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Investigating outcomes in children with chronic fatigue syndrome/myalgic encephalomyelitis (CFS/ME)

Statistical Analysis Plan

Version 1.0 (12 August 2019)

Based on Protocol version 4.0 (11 August 2016)

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 Outcomes in CFS/ME study.

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 this Analysis Plan, but if reported the source of such a post hoc analysis will be declared.

1. Synopsis of study design and procedures

The information in this section is extracted from the study protocol in order to place the analysis plan within the context of the study aims and methods.

1.1. Objectives

1. To identify the number of children who achieve a clinically important change (defined as at least an increase in 10 points, minimal clinically important difference, MCID) [1]) on the SF-36 physical function subscale at 6- and 12-months (follow-up) compared with baseline
2. To describe the characteristics of those children who do or do not achieve a clinically important change (defined above) at 6- and 12-months (follow-up)
3. To identify baseline outcomes which are associated with a clinically important change (defined above) at 6- and 12-months (follow-up)

1.2. Study design and configuration

This is an observational cohort study with follow up at 6- and 12-months. Inclusion criteria include receiving a diagnosis of CFS/ME, being assessed at an out-patient clinic and being aged 8.0-17.99

years. Exclusion criteria are being younger than 8 and older than 18 and if the diagnosis of CFS/ME is not the child's main diagnosis.

1.3. Measures

The self-completed SF-36 physical function subscale, Chalder Fatigue scale, school attendance in the previous term (10, 20, 40, 60, 80, or 100% of a typical week), visual analogue pain rating scale (0-100 score), HADS depression and anxiety subscales (for those aged 12 years and older), Spence Children Anxiety scale, EQ-5D-Y, Clinical Global Impression Scale (ordered categorical outcome). These outcomes are collected at baseline, 6 and 12-months.

2. General analysis considerations

2.1. Analysis population

Those with complete baseline and SF-36 physical function subscale at follow-up.

2.2. 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. EQ-5D-Y will be converted into utilities [6]. All other outcomes will be analysed as reported. Analyses will utilise a dichotomised outcome variable which will represent whether a minimal clinically important difference (MCID) of 10 points on the SF-36 physical function subscale has been achieved between baseline and 6- or 12-months follow-up.

2.3. Procedures for missing data

Missing items in partially completed (sub)scales will be imputed using the methods described in the scale development literature. Questions for which two responses are given will also be coded as missing.

2.4. Follow-up questionnaire window

Questionnaires returned up to 3 months after the follow-up time point specified will be used.

3. Description of participant characteristics

3.1. Disposition

A flow of patients through the study will be summarised in a CONSORT diagram which will include losses to follow-up and the numbers analysed.

3.2. 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.

4. Analysis

The follow-up measures will be summarised as the mean (SD) for the study sample. Categorical variables will be presented as counts and percentages.

Summary statistics at baseline and follow-up will also be presented stratified by those who did, and those who did not, achieve at least the MCID on the SF-36 physical function subscale between baseline and follow-up.

4.1. Association between baseline outcomes and a clinically important change in the SF-36 physical function subscale

To investigate baseline outcomes or other characteristics (e.g. months since onset of chronic fatigue) which are associated with a clinically important change, logistic regression models of the dichotomous outcome variable, which represents whether a child has or has not achieved at least the MCID on the SF-36 physical function subscale at follow-up, will be adjusted for gender and age, and:

1. individual outcomes/characteristics at baseline
2. multiple outcomes/characteristics at baseline

In addition, these models will be additionally adjusted (as appropriate) for variables which may confound the association between baseline outcomes and a clinically significant improvement.

The estimated effect will be presented as odds ratio (OR) with a 95% confidence interval (CI) and p-value.

5. Tables and figures

5.1. Subject characteristics and background summaries

Figure 1. Consort flow diagram

Table 1. Baseline demographics and clinical characteristics of recruited patients

Supplementary Table 1. Baseline demographics and clinical characteristics of recruited patients stratified by completion of SF-36 physical function subscale at follow-up

Supplementary Table 2. Baseline demographics and clinical characteristics of recruited patients stratified by dichotomous outcome at follow-up

5.2. Outcome summaries

Table 2. Summary statistics of measures at follow-up stratified by dichotomous outcome

Table 3. Effect estimates of association between baseline outcomes and dichotomous outcome at follow-up

References

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