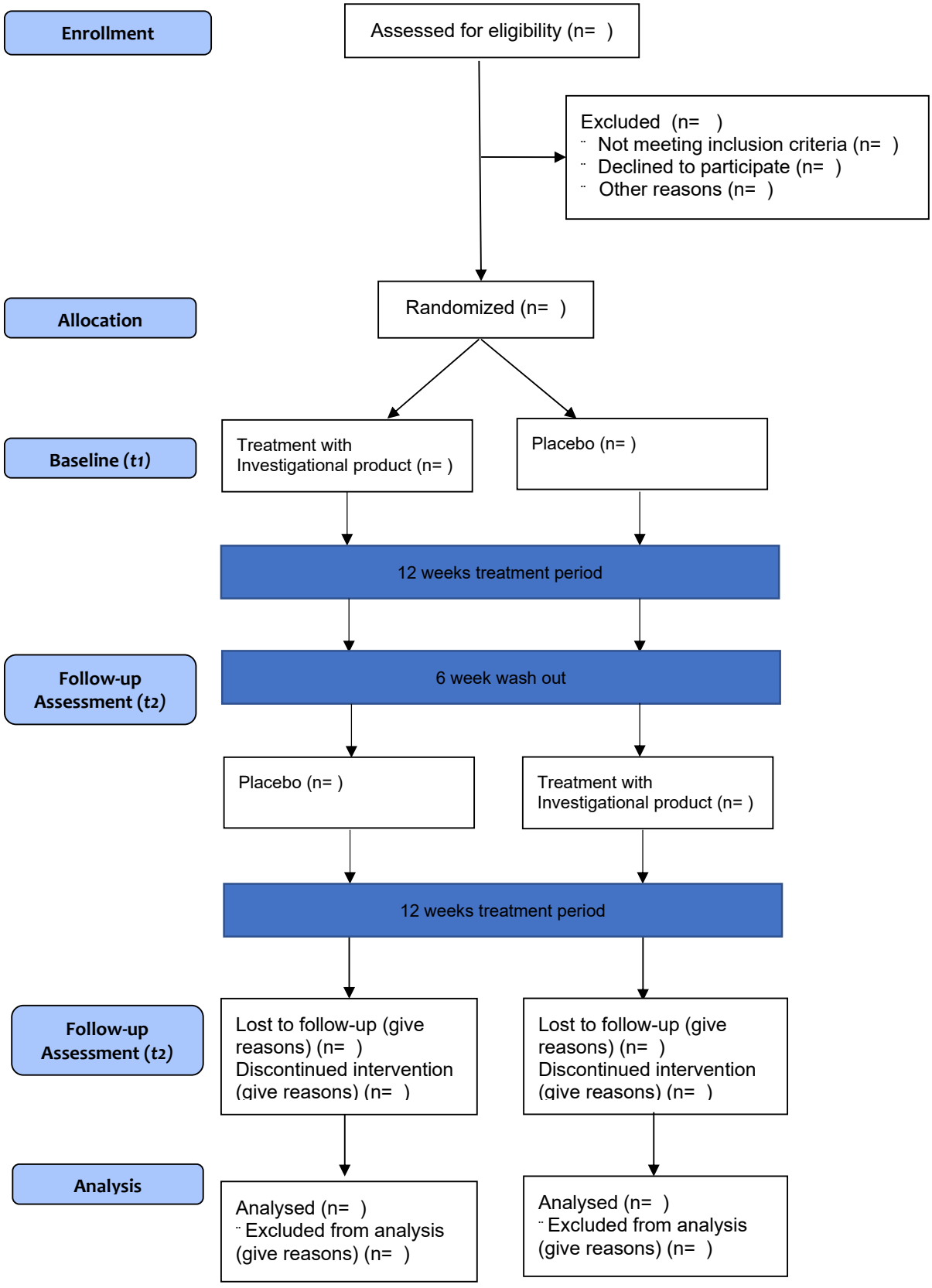
Interim analysis was not performed.

3.8. Handling of Missing Data

It is inevitable that some data will be missing. If less than ten percent of the total data is missing then no change to the ITT analysis will be made.

4 DESCRIPTIVE STATISTICS

4.1. Recruitment and Follow-up



4.2. Baseline Characteristics

Baseline population will be summarised using mean and standard deviations. Due to the crossover design, treatment and control groups will be identical and so will not be compared at baseline. The data summarised will include mean age, proportion of each sex and mean severity as measured by FSHD Clinical Severity Score and Clinical Score and Motor Function Measure at screening. Genetic results will be described using mean D4Z4 contraction length and the range. Presence of comorbidities will be described using percentage incidence. Baseline scores for other secondary outcome measures including, FSHD-COM, FSH-HI, PedsQL, Activlim and MRI will also be summarised using mean and standard deviations (SD).

Demographic	
Age at screening	Mean (SD, range)
Age at onset of FSHD symptoms	Mean (SD, range)
Female Sex, n (%)	
MFM score	Mean (SD)
D4Z4 Contraction (size kb)	Mean (range)
D4Z4 Repeats (number)	
Independently Ambulant	
Wheelchair dependent	
Weakness	
Facial Weakness	
Scapular Winging	
Beevor's sign	
Functional Outcomes Baseline Data	
MFM	
PUL2.0	
FSHD-CSS	
FSHD-CS	
FSHD-COM	
QMT	
MMT	
6MWT	
StepWatch	
Activlim	
PedsQL	
MRI	
Fat Replacement	
Atrophy	
Oedema	

4.3. Protocol Deviations

Participants who do not complete both treatment periods will be seen as a major protocol deviation.

4.4. Compliance

Compliance and participant adherence to study investigational product will be analysed based upon number of sachets returned to pharmacy compared to expected and will be described in the manuscript or supplementary information using a table. The table will comprise headings number of sachets dispensed, actual number of sachets returned, expected number of sachets returned and

the difference in expected and actual number returned. The difference in expected and actual number of sachets returned provides an assessment of number of sachets and therefore doses missed and indicates compliance. The percentage adherence for each participant will also be calculated and the summary mean for each group calculated. This will be calculated as the number of sachets consumed divided by the number expected to be consumed.

5 ANALYSIS OF THE PRIMARY OUTCOME(S)

5.1. Main Analysis

The primary outcome is the change in Motor Function Measure (MFM) score from baseline to 12 weeks. The MFM is Standardised assessment tool validated in NMD including FSHD. It contains 32 items scored on a 4-point scale assessing functional ability in axial, proximal and distal muscles throughout the body.

This analysis makes two assumptions, namely: no period effect and no treatment-period interaction.

Changes from baseline to 12 weeks (from baseline to week 12 in period 1 and from week 18 to 30 in period 2) in the MFM score will be summarised descriptively as mean changes and their SDs, presented separately for creatine monohydrate and placebo periods. Comparisons between the treatment groups will be made using mixed effects models applied to the change in the MFM score from baseline during the two periods, with a fixed effect for treatment and period and using a random effect to allow for the multiple observations within an individual. Results will be presented as a mean difference in change and its 95% confidence interval (CI).

5.2. Subgroup Analyses

None

6 SECONDARY OUTCOMES

6.5 The Performance of the Upper Limb 2.0 (PUL2.0) which is a measure of upper limb function.

This is a standardised assessment tool containing 22 strength-dependent items assessing functional ability in proximal, mid and distal muscles of the dominant upper limb.

The Performance of the Upper Limb scale is a functional assessment tool that focuses on the upper limb, as opposed to the 6MWT that focuses on the lower limb. It includes items that are useful measures of proximal shoulder girdle weakness as seen in FSHD, but it also has many measures of distal functioning that would not classically be affected in FSHD. Thus, it is a good secondary outcome measure but would not be appropriate as the primary outcome measure.

For each participant the difference between baseline and endpoint scores for the PUL for each treatment period within the crossover trial design will be calculated (from baseline to week 12 in period 1, and from week 18 to 30 in period 2).

This will be analysed in the same way as described for the primary outcome in Section 5.1.

6.6 The 6 Minute Walk Test (6MWT)

The 6MWT assesses the maximum distance walked in 6 minutes. It will be conducted over a 20m indoor non-carpeted track incorporating the GAITRite mat (which includes step length, stride length, cadence, symmetry, heel contact, speed). Lap times and split-distances for each minute will

be collected. Standardized encouragement of maximal performance will be used. Rate exertion will be measured on an OMNI walk/run Borg scale. The walk will be performed over a GAITRite mat for further data collection.

The 6-minute walk test has been used for many years as both a clinical tool and as a clinical trial outcome measure to assess disease severity in many muscle and nerve conditions. It is commonly used as a primary outcome measure in Duchenne muscular dystrophy where the lower limbs are more severely affected early on in the disease. In FSHD the disease tends to affect upper limbs more severely than lower limbs early on, but in many patients, lower limbs do become affected. As such the 6MWT is a useful outcome measure and has been shown to be valid and reliable in patients with FSHD.

For each participant the difference between baseline and endpoint scores for the 6MWT for each treatment period within the crossover trial design will be calculated (from baseline to week 12 in period 1, and from week 18 to 30 in period 2).

This will be analysed in the same way as described for the primary outcome in Section 5.1.

6.7 The FSHD-Composite Outcome Measure (FSHD-COM)

A newly developed FSHD composite measure yet to be validated in children. It includes 14 items scored on a 5-point scale assessing upper limb, lower limb, trunk and hand function and balance.

The FSH-COM is a composite outcome measure under development by Dr Rabi Tawil and his team in Rochester, USA. It has not yet been published or validated for use in children. As an aspect of this trial we hope to assess its test re test reliability and content validity as an outcome measure for future clinical trials in children with FSHD.

For each participant the difference between baseline and endpoint scores for the FSHD-COM for each treatment period within the crossover trial design will be calculated (from baseline to week 12 in period 1, and from week 18 to 30 in period 2).

This will be analysed in the same way as described for the primary outcome in Section 5.1.

6.8 The FSHD Clinical Severity Scale

A validated scale to give a single score on a ten-point scale that can be age corrected to measure overall severity based upon mobility and function.

The FSHD Clinical Severity Scale (CSS) that we will use for this trial will be the modified Ricci scale in use currently by the Fields Centre for FSHD and Neuromuscular Research in Rochester, USA. This scale takes into account the cephalo-caudal natural progression of FSHD and has been modified by van Overveld to take into account patient's age as well.(5, 6)

This will be analysed in the same way as described for the primary outcome in Section 5.1.

6.9 The FSHD Clinical Score

This is a validated scale that looks at a variety of muscle groups to produce a composite score that is specific to FSHD.(7) It is not a sensitive enough tool to be used as a primary outcome measure, but it would be useful to compare this measure against the FSHD Clinical Score (FCS) as they provide much the same information but there is no consistency about which tool should be used clinically or in clinical trials.

6.10 Step Watch

All participants will be asked to wear a StepWatch counter at all waking moments for one week at baseline and then again for one week towards the end of each treatment period. This will provide data on how active the participant is at baseline and after receiving the active agent and the placebo.

This will be analysed in the same way as described for the primary outcome in Section 5.1.

6.11 The FSH-Health Index (FSH-HI)

The FSH-Health Index (FSH-HI) is a patient reported outcome measure that is being developed by Dr Chad Heatwole and his team in Rochester, USA. It has not yet been validated for use in children with FSHD, but the study investigators are planning to collaborate with Dr Heatwole and his team to gather data to compare against established patient reported outcome measures. This will become part of a larger group of studies gathering data to validate the measure's use in clinical use and within clinical trials in children with FSHD.

This ordinal data will be analysed using the Wilcoxon signed ranks test.

6.12 PedsQL

The PedsQL is a validated tool for assessment of patient reported outcome measures that has advantages of providing condition-specific as well as generic measurement tools. All participants will be asked to complete the PedsQL questionnaire at baseline and at each study visit.

This will be analysed in the same way as described for the primary outcome in Section 5.1.

6.13 Activlim

This is a patient reported outcome measure that is validated for use in neuromuscular disorders to measure patients' reported activity levels.(8) Each question can be scored zero to two with the higher score suggestive of less disease impact. Each question can be totaled to give a cumulative score.

This will be analysed in the same way as described for the primary outcome in Section 5.1.

6.14 Physical Activity Questionnaire

This questionnaire asks patients and care-givers to record the physical activity over the prior week. It is used to gauge whether a participant's general level of activity has increased or decreased compared to baseline. For each question there are five possible answers on a scale scoring one to five points. The points for each question can be totaled to give an overall Physical Activity score.

This will be analysed in the same way as described for the primary outcome in Section 5.1.

6.15 Muscle MRI

MRI images will be analysed using visual semi-quantitative measures. Each domain (fat replacement, oedema, atrophy) will be scored in pre-selected muscles, chosen due to previous published data suggesting increased frequency of involvement of these muscles in FSHD. Each participant's scores for each MRI study will be added together to give a cumulative total for each domain.

6.15.1 MRI – Fat Replacement

This will be analysed in the same way as described for the primary outcome in Section 5.1.

6.15.2 MRI – Oedema

This will be analysed in the same way as described for the primary outcome in Section 5.1.

6.15.3 MRI – Muscle Atrophy

This will be analysed in the same way as described for the primary outcome in Section 5.1.

6.16 Functional Mobility Scale

At visit 1 (outcome measures sub-study) the FMS will be completed. This scale classifies the functional mobility of children taking into account their use of mobility aids. Published by Graham et al 2004, it rates the child's walking ability at 3 distances: 5, 50 and 500 meters (representing the child's current typical mobility at home, school and in the community).

This will be analysed in the same way as described for the primary outcome in Section 5.1.

6.17 Global Rating of Change

This is a very simple tool that is designed to quantify a patient's improvement or deterioration over time. We will be using this tool to ensure stability or change of functional state between assessments. The GRC asks the participant or guardian to rate functional state.

This ordinal data will be analysed using the Wilcoxon signed ranks test.

6.18 Subgroup Analyses

None

7 SAFETY OUTCOMES

Safety laboratory data, including blood haemoglobin, total white cell count, neutrophil count, platelet count, sodium, potassium, urea and creatinine levels and liver function test levels will be assessed to ensure there is no treatment emergent adverse effect on blood safety markers.

For each participant the difference between baseline and endpoint scores for the safety parameters for each treatment period within the crossover trial design will be calculated (from baseline to week 12 in period 1, and from week 18 to 30 in period 2).

Safety data will be summarized in a table highlighting the descriptive statistics of number and percentage of participants suffering from each adverse event, providing that the adverse event was suffered by at least two participants. All SAEs and SUSARs will be reported individually.

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