# Investigating chronic fatigue syndrome/myalgic encephalomyelitis (CFS/ME) in younger children (5-11-years-old)

Statistical Analysis Plan
Version 1.0 (November 2019)

Based on Protocol version 8 (13st March 2019)

Contents

## Introduction & purpose

This document details the rules proposed and the presentation that will be followed, as closely as possible, when analysing and reporting the main results from the EXPLORER, MAGENTA and RECOVERY studies.

The purpose of the plan is to:

1. Ensure that the analysis is appropriate for the aims of the study, reflects good statistical practice, and that interpretation of a priori and post hoc analyses respectively are appropriate
2. Explain in detail how the data will be handled and analysed to enable others to perform the actual analysis in the event of sickness or other absence

Additional exploratory or auxiliary analyses of data not specified in the protocol are permitted but fall outside the scope of this analysis plan (although such analyses would be expected to follow Good Statistical Practice).

The analysis strategy will be made available if required by journal editors or referees when the main papers are submitted for publication. Additional analyses suggested by reviewers or editors will, if considered appropriate, be performed in accordance with the Analysis Plan, but if reported the source of such a post hoc analysis will be declared.

Amendments to the statistical analysis plan will be described and justified in the final report of the study.

## Synopsis of study design and procedures

**Objectives**

Primary Objectives

1. To describe the baseline characteristics of children in terms of demographic characteristics and clinical characteristics: fatigue, pain, school attendance, anxiety
2. To identify the proportion of children with CFS/ME who make a clinically important change (as represented by the minimal clinically important difference (MCID)) on the SF-36 physical function subscale at 6 months.
3. To identify factors which predict improvement on the SF-36 physical function subscale.

Secondary Objectives

1. To describe the strength of relationship between school absenteeism as reported by schools and school absenteeism as reported by the family.
2. To report the number of participants consenting to school data being collected (acceptability) and the number of schools returning data (feasibility).
3. To report response rates to the PEDSQL core scale and fatigue scale at baseline and 6 month follow-up (acceptability).

**Study design and configuration**

Analyses will include data from three studies:

- EXPLORER: an observational cohort study with baseline data and follow up at 6 and 12 months. Inclusion criteria include: receiving a diagnosis of CFS/ME, being assessed at the RUH specialist CFS/ME service, and being aged 5-11 years.
- RECOVERY: an observational cohort study with baseline data and follow up at 6 and 12 months. Inclusion criteria include: receiving a diagnosis of CFS/ME, being assessed at the RUH specialist CFS/ME service, and being aged 8-11 years.
- MAGENTA: a randomised control trial comparing Graded Exercise Therapy with Activity Management[1] with baseline data and follow up at 6 and 12 months. Inclusion criteria include receiving a diagnosis of CFS/ME, being assessed at the RUH specialist CFS/ME service and being aged 8 – 11 years. Exclusion criteria are: being referred to Cognitive Behavioural Therapy (CBT) at the initial assessment appointment, being severely affected.

See EXPLORER, RECOVERY and MAGENTA protocols for full study methods.

**Outcome measures**

- Baseline clinical assessment form capturing: diagnostic criteria for CFS/ME; symptoms; co-morbid medical conditions; number of months from onset to assessment
- The self-completed SF-36 physical function subscale (continuous variable)
- Chalder Fatigue Scale (continuous variable)
- school attendance in the previous term collected as a percentage (10, 20, 40, 60, 80, and 100%), self-report
- School attendance in the previous term as reported by schools (0-100%)*
- Visual analogue pain rating scale as a continuous variable (0-100)
- Spence Children Anxiety Scale (continuous variable)
- PedsQL Core Scale Short From (continuous variable)*
- PedsQL Fatigue Scale (continuous variable) *

* Only available for participants in EXPLORER

## General analysis considerations

**Derived variables**

The SF-36 physical function subscale [2], HADS anxiety and depression subscales [3], Chalder fatigue scale [4] and Spence Children Anxiety scale [5] will be summarised as referenced.

For the second primary objective (to identify the proportion of children with CFS/ME who make a clinically important change (as represented by the minimal clinically important difference (MCID)) on the SF-36 physical function subscale at 6 months), analyses will utilise dichotomised outcome variables which will represent whether a minimal clinically important difference (MCID) of 10 points on the SF-36 physical function subscale[6] has been achieved between baseline and 6 months follow-up. The SF-36 physical function will be kept as a continuous variable for the third primary outcomes.

For the third primary objective (to identify factors which predict improvement on the SF-36 physical function subscale), analyses will utilise dichotomised variables for emotional functioning. For children 8-11-years the emotional functioning outcome measures is the Spence Children Anxiety scale, and the variable be dichotomised using the established Spence Children Anxiety scale cut-offs. For children aged 5-7-years, the emotional functioning outcome measures is the PedsQL- emotional function subscale, which will be dichotomised as above or below the bottom quartile for this subscale as per.[7]

**Procedures for missing data**

Outcome measures will be coded as missing if more than one question is missing, apart from the Spence Children Anxiety Scale, which will be coded as missing when there are more than two missing items.

If appropriate, analysis considering missing data for the primary outcomes only will be explored using methods such as multiple imputation (under the assumption of missing at random (MAR)).

**Follow-up questionnaire window**

Questionnaires returned up to 1 month from the baseline time point, and 3 months after the month time point will be used. We will carry out a sensitivity analysis, including questionnaires outside of this timeframe.

**Analyses of multiple data sets**

Analyses will initially be carried out on the combined data sets. If any of the baseline factors are associated with improvement in the SF-36 physical function subscale at 6 months (primary outcome 3), then analysis will be stratified by 1. EXPLORER study 2. RECOVERY study 3. GET arm of the MAGENTA trial 4. Activity Management of the MAGENTA trial, in order to check for an interaction effect.[8]

**Analyses of emotional functioning**

We will explore the effect of emotional functioning overall and within each age-group (5-7-years and 8-11-years) separately by fitting an interaction term for emotional functioning by age-group.

## Description of participant characteristics

A flow of patients through the study will be summarised in a CONSORT diagram which will include: the number of patients assessed for each study, the number of patients eligible for each study (and reasons for exclusion), the number of participant who consented to each study (and the reason for not-consenting), the number lost to follow-up and the numbers analysed.

**Baseline characteristics**
The study sample will be described by the baseline characteristics in Table 1.

Continuous data which are approximately normally distributed will be summarised in terms of means and standard deviations. Categorical data will be summarised in terms of frequency counts and percentages.

## Analyses

**Primary Objectives 1:** To describe the baseline characteristics of children in terms of demographic characteristics and clinical characteristics: fatigue, pain, school attendance, anxiety and depression.

Summary statistics of baseline characteristics will be presented.

**Primary Objective 2:** To identify the number of children with CFS/ME who make a clinically important change (as represented by the minimal clinically important difference (MCID)) on the SF-36 physical function subscale at 6 months.
The number of those reaching at least a 10 point improvement on the SF-36 physical function (the MCID) at 6 months will be presented, with a 95% confidence interval.

**Primary Objectives 3:** To identify factors which predict improvement on the SF-36 physical function subscale.

To use linear multiple regression models to investigate the baseline outcomes (exposure variables) which are associated with improvement on the SF-36 physical function subscale at 6 months (outcome variable). Adjusting for confounders: baseline SF-36 physical function subscale and gender. The exposure variables:

- Age
- Time to assessment
- Emotional functioning: Spence Children Anxiety Scale (continuous variable) / PedsQL Core Scale Short From: Emotional Functioning subscale (EF-5 items) (continuous variable)
- Pain rating scale as a continuous variable (0-100)

**Secondary Objectives 1**: To describe the strength of relationship between absenteeism as reported by schools and absenteeism as reported by families.

To use simple linear regression models to investigate the strength of relationship between baseline school-reported absenteeism and baseline self-reported school absenteeism. I will report the correlation coefficient, 95% confidence interval and the p value.

**Secondary Objectives 2**: Feasibility and acceptability of collecting school attendance records from school and PEDS-QL

Summary statistics of completion rates will be presented.

**References**


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