Statistical Analysis Plan

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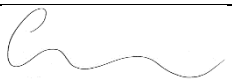
Study CI	Esther Crawley	Professor of Child Health		6th Oct 2021

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Abbreviations

BRTC	Bristol Randomised Trials Collaboration
BTC	Bristol Trials Centre
CBT	Cognitive Behavioural Therapy
CFS	Chronic Fatigue Syndrome
CI	Confidence interval
CONSORT	Consolidated Standards of Reporting Trials
DSMC	Data and Safety Monitoring Committee.
FITNET	Fatigue In Teenagers on the interNET
GP	General Practitioner
IMD	Index of Multiple Deprivation
ITT	Intention to Treat
MCID	Minimum Clinically Important Difference
ME	Myalgic Encephalomyelitis
NHS	National Health Service
NICE	National Institute for Health and Clinical Excellence
PROMs	Patient Reported Outcome Measures
RCT	Randomised Controlled Trial
SD	Standard Deviation
SF-36-PFS	Short Form 36 Physical Function Subscale
TSC	Trial Steering Committee
UK	United Kingdom

1. INTRODUCTION & PURPOSE

This document details the rules proposed and the presentation that will be followed, as closely as possible, when analysing and reporting the results from FITNET-NHS.

The purpose of the plan is to:

1. Ensure that the analysis is appropriate for the aims of the trial, reflects good statistical practice, and that interpretation of a priori and post hoc analyses respectively is 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).

This analysis plan and any subsequent revisions will be published in an open access online repository and therefore date stamped and publicly available. Additional analyses suggested by reviewers or editors of journals 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 trial.

2. SYNOPSIS OF STUDY DESIGN AND PROCEDURES

The following summary of the study design is solely to inform this statistical analysis plan. The study protocol (Baos et al 2018) and update (Anderson et al 2019), and findings of the internal pilot phase have all been published in open access journals.

2.1 Trial objectives and aims

The overall aim of this study is to investigate whether CBT specifically designed for CFS/ME and delivered over the internet (FITNET-NHS) is effective and cost-effective compared to Activity Management for children with CFS/ME who do not have access to a local specialist CFS/ME service.

2.1.1 Primary objective

Estimate the effectiveness of FITNET-NHS compared to Activity Management in the NHS for paediatric CFS/ME.

2.1.2 Secondary objectives

Estimate the effectiveness of FITNET-NHS compared to Activity Management for those with mild/moderate co-morbid mood disorders (anxiety/depression).

Estimate the cost-effectiveness of FITNET-NHS compared to Activity Management.

Estimate the cost-effectiveness of FITNET-NHS compared to Activity Management for those with mild/moderate co-morbid mood disorders (anxiety/depression).

2.2 Trial design and configuration

A two parallel group randomised controlled trial, with internal pilot.

2.3 Setting

2.3.1 Primary Care Regions with No Specialist CFS/ME Service

In the first instance, children and young people (aged 11-17 years) will be assessed by their GP, referred for local paediatric assessment (NICE guidance) and have bloods tests to exclude other causes of fatigue (NICE 2007). If there is no local specialist paediatric CFS/ME service (about 90% of UK), GPs and paediatricians (or equivalent specialist doctors) will be able to refer those with CFS/ME to the Bath Specialist paediatric CFS/ME Service. The Bath Specialist CFS/ME Service already receives >150 referrals annually from across the UK but is only able to offer assessment or minimal Activity Management.

2.3.2 Bath Specialist CFS/ME Service

Referrals will be accepted by the Bath Specialist CFS/ME Service if the child has been assessed by a paediatrician (or equivalent specialist doctor) and has had screening blood tests done, in accordance with NICE guidance (NICE, 2007).

2.4 Eligibility criteria

2.4.1 Inclusion criteria

- Age between 11 and 17 years inclusive.
- Diagnosis of CFS/ME (made according to NICE guidance) at clinical assessment (NICE, 2007).
- Children without access to a local specialist CFS/ME service.

2.4.2 Exclusion criteria

- Not disabled by fatigue.
- Fatigue due to another cause.
- Children or parents unable to complete video calls (e.g. Skype) or FITNET-NHS modules (e.g. unable to read FITNET-NHS material, or significant developmental problems, or limited internet access, unwilling/unable to set up a personal email address / videocall account).
- Report pregnancy at assessment.

2.5 Description of interventions

2.5.1 Activity Management (Comparator)

Activity Management via telecare will be delivered by specialist CFS/ME clinicians (including Occupational Therapists, Psychologists, medics, Physiotherapists) from the Bath Specialist CFS/ME Service. Participants (parent/carer attendance is optional) will have up to six video (e.g. Skype) appointments (one assessment and up to five follow up, this is an increased upper limit on the number of sessions, introduced 23/10/2017). Activity Management therapy over video call will be delivered using the same treatment principals as face to face Activity Management treatment.

Specialist clinicians will have a check list of mandatory, flexible and prohibited items to discuss during the initial assessment and follow-up video call sessions with the participant and will use a check list to collect data on which aspects were discussed. This will capture

information on the delivery of Activity Management by specialist service clinicians by collecting information on how many assessments and follow up video (e.g. Skype) calls were made to participants, how many telephone calls to local clinicians were provided and which mandatory and flexible areas were used in the treatment sessions.

2.5.2 FITNET-NHS (Intervention)

FITNET (Fatigue In Teenagers on the interNET) is an internet-delivered CBT package created for paediatric CFS/ME in the Netherlands. The programme has psycho-educational and CBT sections for children and a parallel programme for their parents. Children and their parents have separate accounts and log-ins. The psycho-educational sections are available after receiving log-in codes. These include: information on CFS/ME; the causes of CFS/ME; the relationship between CFS/ME, anxiety, depression and other illnesses; how the diagnosis is confirmed; treatment for CFS/ME; how to explain CFS/ME to friends and what the future (without CFS) is likely to look like. The CBT section is activated by a clinical psychologist once the child/parent has completed the psycho-educational sections.

Participants will work through 19 interactive modules: first they will complete the psycho-educational modules, then work through CBT modules over 6 months. Parent modules explore and address parent's beliefs and behaviours towards their child with CFS/ME focussing on their role as carers. The modules for participants introduce CBT, present CFS/ME as a multi-factorial model, discuss the role of the family and develop treatment goals. The CBT modules focus on cognitive behavioural strategies with instructions on exercises for identifying, challenging and changing cognitive processes. Modules 1, 2 and 4 introduce CBT and explain the role of therapists, present CFS/ME as a multifactorial model with predisposing, precipitating and maintaining factors and discuss the role of the family. Modules 3 and 5 focus on treatment goals including the goal of full-time education. Modules 6 to 19 focus on cognitive behavioural strategies with instructions on exercises on identifying, challenging and changing cognitive processes that contribute to CFS/ME. Children will be asked to do homework (answer questions and complete diaries). Whilst children are able to complete the modules at their own pace, they will be encouraged to work on and complete modules before the next appointment.

After parents complete the psycho-educational sections, they separately complete the remaining CBT modules. These explore and address parent's beliefs and behaviours towards their child with CFS/ME. In children younger than 15 years, parents are supported to act as a coach. In those older than 15, parents are encouraged to step back and support their child taking responsibility for their treatment. Parents complete diaries and questionnaires and there is a review function of all completed modules.

The FITNET-NHS clinical psychologists will make appointments and provide e-consultations. E-consultations are an email exchange between the therapist and the participants which functions only on the FITNET-NHS platform. In addition, participants and parents are required to complete homework (for example, sleep-wake, and thoughts and feelings diaries). These will be discussed in the e-consultations and used to support behaviour change. The therapist works with parents and children separately and responding together is discouraged. Therapist and participants/parents arrange a convenient date and time for e-consultations, usually every 2 weeks, unless the participant/parent and therapist feel the need for this to be different. Participants and parents will be asked to complete homework/tasks within specified time frames. Therapists will also respond to participants parents within the specified time frame.

2.6 Randomisation procedures

An automated web randomisation service operated by the Bristol Randomised Trials Collaboration (BRTC) will be used. Participants will be randomised in a 1:1 ratio to receive either FITNET-NHS or Activity Management. Allocation will use minimisation to facilitate balance by age (two categories, 11-14 and 15-17 years) and gender and retain a random component to prevent accurate prediction of allocation (i.e. preserve allocation concealment). Because of the nature of the intervention, it is not practical to blind either the participant, family or the clinical service to treatment allocation.

2.7 Trial committees

FITNET-NHS has an independent Trial Steering Committee (TSC) and independent Data and Safety Monitoring Committee (DSMC). Safety outcomes will be reviewed by the Data and Safety Monitoring Committee and reported to the Trial Steering Committee.

2.8 Outcome measures

2.8.1 Primary outcome

Our primary outcome will be disability measured using the Physical Function Scale (SF-36-PFS) measured 6 months after randomisation. Disability is an important outcome (Parslow et al 2015) for children with CFS/ME and we have shown it is sufficiently sensitive in this patient group. We want to allow children with CFS/ME the longest possible window to return outcome data and therefore the permissible measurement window will be between 5 and 9 months after randomisation. (Ware 1993, Ware & Sherbourne 1992).

2.8.2 Secondary outcomes

All secondary outcomes are measured at 3, 6 and 12 months unless otherwise specified. Secondary outcomes include:

1. Physical Function: SF36-PFS (Ware & Sherbourne 1992) measured at 3 and 12 months after randomisation.

2. Fatigue: Chalder scale (Chalder et al 1993) and Checklist Individual Strength (CIS) fatigue severity subscale (Beurskens et al 2000).

3. School attendance (self-report school or home tuition)

4. Mood: Revised Children's Anxiety and Depression Scale (RCADS)(Chorpita et al 2000, Chorpita et al 2005)

5. Pain visual analogue scale (Hawker et al, 2011)

6. Clinical Global Impression Scale (White et al 2011)

7. Quality of Life (EQ-5D-Y) [47] (Ravens-Sieberer 2010, Wille 2010)

8. Parental completed: Healthcare Resource Use questionnaire

9. Parental completed: Work Productivity & Activity Impairment Questionnaire General Health (WPAI:GH) (Reilly et al 1993)

All these measures are important and relevant domains (Parslow et al, 2015) that are used in UK services, CAMHS and/or tested in previous trials (Nijhof et al 2012, Crawley et al 2018). The EQ-5D-Y, Healthcare Resource Use questionnaire, and WPAI:GH will be considered in the health economics analysis plan.

The measurement of school attendance is challenging during COVID-19 lockdowns. We will present measures of school attendance assessed before and after March 2020 to consider whether this variable is meaningful during school closure.

2.9 Sample size and justification

The Minimum Clinically Important Difference (MCID) for the SF-36-PFS is 10 points (Brigden 2018) which is approximately 0.4 standard deviations (SD).

2.9.1 Full Study

314 children have been randomised. Assuming 15% attrition (withdrawal or non-provision of primary outcome data) (Nijhof et al 2012, Crawley et al 2018), data on 266 children will be available for the primary analysis. This gives 90% power at 5% significance to detect a 0.4 SD difference on SF36-PFS for our primary outcome.

2.9.2 Secondary outcome:

For the secondary outcome looking at effectiveness in those with a comorbid mood disorder, 40% of 266 children (data analysed) = 106 children will be available for analysis in the co-morbid subgroup. This will give 53% power at 5% significance to detect a 0.4SD difference on SF36-PFS between treatment groups within this co-morbid subgroup group.

2.10 Interim analysis

No interim analyses of the primary outcome measure by trial arm are planned.

3. GENERAL ANALYSIS CONSIDERATIONS

3.1 Analysis populations

Full analysis set (for the primary, secondary and safety analyses in the main results report): All randomised participants who complete the primary outcome measure, in the treatment group to which they were allocated (i.e. an intention to treat, ITT, analysis of observed data).

3.2 Derived variables

Questionnaire measures item responses will be recorded using REDCap electronic data capture tools hosted at the University of Bristol (Harris 2009) and scale scores will be calculated within Stata. Missing items in partially completed scales or subscales will be imputed using the methods described in the scale's development literature where available (Ware 1993).

3.3 Procedures for missing outcome data

The primary analysis will be based upon the observed data only. If primary outcome data are missing, sensitivity analyses will explore how robust the observed primary analysis results are under different assumptions about the missing data mechanism. Baseline variables will be compared between those with complete and those with missing primary outcome data, according to allocated group, in supplementary material.

3.4 Outliers

Outlying scores on the questionnaire measures are unlikely to be extreme enough to be overly influential on treatment effect estimates.

3.5 Software

Data analyses will primarily be carried out using Stata statistical software (StataCorp, College Station, Texas, USA, 2019). The version used will be reported.

4. DESCRIPTION OF PARTICIPANT CHARACTERISTICS

4.1 Disposition

A flow of patients through the trial will be summarised in a CONSORT diagram that will include the eligibility, reasons for exclusion, numbers randomised to the two treatment groups, losses to follow up and the numbers analysed.

4.2 Baseline characteristics

The following data will be collected from participants at baseline (see Table 1): age, sex, ethnicity, months of illness, diagnosis of co-morbid illnesses.

Participants will complete the following questionnaires: SF-36 physical function subscale (SF-36-PFS), Fatigue (using Chalder Fatigue Scale and Checklist Individual Strength (CIS) fatigue severity subscale), school attendance (% possible school attendance), RCADS, Pain visual analogue scale, EQ-5D-Y (EuroQoL health related quality of life questionnaire, Youth version) and Clinical Global Impression Scale questionnaire.

Continuous data will be summarised in terms of the mean, standard deviation, and number of observations. Categorical data will be summarised in terms of frequency counts and percentages.

5. ASSESSMENT OF STUDY QUALITY

5.1 Eligibility checks

Eligibility assessments will be carried out by a specialist nurse during the initial clinical assessment assisted by standardised measures.

5.2 Data validation

Data are collected into REDCap data capture system (Harris 2009) with range checks for variables. All baseline and follow-up data are collected onto REDCap. Baseline data is collected on REDCap as soon as the participant is randomised. An automated email with the link to the follow-up questionnaires is sent to the participant via the REDCap at various follow-up time points.

5.3 Intervention adherence

We will record the number of participants who start their allocated intervention, and the number of modules/sessions completed (Table 2). Therapists will be asked to record the expected number of modules/sessions for each participant.

5.4 Protocol deviations

Protocol deviations which may affect the estimation of the treatment effect will be recorded and reported in the main study reports. For example, we will record instances of a participant being found to be ineligible after random allocation.

5.5 Changes made to the planned statistical analyses

The planned statistical analysis is described in this Statistical Analysis Plan, which has been written by co-investigators who have not had sight of the study data, and which will be signed and made public ahead of the analysis proceeding. Changes to the plan will be highlighted and justified in a revised version of the Statistical Analysis Plan.

Changes to the pre-specified analysis, the need for which is recognised during the analysis, will be highlighted in study reports and publications, and fully justified.

6. ANALYSIS OF EFFECTIVENESS

6.1 Primary analysis

The null hypothesis to be tested is that the population mean SF-36-PFS score at six months follow-up is equal between groups allocated to FITNET-NHS or to Activity Management. This null hypothesis will be tested in an intention-to-treat analysis, which will compare study participants who completed the required measures, in the treatment groups to which they were allocated (the full analysis population). We will employ multivariable linear regression adjusting for baseline values of the outcome, baseline age and gender. The treatment effect will be estimated as an adjusted difference between sample means, which will be presented with 95% confidence interval and p-value (Table 3).

The adjusted difference in means will be estimated in a linear regression model with patient response at six months post-randomisation (y_i) as the outcome variable and covariates: treatment allocation (x_{1i}=1: FITNET-NHS; x_{1i}=0: activity management), baseline SF-36-PFS (x_{2i}), age at recruitment (x_{3i} as a continuous measure), and gender (x_{4i}=1: male; x_{4i}=0: female). Finally a dummy variable distinguishing those participants without a baseline assessment of outcome (x_{5i}=1: no baseline assessment; x_{5i}=0: baseline assessment available) (Groenwold 2012). A normal distribution is assumed for the residual errors: $e_i \sim N(0,\sigma_e)$. The coefficient for the treatment allocation covariate (β_1) is the intention to treat estimate of treatment effectiveness, comparing FITNET-NHS to activity management. In statistical notation:

$$y_i = \beta_0 + \beta_1 x_{1i} + \beta_2 x_{2i} + \beta_3 x_{3i} + \beta_{4t} x_{4i} + \beta_5 x_{5i} + e_i$$

The residuals from the model will be checked for a normal distribution, and as having a similar standard deviation in the two treatment groups. If the model assumptions are grossly violated, a sensitivity analysis will be conducted comparing the confidence interval to that from a bias corrected and accelerated percentile bootstrap method.

6.2 Sensitivity analysis

Sensitivity analyses to assist with the interpretation of the primary result will also be presented in Table 3. For the primary outcome we will conduct sensitivity analyses in which we further adjust our primary analysis model for prognostic variables (i.e. baseline variables presented in Table 1) for which there is a baseline imbalance between intervention arms (more than half a standard deviation between means, more than 0.1 between proportions). This analysis will also adjust for any variation across participants in the time between randomisation and the six-month outcome assessment.

The primary analysis will be repeated with the addition of a binary covariate, distinguishing participants recruited before and after 1st September 2019, i.e. according to whether the six-month assessment is due before or during the COVID-19 pandemic.

During the COVID pandemic, we are aware of delays following allocation before which treatment could commence. We will conduct a sensitivity analysis that reproduces the primary outcome analysis, but for any participants who did not commence their intervention until after the 3-month assessment point, and hence may not have completed the intervention by the 6-month primary assessment point, their data from the 12-month assessment (if available) will be used instead. To help interpret this analysis, it will also be conducted with omission of those participants who did not commence their intervention until after the 3-month assessment point.

We will estimate the effectiveness of FITNET-NHS compared with Activity Management for the SF-36-PFS primary outcome in participants completing one or more modules/sessions of their allocated intervention. This is a change from the corresponding sensitivity analysis described in the published protocol paper (Anderson 2019), which can more easily be applied in an equivalent manner to participants irrespective of their allocation. Estimates from this analysis will be interpreted cautiously, with reference to the baseline measures of included participants, as this approach may allow biased estimates.

6.3 Secondary analyses

The primary analysis will be adapted to each of the other questionnaire measures at first and second follow-up assessments in turn (with the twelve-month assessment of SF-36-PF included as a secondary outcome). The corresponding baseline measure of the questionnaire being analysed will be included (Table 4).

The primary analysis will also be adapted to the Clinical Global Impression Scale, with an ordered logistic regression model being employed. The seven response categories will be kept separate when included in this model (Table 5). There is no baseline assessment of this measure.

6.4 Sub-group analysis

In a single pre-defined subgroup analysis, we will estimate the effectiveness of FITNET-NHS compared with Activity Management on the primary outcome in participant subgroups defined by the presence or absence of baseline anxiety or depression, defined by using the age and gender specific clinical thresholds for each sub-scale on the RCADS. Evidence that the intervention effect differs between subgroups will be examined by

adding interaction terms to the multivariable linear regression model for the SF-36-PFS primary outcome only.

7. ANALYSIS OF SAFETY

7.1 Deterioration in physical function

The FITNET-NHS trial will investigate whether young people randomised to one arm are at higher risk of having a serious deterioration compared to another arm (Table 6). We will define a serious deterioration in health as:

1. Clinician defined clinical change or illness reported to the clinician and forwarded on to the study team (clinical-reported serious deterioration in health) during treatment. This will be unexpected or unexplained deterioration in health as defined by the clinician or unexpected health outcomes that are not normally seen by CFS/ME specialist clinicians.

2. A decrease of ≥20 in SF-36-PFS between baseline and 3, 6 or 12 months; or scores of "much" or "very much" worse on the Clinical Global Impression scale

3. Withdrawal from treatment and participant or parent/carer says this is because they are feeling worse

In supplementary material we will present these data separately for participants completing their twelve months follow-up prior to April 2020, and for participants whose follow-up was at least partly in the pandemic period.

7.2 Safety Analyses

The DSMC will specify how many independent safety reviews should be conducted and when these should be done. These reviews will only investigate safety outcomes and will be conducted by a statistician with un-blinded results provided to the DSMC. These data will be reviewed by the DSMC and reported to the TSC.

8. REPORTING/PUBLISHING

Reporting of the FITNET-NHS methodology and results will follow the CONSORT guidelines, including the extension for non-pharmacological treatments (www.consort-statement.org/).

9. REVISIONS TO THE STATISTICAL ANALYSIS PLAN

Revisions in subsequent versions of the statistical analysis plan will be recorded here.

10. PRIMARY REPORT TABLES AND FIGURES

Table 1. Characteristics of the randomised participants at baseline

	FITNET-NHS (n=)	**Activity Management (n=)**
Mean age (SD)		
Number female (%)		
Number white British ethnicity (%)		
Median months since illness onset (25^{th}, 75^{th} percentiles)		
Number comorbid anxiety[1] (%)		
Number comorbid depression[1] (%)		
Mean SF-36 Physical Function score (SD)		
Mean Chalder Fatigue score (SD)		
Mean CIS Fatigue score (SD)		
Mean pain VAS (SD)		
School attendance in the previous week[2]:		
Number recruited during school closure (%)		
Number 0 days (%)		
Number 0.5 days (%)		
Number 1 day (%)		
Number 2 days (%)		
Number 3 days (%)		
Number 4 days (%)		
Number 5 days (%)		

1. Determined using the RCADS.
2. Data has been collected on the number of hours of home tuition; this will be reported in the text accompanying this table.

Table 2. Treatment fidelity and adherence

	FITNET-NHS (n=)	**Activity Management (n=)**
Number not starting allocated treatment (%)		
Number completing 80% or more of expected modules / sessions of allocated treatment (%)		
Number starting allocated treatment more than three months after allocation (%)		

Table 3. Summary statistics and treatment effect estimates for the Short Form 36 physical function at 6- (primary outcome measure) and 12-months

	FITNET-NHS	**Activity Management**	**Difference in means (95% CI)**	**p-value**
	Mean (SD), N	**Mean (SD), N**		
Primary analysis (6 months)				
Sensitivity analyses:				
6 months: Further covariates[1]				
6 or 12 months according to start of allocated intervention				
6 months: Participants attending 1+ sessions				
Subgroup analysis[2]:				
6 months: Participants with co-morbid mood disorder				
6 months: Participants with no co-morbid mood disorder				
Secondary analysis:				
12 months				

1. Covariates added for measures not balanced at baseline, and for exact time of primary outcome completion
2. P-value is for interaction

Table 4. Summary statistics and treatment effect estimates for the secondary outcome questionnaire measures at 6 months and 12 months

	FITNET-NHS	**Activity Management**	**Difference in means (95% CI)**	**p-value**
	Mean (SD), N	**Mean (SD), N**		
Chalder Fatigue 6 months				
Chalder Fatigue 12 months				
CIS Fatigue 6 months				
CIS Fatigue 12 months				
Pain VAS 6 months				
Pain VAS 12 months				
School attendance 6 months[1]				
School attendance 12 months[1]				

1. As a proportion of full time

Table 5. Participant-rated Clinical Global Impression Scale of change in overall health from baseline

	FITNET-NHS	**Activity Management**	**Odds ratio (95% CI)**	**p-value**
Change from baseline (6 months)				
Much better or very much better (%)				
Minimal change (%)[1]				
Much worse or very much worse (%)				
Change from baseline (12 months)				
Much better or very much better (%)				
Minimal change (%)[1]				
Much worse or very much worse (%)				

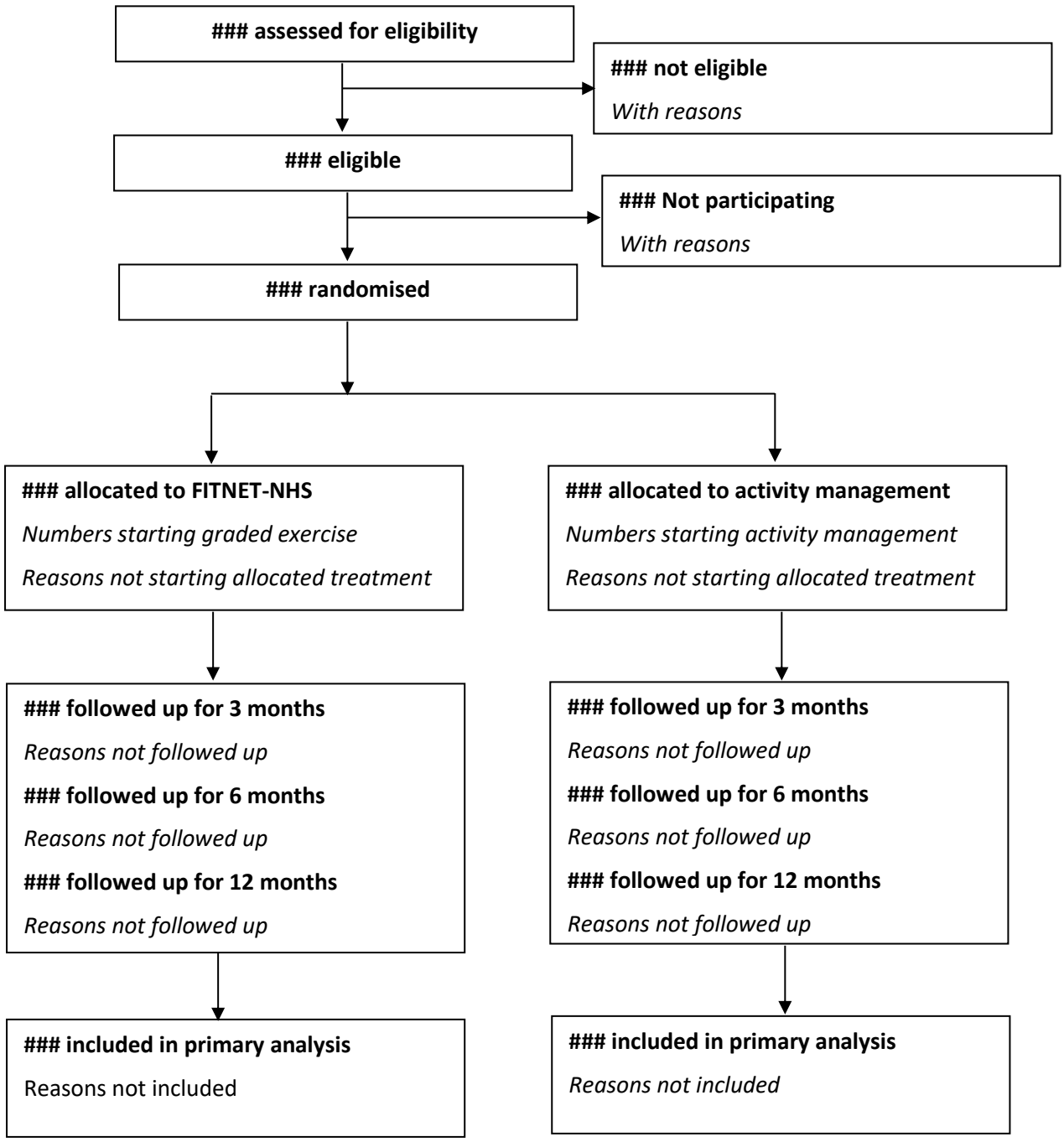
1. Includes the responses “no change”, “a little better”, and “a little worse”. Categories are not combined when estimating the odds ratio

Table 6. Safety measures

	FITNET-NHS (n=)	**Activity Management (n=)**
Number of participants with clinician report of worsening condition (%)		
Number of participants reporting worsening condition on withdrawing from treatment (%)		
Number of participants with evidence of worsening condition from SF-36 Physical Function or the Clinical Global Impression scale (%)[1]		
Number of participants with any evidence of worsening condition – one or more of the above (%)		

1. A decrease of ≥20 in SF-36-PFS between baseline and 3, 6 or 12 months; or scores of "much" or "very much" worse on the Clinical Global Impression scale

Figure 1. CONSORT recruitment and retention flow chart



11. REFERENCES

Anderson, E., *et al.* Investigating the effectiveness and cost-effectiveness of FITNET-NHS (Fatigue In Teenagers on the interNET in the NHS) compared to activity management to treat paediatric chronic fatigue syndrome (CFS)/myalgic encephalomyelitis (ME): amendment to the published protocol. *Trials*, *2019.* **20:** 750.

Beurskens, A.J.H.M., et al., *Fatigue among working people: validity of a questionnaire measure.* Occupational and Environmental Medicine, 2000. **57**:353-357.

Baos, S., et al., *Investigating the effectiveness and cost-effectiveness of FITNET-NHS (Fatigue In Teenagers on the interNET in the NHS) compared to Activity Management to treat paediatric chronic fatigue syndrome (CFS)/myalgic encephalomyelitis (ME): protocol for a randomised controlled trial.* Trials, 2018. **19**:136.

Brigden, A., et al., *Defining the minimally clinically important difference of the SF-36 physical function subscale for paediatric CFS/ME: triangulation using three different methods.* Health and quality of life outcomes, 2018. **16**:202-202.

Chalder, T., et al., *Development of a fatigue scale.* J Psychosom Res, 1993. **37**:147-53.

Chorpita BF, et al., Assessment of symptoms of DSM-IV anxiety and depression in children: a revised child anxiety and depression scale. Behaviour Research and Therapy, 2000. **38**: 835-855.

Chorpita, B.F., C.E. Moffitt, and J. Gray, *Psychometric properties of the Revised Child Anxiety and Depression Scale in a clinical sample.* Behav Res Ther, 2005. **43**:309-22.

Crawley, E.M., et al. *Clinical and cost-effectiveness of the lightning process in addition to specialist medical care for paediatric chronic fatigue syndrome: Randomised controlled trial.* Archives of Disease in Childhood, 2018. **103**:155-164.

Groenwold RHH, et al., *Missing covariate data in clinical research: when and when not to use the missing-indicator method for analysis.* CMAJ, 2012. **184:** 1265-1269.

Harris, P.A., et al., *Research electronic data capture (REDCap)--a metadata-driven methodology and workflow process for providing translational research informatics support.* Journal of biomedical informatics, 2009. **42**:377-381.

Hawker, G.A., et al., *Measures of adult pain: Visual Analog Scale for Pain (VAS Pain), Numeric Rating Scale for Pain (NRS Pain), McGill Pain Questionnaire (MPQ), Short-Form McGill Pain Questionnaire (SF-MPQ), Chronic Pain Grade Scale (CPGS), Short Form-36 Bodily Pain Scale (SF-36 BPS), and Measure of Intermittent and Constant Osteoarthritis Pain (ICOAP).* Arthritis Care Res (Hoboken), 2011. **63 Suppl 11**:S240-52.

Knudsen, A.K., et al., *Long-term sickness absence among patients with chronic fatigue syndrome.* British Journal of Psychiatry, 2011. **199**:430-431.

NICE, *Chronic fatigue syndrome/myalgic encephalomyelitis (or encephalopathy): Diagnosis and management of CFS/ME in adults and children (NICE guidelines CG53)*. 2007: London.

Nijhof, S.L., et al., *Effectiveness of internet-based cognitive behavioural treatment for adolescents with chronic fatigue syndrome (FITNET): a randomised controlled trial.* Lancet, 2012. **379**(9824):1412-8.

Parslow, R., et al., *What matters to children with CFS/ME? A conceptual model as the first stage in developing a PROM.* Arch Dis Child, 2015. **100**:1141-7.

Ravens-Sieberer, U., et al. Feasibility, reliability, and validity of the EQ-5D-Y: results from a multinational study. Quality of Life Research, 2010. **19**:887-897.

Reilly, M.C., A.S. Zbrozek, and E.M. Dukes, *The validity and reproducibility of a work productivity and activity impairment instrument.* Pharmacoeconomics, 1993. **4**:353-365.

Ware, J.E., *SF-36 Health Survey Manual and Interpretation Guide* 1993, The Health Institute, New England Medical Center Boston, Massachusetts

Ware, J.E. and C.D. Sherbourne, *The MOS 36-item short-form health survey (SF-36). I. Conceptual framework and item selection.* Med Care, 1992. **30**:473-83.

White, P.D., et al., *Comparison of adaptive pacing therapy, cognitive behaviour therapy, graded exercise therapy, and specialist medical care for chronic fatigue syndrome (PACE): a randomised trial.* Lancet, 2011. **377**(9768):823-36.

Wille, N., et al. Development of the EQ-5D-Y: a child-friendly version of the EQ-5D. Quality of Life Research, 2010. **19**:875-86.

APPENDIX: DETAILS OF STANDARD ASSESSMENT TOOLS

Chalder Fatigue Scale (Chalder 1993): A self-completed 14-item measure of fatigue, with four response options per question: “better than usual” (score 0), “no more than usual” (score 1), “worse than usual” (score 2) and “much worse than usual” (score 3). Items include “Do you have problems with tiredness?” and “Do you have difficulty concentrating?”. The range of scores is 0 to 42, with higher scores being most fatigue.

The CIS fatigue scale (Beurskens et al 2000) was used to measure fatigue, it consists of 20 statements for which the person has to indicate on a 7 point scale to what extent the particular statement applies to him or her. The statements refer to aspects of fatigue experienced during the previous 2 weeks. The number of items per dimension varies. The dimension “subjective fatigue” has eight items—for example, I feel tired—”reduction in motivation” four items—for example, I feel no desire to do anything—”reduction in activity three items—for example, I don’t do much during the day—and reduction in concentration five items—for example, My thoughts easily wander. Also, by adding the four dimensions a CIS total score can be calculated. Higher scores indicate a higher degree of fatigue, more concentration problems, reduced motivation, and less activity.

Short Form 36 Physical Function (Ware 1993, Ware & Sherbourne, 1992): A self-completed 10-item sub-scale of the Short Form 36. Response options are “Yes, limited a lot”, “Yes, limited a little” and “No, not limited at all”. The range of scores is 0 to 100, with higher scores being the best function.

Pain Visual Analogue Scale (Hawker 2011): The respondent places a line perpendicular to the 100mm long VAS line at the point that represents their pain intensity. The score is determined by measuring the distance from the “no pain” anchor to the respondent’s mark. The range of scores is 0 to 100, with higher scores indicating greater pain intensity.

Clinical Global Impression Scale (White 2011): Participant completed, assessing change from baseline with seven response categories. Here we follow White and colleagues in grouping the response categories into negative change (“Very much worse” or “Much worse”), minimal change (“A little worse”, “No change” or “A little better”), and positive change (“Much better” or “Very much better”).

The Revised Children’s Anxiety and Depression Scale (RCADS, Chorpita et al 2000, 2005) consists of 47 items developed to measure DSM-IV relevant symptoms of anxiety disorders (GAD, SAD, SoP, Panic disorder, OCD) and Depression in children. It is scored on a 4-point scale (0 = never, 1 = sometimes, 2 = often and 3 = always).