Full title: Investigating the effectiveness and cost-effectiveness of using 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) in the United Kingdom: A randomised controlled trial (FITNET-NHS)

Short title: How effective is FITNET-NHS for children and young adults with CFS/ME

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Table of Contents

Abbreviations

AE	Adverse Event
BRTC	Bristol Randomised Trials Collaboration,
CAMHS	Child and Adolescent Mental Health Services
CBRSQ	Cognitive Behavioural Responses to Symptoms Questionnaire
CBT	Cognitive Behavioural Therapy
CDC	Centre Disease Control
CFS/ME	Chronic Fatigue Syndrome/ Myalgic Encephalomyelitis
CI	Confidence Interval
CMRC	UK CFS/ME Research Collaborative
CNCEQ-R	Children's Negative Cognitive Error Questionnaire Revised
CRN	Clinical Research Networks
DSMC	Data Monitoring and Safety Committee
EQ-5D-Y	EuroQoL health related quality of life questionnaire, Youth version
FITNET	Fatigue In Teenagers on the interNET
FITNET-NHS	Fatigue In Teenagers on the interNET in the NHS (UK version of FITNET)
GET	Graded Exercise Therapy
GP	General Practitioner
HES	Hospital Episode Statistics
IMD	Indices of Multiple Deprivation
MCID	Minimally Clinically Important Difference
MHLDDS	Mental Health and Learning Disabilities Data Set
NHS	National Health Service
NICE	National Institute of Health & Care Excellence
NIHR	National Institute of Health Research
PIL	Patient Information Leaflet
QALY	Quality Adjusted Life Year
RCADS	Revised Children's Anxiety and Depression Scale
REC	Research Ethics Committee
RedCAP	Research Electronic Data Capture
RCT	Randomised Controlled Trial
SAE	Serious Adverse Event
SF-36-PFS	Short Form 36 item health questionnaire, Physical Function Scale
SPRC	NIHR National School of Primary Care Research
TMG	Trial Management Group
TSC	Trial Steering Committee
UK	United Kingdom
WPAI:GH	Work Productivity & Activity Impairment Questionnaire General Health

1. SUMMARY

This large randomised controlled trial (RCT) will investigate the relative clinical- and cost-effectiveness of the FITNET-NHS (Fatigue In Teenagers on the interNET in the NHS) intervention compared with Activity Management, among children with Chronic Fatigue Syndrome or Myalgic Encephalomyelitis (CFS/ME) who do not have a local National Health Service (NHS) specialist CFS/ME service. The FITNET-NHS intervention delivers specialist cognitive behavioural therapy (CBT) for CFS/ME via the internet at home. Participants and their parents work through 19 modules and have e-consultations with therapists. A Dutch study showed FITNET (Fatigue In Teenagers on the interNET) to be effective compared with standard medical care (63% of children in the FITNET arm had recovered at 6 months compared with 8% in the standard medical care arm). Activity Management is used as the comparator in this study as it is recommended by the National Institute of Health & Care Excellence (NICE) and is currently the best alternative for children in regions without a local specialist CFS/ME service. Activity Management will be delivered by specialist clinicians (including Occupational Therapists, Psychologists, medics, Physiotherapists) from Bath Specialist CFS/ME Service via up to six video (e.g. Skype) calls and then handed over to local providers (GPs, paediatricians, nurses and therapists) who will be supported by up to 3 telephone calls from the specialist clinician.

Children will be referred from primary care throughout the UK to the Bath Specialist CFS/ME Service where potentially eligible children will be identified and invited to eligibility screening prior to randomisation. The first phase of the trial is an internal pilot study which will use integrated qualitative methods to examine the acceptability of the treatment arms and the feasibility of recruitment. The full study will assess whether FITNET-NHS is clinically effective. The primary outcome is disability at 6 months, measured using the SF-36-PFS (Physical Function Scale) questionnaire. The trial is powered to perform a secondary subgroup analysis investigating the effectiveness of FITNET-NHS in those with co-morbid mood disorders. The full study will also assess whether FITNET-NHS is cost-effective in a cost-utility analysis from an NHS perspective. If FITNET-NHS is clinically effective and cost-effective, its provision by the NHS has the potential to deliver substantial health gains for the large number of children suffering from CFS/ME but unable to access treatment because there is no local specialist service.

2. BACKGROUND

2.1 Chronic Fatigue Syndrome or Myalgic Encephalomyelitis in Children

Paediatric CFS/ME is common in the UK, with estimated prevalence between 1% and 2.4% [1, 2]. CFS/ME is defined as generalised fatigue, causing disruption of daily life, persisting after routine tests and investigations have failed to identify an obvious underlying 'cause' [3, 4]. Children with CFS/ME are disabled [5, 6], and use significant health care resources over a considerable period prior to accessing CFS/ME treatment [7]. Only 8% of children appear to recover within 6 months with usual care [8]: this is consistent with adult data [9]. Usual care includes no treatment, treatment delivered by GPs or by therapists that are not specialised in CFS/ME. Parents often stop or reduce time at work in order to care for affected children [10].

NICE guidelines recommend a minimum 3 months duration of fatigue before making a diagnosis in children [4]. NICE recommends that children with CFS/ME are offered either Cognitive Behavioural Therapy (CBT, which focuses on cognitive behavioural strategies to identify, challenge and change cognitive processes and resume activities), Graded Exercise Therapy (GET, which stabilises physical activity levels, before gradually increasing at a manageable rate) or Activity Management (a goal-oriented and person-centred approach tailored to the needs of the person which establishes a baseline for all activity; mainly cognitive, such as school and homework, in children and adolescents, which is then increased) [4, 11]. There is good evidence that CBT and GET are moderately effective in

adults with CFS/ME. Four systematic reviews have shown that CBT and GET are moderately effective in improving function and reducing fatigue [12-15]. In particular, the PACE trial showed that both CBT and GET were more effective than specialist medical care or specialist medical care plus adaptive pacing therapy (a form of activity management that does not routinely increase activity but uses the envelope theory (patients work within their envelope of energy)) [16].

There is less evidence for the treatment of paediatric CFS/ME. However, when children are offered treatment the outcomes appear to be better than those seen in adult trials. We have conducted two systematic reviews [8, 17] to investigate treatment outcomes for paediatric CFS/ME, as well as an unpublished systematic review investigating recovery in paediatric CFS/ME using observational and trial data (PROSPERO registration CRD42014009303). These supplement two previous systematic reviews on interventions in paediatric CFS/ME [12, 18]. All five reviews identified good evidence from four RCTs (including the Dutch FITNET) that CBT is effective for paediatric CFS/ME [8, 19-21]. Only the FITNET trial investigated internet-delivered CBT, and none of the published paediatric trials reported on cost-effectiveness. The retention strategies for collecting outcome measures that we will use in this study were developed for the SMILE trial [22, 23], which has not yet been published. The consent and randomisation process used is from the MAGENTA trial [24] which is currently recruiting. A search of trial registries located no other relevant trials.

The FITNET trial, which was conducted in children with CFS/ME in the Netherlands (Lancet, 2012 [8]), showed that internet-based CBT was effective compared to usual care at 6 months. Usual care in the FITNET trial was not quantified but participants probably had access to individual or group-based rehabilitation programmes, cognitive behavioural therapy face-to-face, or graded exercise treatment, or both, and was provided by physical therapists who were often not specialists in CFS/ME. Compared with usual care, children in the FITNET arm were more likely to attend school full-time (75% vs 16%, relative risk 4•8, 95% CI 2•7–8•9; p<0•0001), more likely not to have severe fatigue (85% vs 27%, 3•2, 2•1–4•9; p<0•0001), and more likely to have normal physical functioning (78% vs 20%, 3•8, 2•3–6•3; p<0•0001). Children in the FITNET arm were more likely to have recovered (defined as no longer severely fatigued or physically impaired; attending school; and perceived themselves as completely/ nearly completely recovered) (63% vs. 8%, relative risk 8•0, 95% CI 3•4–19•0; p<0•0001). Improvement was maintained at 12 months. The FITNET-NHS (Fatigue In Teenagers on the interNET in the NHS) intervention has been developed, based on the Dutch FITNET [8] and tailored to deliver specialist CBT treatment for children and young adults with CFS/ME over the internet in the UK and its effectiveness and cost-effectiveness will be assessed in this study.

2.2 CFS/ME and Co-Morbid Mood Disorders

Co-morbid anxiety and depression affect more than 30% of children with CFS/ME [25, 26]. UK adolescents with CFS/ME presenting to specialist CFS/ME services, are more likely to have symptoms suggesting probable depression than are adults. Most, but not all [27], studies in adults suggest that CBT is less effective in patients with co-morbid depression [16, 28] compared to those without depression. The only study investigating predictors of treatment outcome in adults treated with internet delivered CBT showed the treatment benefit to be less in those with than without co-morbid depression [29]. However, CBT appears to be a more effective treatment than GET for adults with CFS/ME and depression [15, 16]. The paediatric trials conducted to date have either excluded children with co-morbid mood problems [19] or not been powered to investigate treatment efficacy in this group [8, 20, 21]. As a substantial proportion of children diagnosed with CFS/ME have comorbid mood problems, the NHS needs to know whether specialist treatment for CFS/ME is effective in this subgroup. FITNET-NHS is designed to treat children with co-morbid mood disorders as well as CFS/ME and this study is powered to test whether the effects of FITNET-NHS differ in this subgroup of children. Negative thinking patterns contribute to the development and maintenance of depression and have not previously been investigated in paediatric CFS/ME. This study will investigate whether adolescents with CFS/ME and co-morbid depression

differ from those who are not depressed on cognitive errors and cognitive and behavioural responses to symptoms of CFS/ME.

2.3 Current NHS Policy and Practice

NICE guidance states that children with CFS/ME should be offered referral to a specialist service immediately if they are severely affected, within 3 months if they are moderately affected and within 6 months if they are mildly affected [4]. However, only ~10% of UK children have access to a local NHS specialist service and, eight years after the NICE guidance was published, most children cannot access the treatment they require because they live too far away from a specialist service. For those that do access a service, few are assessed within NICE-recommended time scales [7]. In some cases, general practitioners (GPs) and paediatricians (or equivalent specialist doctors) will advise on sleep, symptom control and activity management, but the specialist CBT for CFS/ME, for which there is an evidence base, is not available other than through specialist services.

Few studies have investigated the acceptability, efficacy and cost-effectiveness of internet-delivered CBT for children. A systematic review from the National Collaborating Centre for Mental Health on E-therapies for children and young people with mental health problems concluded that, although e-mediated CBT appears to be potentially useful, further evaluation was required before it is used within the NHS [30]. Use of internet delivered CBT for treating long–term paediatric chronic disease is innovative and has the potential to be adapted to other long term conditions.

2.4 Justification of Research

There is good evidence that CBT is effective in the treatment of paediatric CFS/ME [19-21]. However, most children in the UK are unable to access specialist CBT for CFS/ME delivered face to face. Therefore, delivery of specialist CBT using the internet is an attractive option. In this study we will demonstrate whether implementation of FITNET-NHS in the UK is feasible and acceptable during the internal pilot study, and whether it is effective and cost-effective during the full trial. We will also identify whether the effects of FITNET-NHS differ between children with and without co-morbid mood disorders and how the patterns of cognition of those with co-morbid mood disorders are different from those without. We have chosen Activity Management (delivered via telecare) as the comparator intervention because it is the only NICE-recommended [4] approach offered by some paediatricians (or equivalent specialist doctors) outside specialist services. If FITNET-NHS is effective and cost-effective, its provision by the NHS has the potential to deliver substantial health gains for the large number of children suffering from CFS/ME but unable to access treatment because there is no local specialist service. In addition, more evidence is required to evaluate the delivery of internet CBT to children in the UK.

3. AIMS & OBJECTIVES

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. The objectives of the internal pilot study will inform the design of a full-scale, adequately powered trial.

The objectives of the internal pilot study are:

1. Examine whether it is feasible to recruit to a RCT of FITNET-NHS versus Activity Management (delivered via telecare) from primary care across different regions of the UK.
2. Examine whether FITNET-NHS and Activity Management are acceptable interventions for children in different regions of the UK.

The objectives of the full trial are:

3. Estimate the effectiveness of FITNET-NHS compared to Activity Management in the NHS for paediatric CFS/ME.
4. Estimate the effectiveness of FITNET-NHS compared to Activity Management for those with mild/moderate co-morbid mood disorders (anxiety/depression).
5. Estimate the cost-effectiveness of FITNET-NHS compared to Activity Management.
6. Estimate the cost-effectiveness of FITNET-NHS compared to Activity Management for those with mild/moderate co-morbid mood disorders (anxiety/depression).
7. Explore differences in the way adolescents with CFS/ME with depression think compared to those without depression

4. METHODS

4.1 Trial Design

This is an RCT comparing FITNET-NHS with Activity Management in children with CFS/ME. Participants will be allocated in a 1:1 ratio, minimised by age and gender, to each of the interventions. An internal pilot study will be conducted with continuation of the trial based on achieving defined stop criteria (see Section 6.3). Integrated qualitative research methods will be used to optimise recruitment and retention. The participant flow diagram is shown in Figure 1.

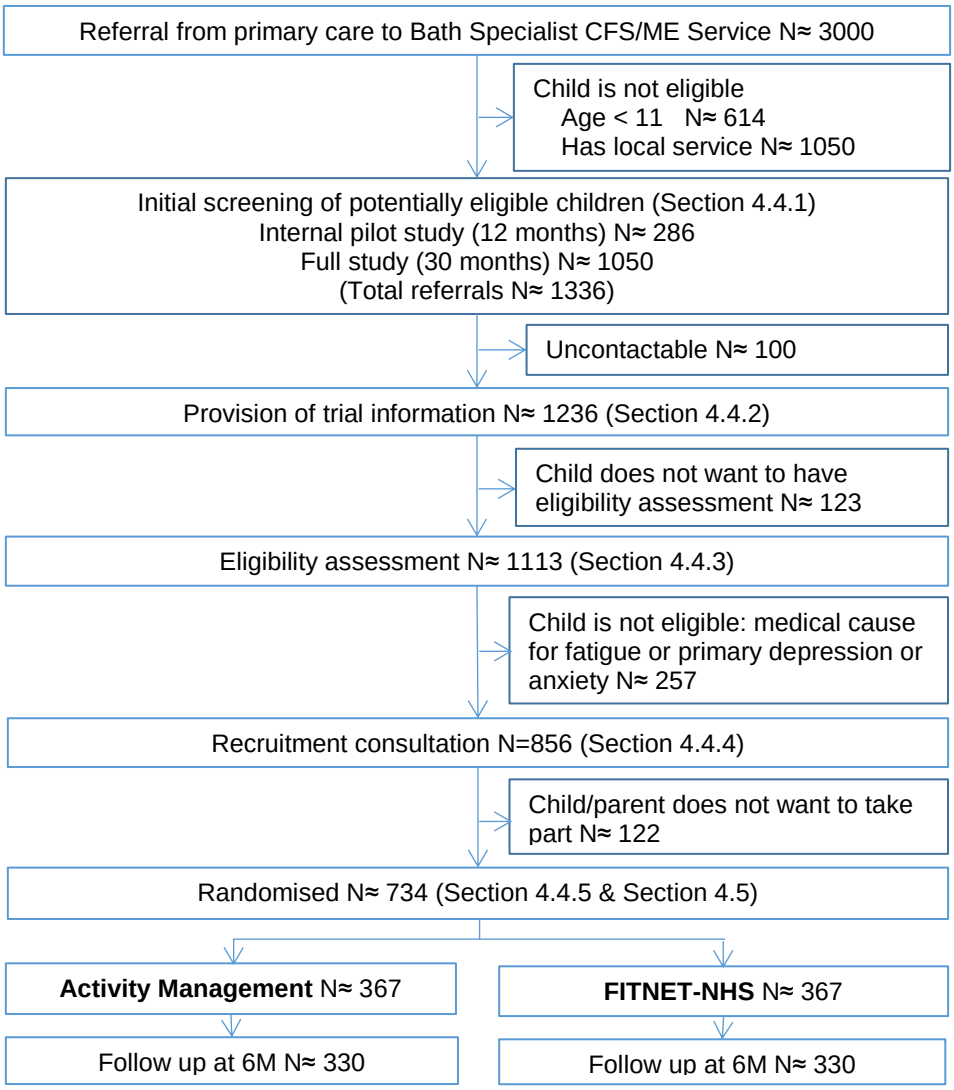

Figure 1. FITNET-NHS flow diagram with estimated numbers (total numbers incorporate the internal pilot into the full trial).

4.2 Setting

4.2.1 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 [4]. 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.

4.2.2 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 [4].

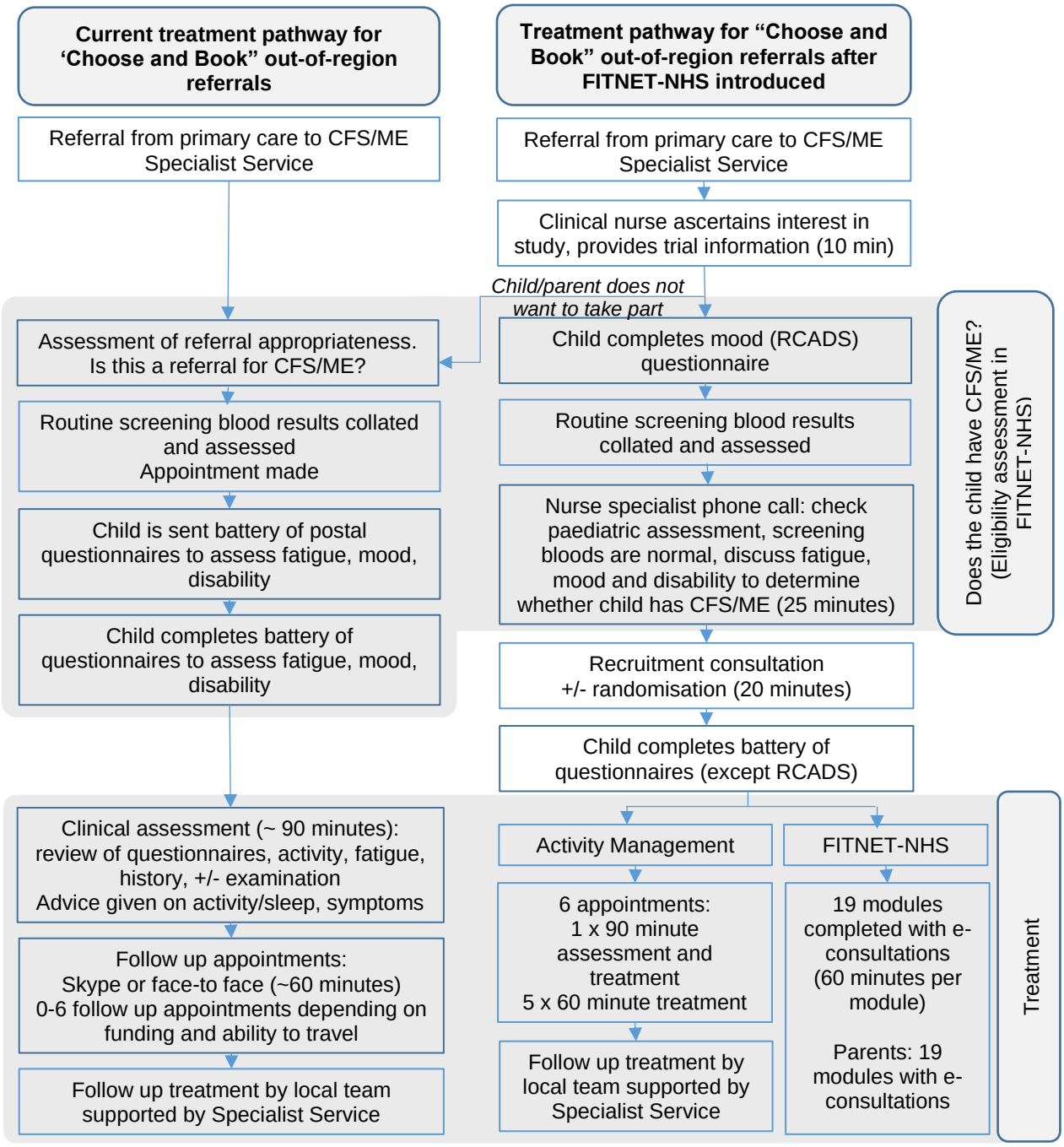

Figure 2. Differences between the standard care and research study treatment pathways

Figure 2 shows how the current treatment pathway for out-of-region referrals to Bath Specialist CFS/ME Service will change when the study starts. Participants will be given the opportunity to take part in the study at the point that the referral is processed.

4.2.3 Referral for treatment

Participants are referred via standard clinical referral from GPs across the UK to the Bath RUH. All the research processes are taken care of by the Bath RUH team (see below).

We will also offer UK 'superpractices' and GP surgery conglomerations (e.g. Birmingham Modality) the option of being set up as Patient Identification Centre (PIC) sites. The PIC site work will involve:

- Database search to identify patients aged 11-17 years with recent diagnosis of CFS/ME or post-viral syndrome
- GP approval of list of patients for mailing out invitation letter
- Letter mailout (directly to the child if aged 16-17 years or to the parent/carer if aged 11-15 years) to invite families to consider the trial and ask them to make a GP appointment for a clinical referral to Bath RUH if they are interested.

GP surgeries across the UK may also be provided with a patient poster and/or flyer to display in their surgeries if they would like this.

4.3 Trial Population

Children and young people, aged 11-17 years, with CFS/ME who do not have a local specialist CFS/ME service will be recruited at the Bath Specialist CFS/ME Service.

4.3.1 Inclusion criteria

1) Children aged 11 to 17 years
2) Children with CFS/ME (defined using NICE guidance [4], see Table 1)
3) Children with no local specialist CFS/ME service.

4.3.2 Exclusion criteria

1) Children not disabled by fatigue
2) Children whose fatigue is due to another cause
3) 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 development problems, or limited internet access, unwilling/unable to set up personal email address/video call (e.g. Skype) account).
4) Children who report pregnancy at assessment

4.4 Eligibility Screening, Recruitment and Consent

4.4.1 Initial Screening

The clinical team at Bath Specialist CFS/ME Service will review the referrals and perform an initial screening. Potentially eligible patients will be added onto a screening log (the eligibility assessment will include: Child age 11-17, thought to have CFS/ME and with no local specialist service and additional information such as a paediatric assessment and screening bloods).

The screening log will be maintained by a member of the clinical team which will include information on every child assessed. Details on whether the child was approached to take part in the study and reasons for non-approach will also be recorded (e.g. clinician forgot, or not eligible). Reasons for non-eligibility will also be recorded. Each patient will be allocated a unique research number. The research numbers will be linked to the patient name and the link will be held separately in the NHS centre.

4.4.2 Provision of trial information and consent to contact

Potentially eligible patients will be contacted via phone call by the clinical team to discuss CFS/ME treatment from Bath Services, the possibility of taking part in research study and identify those who may be interested in taking part. The initial phone call from the service should only take about 10 minutes. Patients interested in the FITNET-NHS study are sent a study information pack on-line (an email with a link to the participant information leaflet (PIL), the Revised Children's Anxiety and Depression Scale (RCADS) questionnaire (with an additional question for them consenting to the data being used for research purposes if they later decide to consent to the study), and a consent to contact form). The PIL will be sent as a pdf link via email. The consent to contact form will be sent as a link via email, which will be signed electronically on a secure electronic system used for data capture called REDCap (Research Electronic Data Capture http://project-redcap.org/). The RCADS questionnaire will also be sent as a REDCap link via email. On completion of the consent form and RCADS questionnaire the participant can automatically submit their responses electronically. The specialist nurse (part of the clinical team) will review the completed questionnaires to complete final eligibility checks for the study.

4.4.3 Eligibility assessment

The specialist nurse will ensure consent to contact and consent to record the recruitment discussion are complete. The specialist nurse will offer an eligibility assessment via telephone/video call with both the potential patients and their parents/carers (screening on fatigue, symptoms, disability, medical assessment screening bloods, screening for mood disorders (including RCADS) to exclude other diagnoses).

The specialist nurse will determine if the child has CFS/ME using questions used by the Bath Specialist CFS/ME Service on length of illness and other symptoms. These include four questions on fatigue: i) debilitating persistent or relapsing fatigue for at least 3 months, but not life-long; ii) not the result of ongoing exertion and not substantially alleviated by rest; iii) post-exertional malaise; and iv) severe enough to cause substantial reduction in previous levels of occupational, educational, social or personal activities, one on length of illness and twelve on symptoms. Those children who answer yes to these questions and therefore have 3 months of disabling fatigue plus one symptom [4] (NICE guidance) will be eligible. The NICE guidance will be used and not the Centre Disease Control (CDC) criteria [31] based on the relevance of NICE criteria to the NHS. The specialist nurse will also identify children who fulfil the CDC diagnostic criteria (Table 1) at the eligibility assessment as this will enable us to compare our results with those of other trials.

Table 1. Differences between NICE guidance and CDC criteria

	NICE guidance	CDC criteria
Months of fatigue	3 months (paediatric)	6 months
Symptoms	1 or more of: • post exertional malaise • difficulty sleeping • cognitive dysfunction • muscle and/or joint pain • headaches • painful lymph nodes • general malaise • dizziness and/or nausea • palpitations	4 or more of: • post-exertion malaise lasting > 24 hours • unrefreshing sleep • significant impairment of short-term memory or concentration • muscle pain; pain in the joints without swelling or redness • headaches of a new type, pattern, or severity • tender lymph nodes in the neck or armpit • a sore throat that is frequent or recurring

Exclusionary diagnoses	Conditions that explain the fatigue	Any active medical condition that may explain the presence of chronic fatigue. Any past or current diagnosis of: • major depressive disorder • bipolar affective disorders • schizophrenia of any subtype • delusional disorders of any subtype • dementias of any subtype • anorexia nervosa • or bulimia nervosa Alcohol or other substance abuse within 2 years. Severe obesity (BMI > 45).

During the eligibility assessment the specialist nurse will exclude other diagnoses that could cause significant fatigue by checking that screening blood tests [4] (Table 2) are normal and that patients have been reviewed by a paediatrician (or equivalent specialist doctor). They will ensure that patients do not have depression or anxiety that is sufficiently severe to cause their fatigue by reviewing results from the RCADS [32, 33]. The RCADS has 47 items with subscales that assess obsessive-compulsive disorder, social anxiety, panic, generalised anxiety, separation anxiety and depression with age- and sex-adjusted thresholds for each subscale [34]. Children who score above the threshold will be considered to have a co-morbid mood problem. Those scoring close or above the threshold will answer further screening questions to determine whether they are at risk of harm and/or whether their mood disorder is sufficiently severe to explain the fatigue. This will include questions about whether they want their low mood or anxiety or their fatigue treated first as well as questions about hopelessness, their sleep pattern, eating and whether they are experiencing anhedonia). Those who are considered as primarily having a mood problem or other cause for their fatigue (rather than CFS/ME) will be told about the provisional diagnoses, offered referral to the appropriate provider and excluded from this trial. The referrer will be informed about alternative diagnoses and signposted to relevant services.

Table 2. Screening blood tests recommended by NICE adapted from guidance [4].

Full blood count	Screening blood tests for gluten sensitivity
Creatinine, Urea and electrolytes	Serum Calcium
Thyroid function	Creatine Kinase
Erythrocyte sedimentation rate/plasma viscosity	Ferritin levels
C-reactive protein	Liver function tests
Random blood glucose	Vitamin D (if housebound)

Following the baseline assessment, the research team will not routinely monitor depression or anxiety throughout the study. Participants will be made aware of this and if they are worried about anxiety or depression they should discuss this with their routine care providers (e.g. GP, paediatrician or equivalent specialist doctor). If a participant spontaneously discloses information during the course of the study, the study team will suggest a discussion with their routine provider and inform them about relevant services if appropriate. Participants will be made aware that if they report risk outside of business hours, it may not be followed up on until business hours resume.

4.4.4 Recruitment consultation

If the child is eligible and they and their parent/carer are willing, the research team at Bath Specialist CFS/ME Service will arrange a telephone/video call recruitment consultation. The research team will explain the trial design and interventions; ensure the child and parent/carer have had an opportunity to read the age appropriate PIL and answer any questions about the research project. The eligibility assessment and recruitment discussions usually take place during one telephone/video call and will take about 45 minutes, although potential participants can have as long as required to make an informed decision. If the child and/or their parent/carer request a separate appointment, the eligibility assessment and recruitment consultations can also take place over separate telephone/video calls.

At the start of the recruitment discussion, the recruiter will confirm consent/assent for the recruitment discussion to be recorded and check that the parent/child continues to be happy to have the discussion recorded before discussing the FITNET-NHS trial, the study design, interventions, participant burden, potential risks and benefits of taking part.

4.4.5 Informed consent/assent

If patients are willing to take part in the FITNET-NHS trial, the researcher will request consent/assent from children and parents/carers during the telephone/video call recruitment consultation using an on-line consent form, which will be signed electronically on the secure electronic system; REDCap. Patients aged 11-15 will complete an assent form, while patients aged 16-17 and parents/carer will be asked to complete a consent form.

If potential participants decide not to take part in the FITNET-NHS trial they will receive reassurance that this is their decision, that we respect this decision and that it will not affect the standard of care that they will receive. They will be asked if a researcher can talk to them about why they have declined in order to understand more about patient views and to improve the trial. Verbal agreement will be recorded during the recruitment consultation. Further consent for an interview will be obtained at the time of the interview.

4.5 Randomisation

The research team will perform randomisation while the participant is still on the telephone/video call. Participants will be informed of their allocated intervention at the end of the recruitment consultation. If for any reason the service is unobtainable, randomisation will be completed during the next working day and the participant will be told of the results by phone. GPs will be told what intervention the child will receive.

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 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.

4.6 Interventions

Bath Specialist CFS/ME Service will provide both treatment arms. Both interventions will be delivered so that participants receive treatment at home, on-line.

4.6.1. 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). Activity Management therapy over video call will be delivered using the same treatment principals as face to face Activity Management treatment.

During the assessment, the clinicians will discuss the different types of cognitive activity (high concentration and low concentration) which will vary according to age. This assessment will take up to 90 minutes. The clinician will carry out a detailed assessment of activity with the participant. Participants will receive information on CFS/ME, activity management, sleep and symptom management. The participant and therapist will agree a "baseline" which is the average level of such activity. Participants will be encouraged to increase their activity.

The first follow up video call will be arranged two to six weeks after assessment depending on participant and their parent/carer preference. Further follow up video calls will be organised with gaps of two to six weeks between them. During the follow up video calls the clinician will review physical and cognitive activity and sleep and help participants problem-solve. Participants will be encouraged to increase activity until they are able to do up to 8 hours of activity a day. These follow-up calls will take approximately 60 minutes each time. Following the course of video calls the participant's clinician will call the participant's nominated local therapist or doctor to deliver care. Local providers in primary or secondary care can include GPs, paediatricians (or equivalent specialist doctors) or therapists (e.g. from Child and Adolescent Mental Health Services (CAMHS)) or paediatric secondary care, physiotherapists, occupational therapist, psychologists, specialist nurses). Most will provide follow up face to face but some may use telephone calls to follow patients up. The clinician will discuss the case on the phone or by letter (as is normal clinical practice) and ask for review within six to eight weeks. The clinical letter routinely provides detailed advice for the child and parent/carers on implementing Activity Management. Local providers will have up to 3 telephone calls, if required, from the specialist clinician from Bath Specialist CFS/ME Services to advise on treatment options, suggestions to overcome barriers or symptom control.

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.

Mandatory: Therapists will discuss the different types of activity (cognitive and physical) which will vary according to age. Participants will be taught how to find their baseline level of activity. Physical activities will vary according to severity. For severely affected children, this might include sitting up in bed, for those with mild CFS/ME, this might include running. High energy cognitive activities include time at school or doing school work, reading, some craft/hobbies, socialising and screen time (phone, TV, computer, other devices). The baseline is the median time spent doing activity and can either be estimated in collaboration with the specialist therapist or calculated after a period of recording activity. Once the baseline is agreed with participants, they will be asked to record the total number of minutes spent each day doing high-energy cognitive activities using paper diaries or the iPhone/iPad app "ActiveME". Participants will be asked to scan and email or post the paper diaries or email outputs from "ActiveME" to the therapists. Recording activity is used to help participants understand whether they are doing the same each day or varying their activity and whether the baseline has been set at the correct level. When participants have managed the baseline for 1-2 weeks, they will be asked to increase this by 10-20% each week [4, 16]. Therapists will discuss problems encountered by participants and provide possible solutions.

Managing setbacks will be discussed (how much to reduce physical activity, school and other cognitive activity and for how long). Participants will continue to increase activity until they are able to do at least 8 hours of cognitive activity a day.

Therapists will complete a checklist for each session to record which mandatory elements were provided.

Prohibited: Detailed discussion of feelings, beliefs and how they change engagement with Activity Management, diaries on feelings and their relationship with behaviour.

Flexible: Advice on exercise, discussion of anxiety and depression in terms of whether they need further treatment.

4.6.2. 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.

4.6.3 Duration of treatment period and follow-up

The duration of treatment will vary between participants. Those allocated to FITNET-NHS will receive treatment for approximately 6 months but this will vary depending on how long it takes participants and their parents to complete the online modules. Participants allocated to Activity Management will receive treatment for approximately 6 months but this may vary depending on the gap between follow up sessions.

Participants in both treatment arms will be asked to provide follow-up data on trial outcome measures 3, 6 and 12 months after randomisation.

4.6.4 Treatment adherence

For both study arms we will record the number of booked treatment sessions where participants did not respond or were not contactable or where there was a late cancellation (within 24 hours without wanting to re-schedule). We will assume that participants and parents who complete 80% of the modules/sessions required have been adherent to treatment and find the interventions acceptable.

4.7 Planned recruitment

4.7.1 Sample Size

Internal Pilot Study: If our internal pilot study is successful then at the end of 12 months following the start of recruitment, we will have received 286 referrals for children with CFS/ME, who are aged 11 -17 from regions where there is no local specialist CFS/ME service (Figure 1). Of these, we estimate 55% (156) will be recruited into the trial. This will allow us to estimate the feasibility of being able to recruit to FITNET-NHS.

Full Study: We plan to randomise 734 children (55% of 1336 referrals). Assuming 10% attrition (withdrawal or non-provision of primary outcome data) [8, 22], data on 660 children will be available for the primary analysis (Figure 1). This gives 97% power at 1% significance to detect a 0.35SD difference on SF36-PFS. The analysis of effectiveness in 198 children with co-morbid mood disorders (30% of those recruited and with data available for analysis (10% attrition)) will have 80% power to detect a 0.4SD difference at 5% significance. A difference of 10 points on the SF-36-PFS is considered to be the Minimally Clinically Important Difference (MCID) [35, 36]. The mean SF-36-PFS is 49.8 with SD 24.8 in children with CFS/ME at assessment by the Bath Specialist CFS/ME service. 0.4SD is 9.92 and therefore our study is powered to detect the MCID of 10 in children with co-morbid mood disorders.

We will perform sensitivity analyses on children who fulfil the CDC diagnostic criteria (see Table 1). We estimate this will be 80% of those randomised (588 with 529 after 10% attrition) which will give us 98% power to detect a treatment effect of 0.35SD difference at 5 % significance at least the MCID.

Sampling for the qualitative studies will ensure that a range of informants (in terms of age, gender, ethnicity, geographical location, socio-economic circumstances, and disease severity) are included (maximum variation sampling), and that participants with particular characteristics of interest can be targeted for interview and to develop emerging findings (theoretical sampling). Interviews will be semi-structured using a topic guide to ensure that they cover the same basic issues while allowing new issues of importance to emerge. All interviews will be audio-recorded with consent using encryption software, transcribed verbatim and anonymised.

Sample size for interviews will be determined by data saturation, i.e. when no new themes are being uncovered. It is anticipated that up to 40 patients (across both treatment arms), 40 parents and 10 trial staff will be interviewed at a location of their choice.

4.7.2 Planned recruitment rates

Recruitment will start in the internal pilot study which will last 12 months (month 7-18 of the study). We have assumed a lag phase in the internal pilot study (see Table 3) with referrals reaching 35/month in the last 3 months which is the referral rate we anticipate throughout the full study.

Table 3. Recruitment and predicted retention during 12 month internal pilot study (months 7 – 18 inclusive). Assumes 90% return rate as in our current trials.

Trial month	7	8	9	10	11	12	13	14	15	16	17	18	Total
Number Referred	6	10	12	16	20	24	28	32	33	35	35	35	286
Number Recruited	3	6	7	9	10	13	15	17	18	19	19	20	156
6 month FU sent							3	6	7	9	10	13	48
Estimated FU return*								3	5	6	8	10	32

*assumes one month delay before return.

Recruitment will continue in the full study phase and we should receive ~1050 referrals over 30 months. This means we will have had a total of 1336 referrals (286 internal pilot and 1050 full study). We have assumed that 100 families will be un-contactable or will not have an eligibility assessment. Fewer than 1% of children refuse blood tests or screening questionnaires prior to assessment in the Bath specialist CFS/ME Service, but we have assumed this will increase to 10% (123 children) in the trial because those referred from outside the specialist region will be referred by GPs with less access to the Bath Specialist CFS/ME service. Figures from our previous trial (SMILE) suggest that 23% (257 children) will not be eligible and 11% (122 children) will not want to take part after the recruitment consultation. We have therefore assumed we will recruit at least 55% of eligible children. We believe this is likely to be pessimistic because the Dutch FITNET trial screened 148 referrals, of whom 141 were eligible for the trial. Of these, 135 (96%) enrolled in the study. In summary, we have conservatively assumed that ~55% of eligible children will be recruited (Figure 1).

4.9 Definition of end of trial

The end of the trial for an individual participant and their parents/carers is 12 months after randomisation. The definition of the end of the trial as a whole is the date when all participants have completed the 12 month follow-up or have been lost to follow-up, all data queries have been resolved and all analyses have been completed.

4.10 Withdrawal of participants from the study

Participants can withdraw from the study at any time without giving a reason. If a participant wants to withdraw from the study, they will be asked to inform the FITNET-NHS team. The participant will be asked whether they want to withdraw from the intervention, further data collection or both. Non-identifiable information already collected from participants will be retained unless the participant requests for it to be destroyed.

4.11 Outcome measures and data collection

4.11.1 Data collection using REDCap

All baseline and follow-up data will be collected onto REDCap, a secure system used by many institutions for large multicentre studies. Data will be entered by participants who will be asked to log into the system and pass authentication before they can access their own data. Several authentication methods are available. The University of Bristol will use table-based authentication, which utilizes the storage of username/password pairs in a database table. In this system, the password in the database table is encrypted as a one-way hash of the password. Participants will be sent a web link to REDCap which will only allow access to their data. They will create a password which they will use each time they log in. REDCap has an auto-log out system that will log participants out after 30 minutes if they have stopped using the database.

An automated reminder email will be sent to participants who have not filled in their baseline questionnaire 7 days after it is first sent, with a further automated reminder email after 14 days if it is still incomplete. Newly recruited participants will also be contacted by phone, text and/or letter to try to gain the baseline data prior to commencing treatment.

At the follow up time points, an email will be sent to participants automatically with a link to complete questionnaires on line. If these are not completed, automated reminders will be sent at 2 weeks and then again at 4 weeks. If data is not completed, we will try and contact participants by phone, text and/or letter. If this is not successful, an email with a link to a reduced set of questionnaires (SF-36-PFS, Chalder fatigue, school attendance, EQ-5D-Y and Clinical Global Impression Scale) will be sent with the aim of capturing a minimal data set.

4.11.2 Baseline data collection

The following data will be collected from participants at baseline (see Table 4): age, sex, post-code (for data on deprivation (Indices of Multiple Deprivation (IMD)), ethnicity, symptoms (CDC and NICE criteria), 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. The Cognitive Behavioural Responses to Symptoms Questionnaire (CBRSQ) [37, 38] and the Children's Negative Cognitive Error Questionnaire Revised (CNCEQ-R) [39] will be administered at baseline only and will be used to explore differences in negative thinking between those participants with CFS/ME and co-morbid mood disorders and those without. The CBRSQ has previously been used with adults with CFS/ME in the PACE trial [40], and with adolescents [*personal communication, Chalder, T. 2015*].

Parents will complete the following questionnaires at assessment: an adapted existing Healthcare Resource Use questionnaire to measure health service use and the adapted 6 item Work Productivity and Activity Impairment Questionnaire General Health V2.0 (WPAI:GH). Table 4 shows the schedule of data collection at baseline and at follow up.

Table 4. Schedule of data collection.

	Data item	Baseline			Follow up		
		Referral letter	Eligibility assessme	Following recruitmen	3 months	6 months	12 months
Assessment data	Age	✓					
	Sex			✓			
	Post code	✓					
	Ethnicity			✓			
	Symptoms List (CDC & NICE criteria)		✓				
	Months of illness		✓				
	Co-morbid conditions		✓				
Questionnaires (completed by child)	SF-36-PFS			✓	✓	✓	✓
	Chalder fatigue and CIS fatigue			✓	✓	✓	✓
	School attendance			✓	✓	✓	✓
	RCADS		✓		✓	✓	✓
	Pain visual analogue scale			✓	✓	✓	✓
	Clinical Global Impressions Scale					✓	✓
	EQ-5D-Y			✓	✓	✓	✓
	CNCEQ-R			✓			
	CBRSQ			✓			
Questionnaires (completed by parent/carer)	Healthcare Resource Use				✓	✓	✓
	WPAI:GH			✓	✓	✓	✓

4.11.3 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 [41] 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.

4.11.4 Secondary outcomes

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

1. SF36-PFS [42] measured at 3 and 12 months after randomisation.

2. Fatigue (Chalder scale [43] and Checklist Individual Strength (CIS) fatigue severity subscale [44])

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

4. Mood (Revised Children's Anxiety and Depression Scale (RCADS) [45])

5. Pain visual analogue scale [46]

6. Clinical Global Impression Scale [16]

7. Quality of Life (EQ-5D-Y) [47]

8. Parental completed: Healthcare Resource Use questionnaire

9. Parental completed: Work Productivity & Activity Impairment Questionnaire General Health (WPAI:GH) [48]

All these measures are important and relevant domains [41] that are used in UK services, CAMHS and/or tested in previous trials [8, 22, 23].

4.11.5 Safety outcomes:

We will prospectively collect data on serious and non-serious adverse events reported to either a clinician or the research team during the intervention or in the follow up period. The FITNET-NHS trial will investigate whether young people randomised to one arm are at higher risk of having a serious deterioration in health compared to another arm. We will define a serious deterioration in health as: (1) clinician-reported serious deterioration in health (reported during FITNET-NHS or Activity Management session); (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; or (3) withdrawal from treatment because of feeling worse (see Section 5 on Safety).

Safety outcomes will be analysed by the Data and Safety Monitoring Committee (DSMC) at 11 months after the start of recruitment, before the trial progresses from internal pilot to full trial and when ~50% of participants have been recruited (estimated 23 months after the start of recruitment).

4.11.6 Outcomes of the internal pilot study

We will use an internal pilot study to test whether our trial processes are feasible and our interventions acceptable. We will obtain consent from those recruited in the internal pilot phase to include their data if the study proceeds to a full trial. Defined stop criteria will be used to determine whether the study should proceed to full trial phase (see Section 6.3 for Stop Criteria).

4.11.6.1 Feasibility of recruitment

We will collect data on the number of children referred from each region (by CRN), the number screened when the referral is received, the number eligible and the number recruited. We will record the number who do not accept their allocation during the recruitment consultation and estimate retention using the percentage of children providing six month data.

To understand whether it is feasible to recruit into this trial, we will combine this information with qualitative data (see section 4.12) collected throughout the internal pilot study. We will conduct in-depth interviews with parents/carers (up to 40) and their children (up to 40) to explore their views on: provision and acceptability of patient information; reasons for accepting or declining participation (see section 4.4.5 on Informed Consent); prior exposure to treatments; and beliefs, expectations and preferences about FITNET-NHS and Activity Management before assignment. We are particularly interested in understanding barriers to participation and will interview (subject to informed consent) those who choose not to participate in the trial, who drop out and who do not accept treatment allocation. We will also interview trial staff (up to 10) to identify possible sources of recruitment difficulties.

To optimise recruitment we will provide training for the recruiting researcher on strategies for improving the presentation of study information that have been shown to increase rates of consent and recruitment. We will audio record all recruitment consultations in the pilot phase to identify possible recruitment difficulties, with the option of continuing to record recruitment consultations as needed for the duration of the full trial for training purposes. The research team will analyse the recruitment consultations regularly, focussing on the interaction between recruiter and potential participant in terms of information provision, recruitment techniques, patient intervention preferences, and trial participation decisions. If analyses of the audio-recordings suggest that any recruitment difficulties are being caused by the recruitment consultation, findings will be shared with the recruiter and suggestions given on how to optimise recruitment.

4.11.6.2 Acceptability of FITNET-NHS and Activity Management

During the interviews with parents/carers (n=40) and their children (n=40) we will explore their views and experiences of treatment (see Section 4.13 on Integrated qualitative methods). During the interviews with trial staff (n=10) we will collect information on the feasibility of delivering the intervention to children; views on internet CBT and CFS/ME.

4.11.7 Outcomes of the full trial

If the internal pilot study demonstrates that it is feasible to recruit to this study and that the participants find FITNET-NHS and Activity Management acceptable, we will proceed to the full trial and cover the additional objectives outlined below:

4.11.7.1 Effectiveness of FITNET-NHS and Activity Management

We will investigate the effectiveness of FITNET-NHS compared to Activity Management using the following participant-completed questionnaires at baseline and 3, 6, and 12 months: SF-36-PFS, Chalder fatigue and CIS fatigue, School attendance, RCADS, Pain visual analogue scale and Clinical Global Impressions Scale. The primary outcome will be measure disability at 6 months using the SF-36-PFS. 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 will be used to assess the effectiveness in children with and without co-morbid mood disorders.

We will collect sufficient data at assessment to enable us to determine whether participants fulfil the CDC diagnostic criteria [31] (disabling fatigue >6 months, plus 4 additional symptoms (listed in Table 2): this will enable us to compare results with those of other studies.

4.11.7.2 Cost-effectiveness of FITNET-NHS and Activity Management

We will measure quality-adjusted life years using the EQ-5D-Y collected at baseline, 3, 6 and 12 months. We will investigate the cost-effectiveness of FITNET-NHS compared to Activity Management using the following parent-completed questionnaires at baseline and 3, 6, and 12 months: WPAI:GH and an adapted healthcare resource use questionnaire to measure the child's health service use (e.g. GP, specialist care or medications), educational service (e.g. school counsellor) and family expenses at baseline, 3, 6 and 12 months. We have tested the acceptability of these inventories in this participant group. The presence or absence of baseline anxiety or depression will be used to assess the cost-effectiveness in children with and without co-morbid mood disorders.

For participants allocated to FITNET-NHS, the FITNET-NHS platform will automatically record the number of times participants and their parents logged in to FITNET-NHS, the number of e-consultations sent by participants and parents and the number of times therapists responded as well as the number of modules completed. We will assume that participants and parents who complete 80% of the modules required have been adherent to treatment. For participants allocated to Activity Management, we will record the number of video (e.g. Skype) calls (assessment and follow up), the length of each call and the number of support calls to local providers.

We will request consent from participants to use routinely collected Hospital Episode Statistics (HES) data and (Mental Health and Learning Disabilities Data Set) MHLDDS from the Health and Social Care Information Centre (HSCIC, also known as NHS Digital), which will allow us to measure paediatric and CAMHS use in both arms. We will collect missing data from parental health care resource use questionnaires from general practice records, which will also be used to check accuracy of reported health care resource use and to determine how many children develop other illnesses. We will request consent to continue to link to administrative data (HES and MHLDDS) for longer term morbidity and service use outcomes. Resource use will be valued using national unit costs where available (e.g. NHS reference costs, Annual Survey of Health and Earnings).

4.12 Integrated qualitative methods

Qualitative research methods will be integrated into the internal pilot study to optimise the recruitment process and investigate acceptability of the interventions and wider trial processes. The research will be flexible in its intensity and comprehensiveness depending on the type of issues that emerge. Sources of difficulties will be fed back to the chief investigator and Trial Management Group (TMG) and suggestions made to change aspects of the design, conduct, organisation or training that could then lead to improvements in how the internal pilot study/full RCT is conducted.

4.12.1 Exploring issues with trial processes

The recruiter will receive a training session offering advice on discussing the study and treatments with patients to optimise recruitment and informed consent [49, 50]. All recruitment consultations in the pilot phase will be audio-recorded (with consent) to identify recruitment difficulties, with the option to continue to record these as necessary (e.g. for training) for the duration of the trial. The research team will analyse the audio-recordings regularly scrutinising the interaction between recruiter and potential participant and exploring information provision, recruitment techniques, patient intervention preferences, and trial participation decisions. If analyses suggest areas of difficulties then findings will be sensitively fed back to the recruiter and suggestions offered on how to overcome them [49, 50].

If the number of eligible patients recruited are lower than expected we may undertake in-depth interviews with members of the clinical and recruitment staff and analyse screening logs to examine problems with the patient pathway.

We will undertake in-depth interviews with parents/carers and their children to understand their views and experiences of trial processes. This will include: provision and acceptability of patient information and reasons for accepting or declining participation. We are particularly interested in understanding barriers to participation and will interview (subject to informed consent) those who choose not to participate in the trial, who drop out of trial follow up or who do not accept treatment allocation at randomisation.

4.12.2 Interviews

We will interview parents/carers and their children about both interventions including any prior exposure to the study treatments; beliefs, expectations and preferences about the treatments before assignment; their experiences and acceptability of the treatments; use of the FITNET-NHS interface; the use of video calls (e.g. Skype) for treatment delivery. We will also interview children and their parents about their use of video call (e.g. Skype) for Activity Management and the FITNET-NHS platform, whether they are acceptable interfaces to use and whether there are particular issues we need to consider in this patient group for the full trial (including whether being treated at home increases or decreases anxiety). Participants will be interviewed once unless they drop out of the trial, in which case we will seek consent to interview them about this to improve the trial.

We will interview (up to 10) trial staff including recruiting researchers and therapists delivering both treatments to ascertain their views on: information provision, recruitment techniques, the feasibility of delivering the intervention to children; changes that need to be made to the interventions offered; engagement, compliance and technical problems with using the FITNET-NHS and video call (e.g. Skype) interface.

Sampling for interviews will ensure that a range of informants (in terms of age, gender, ethnicity, geographical location, and disease severity) are included (maximum variation sampling), and that people with particular characteristics of interest can be targeted to follow-up and develop emerging findings (theoretical sampling). Interviews will be semi-structured using a topic guide to ensure interviews cover the same issues while allowing new issues of importance to emerge. All interviews will be audio-recorded with consent using encryption software, transcribed verbatim and anonymised.

Sample size for interviews will be determined by data saturation, i.e. when no new themes are being uncovered. It is anticipated that up to 40 patients, 40 parents and 10 trial staff will be interviewed.

Interviews will take place via telephone or video call (e.g. Skype). Children, parents and staff being interviewed will be asked to provide on-line consent via the REDCap system.

5. SAFETY

We will collect serious and non-serious adverse events using several methods. Participants and parents/carers can report serious and non-serious adverse events in e-consultations in FITNET and during the Skype follow up sessions of AM.

CFS/ME is by its nature, a fluctuating illness. The description of activity and function in CFS/ME is one of boom-bust which usually occurs over several days and sometimes weeks. “Payback” or “crashes” or “flares” are to be expected in young people whether or not they are undergoing treatment. Payback, crashes or flares, can mean that a child who was previously mobile becomes bed-bound or is unable to go to school. Episodes can last days or occasionally weeks. Treatment is designed to reduce these over time but the risk of flares without treatment, during or post treatment is not known.

Between 30 and 40% of children will experience significant co-morbid anxiety and depression. In most cases, this is because of the prolonged disabling nature of CFS/ME. This means that it is not unexpected for children with CFS/ME to be referred to Child and Adolescent Mental Health Services for treatment. Some children will be started on medical treatment including SSRIs. This is not unexpected. Data on medication for mood will be collected via parent questionnaires and review of medical records of the participating children. Other medication that is frequently used in this patient group (to treat sleep) is melatonin and amitriptyline (which is also used to treat chronic pain).

5.1 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. 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

5.2 Adverse Events

An adverse event is any untoward medical occurrence in a patient which does not necessarily have a causal relationship with the treatment. Data on adverse events will be collected for each participant from the point at which they consent to take part in the study until the end of the follow-up period (12 months).

All adverse events will be recorded on a case record form. At the conclusion of the study and during the safety analyses, all adverse events recorded during the study will be subject to statistical analyses and the analyses and subsequent conclusion will be included in the final study report.

The research team will only notify fatal and unexpected non-fatal adverse events to the trial Sponsor. Expected adverse events include payback, crashes or flares as described above. Expected adverse events will not be reported to the sponsor.

5.3 Serious Adverse Events

Any adverse event will be defined as a serious adverse event if: it results in death, is life threatening, requires hospitalisation or prolongation of existing hospitalisation, results in persistent or significant disability or incapacity.

These will be reported by the clinical team/participant or parent/carer to the research team. All SAEs will be recorded in detail on a case record form and reported to the Sponsor the next working day according to the Sponsor's protocol.

For all unexpected serious adverse events, the subject will be actively followed up, and the investigator (or delegated person) will provide follow-up every five working days after the initial report until the serious adverse event has resolved or a decision for no further follow – up has been taken.

5.4 Safety Analyses

The DSMC will specify how many independent safety analyses should be conducted and when these should be done. There will be one safety analysis conducted 10-11 months after the start of recruitment (before the trial transitions from the internal pilot to full phase). These analyses 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 Trial Steering Committee (TSC).

6. ANALYSES

6.1 Analyses of feasibility of recruitment

We will calculate the percentage of eligible children recruited. This will include the number (%) of those referred who were contacted by the research team, the number (%) who went through eligibility screening and the number (%) who had recruitment consultation. We will compare referrals and the number recruited between CRN regions. We will calculate retention at 6 months, defined as the proportion of children providing outcome data between 5 and 9 months after randomisation.

We will analyse interview transcripts to investigate trial recruitment and feasibility. Analysis will be ongoing and iterative commencing soon after data collection and will inform further sampling and data collection. Transcripts will be imported into NVivo, systematically assigned codes and analysed thematically using techniques of constant comparison. Individuals exhibiting contrasting attitudes ('negative cases') will be studied in detail. The perspectives of the individuals will be paramount, with careful account taken of the context within which the discussion takes place. To check coding reliability, a proportion of transcripts will be double coded and findings compared.

We will listen to a proportion of audio-recordings of the recruitment appointments by the research team to identify any recruitment difficulties. Content analytic methods will be used to describe in a structured manner what was said by whom and how often in the audio-recordings of recruitment sessions. More flexible grounded theory methods will be applied to identify common or divergent themes, particularly focussing on the impact of statements by the recruiter on patients. Targeted conversation analysis will be used to focus in detail on certain sections of the transcripts, for example, the interactions during which randomisation is offered. Findings will be shared with the research team and strategies to overcome difficulties will be discussed.

6.2 Analyses of acceptability of FITNET-NHS and Activity Management

We will analyse data collected from the interviews with patients, parents and trial staff to determine the acceptability of FITNET-NHS and Activity Management, using the techniques described above, paying particular attention to their experiences and acceptability of receiving or delivering the interventions.

6.3 Stop criteria

The STOP criteria have been agreed with the TSC prior to starting recruitment to the study. We will not proceed to the full trial: (1) if the recruitment rate is substantially below target (e.g. less than an average of 15 children per month (~80% of the target specified in Table 3) during the last 6 months of the internal pilot study (allowing for seasonal variation) AND if the qualitative data collected suggests that we cannot improve recruitment by changing recruitment methods, OR (2) the qualitative data suggests the interventions are not acceptable to children and/or their parents.

6.4 Analyses of effectiveness of FITNET-NHS compared to Activity Management

We will compare the mean SF-36-PFS scores at six months according to randomised allocation among participants with measured outcomes, using multivariable linear regression adjusting for baseline values of the outcome, baseline age and gender. Similar regression analyses will be conducted for secondary outcomes (linear regression for numerical outcomes and logistic regression for binary outcomes). For the primary outcome, we will conduct sensitivity analyses in which we adjust for prognostic variables for which there is a baseline imbalance between intervention arms. Further sensitivity analyses will use imputation methods to deal with missing data (if appropriate). Three month and twelve-month outcome data will be analysed similarly. We will estimate the effectiveness of FITNET-NHS compared with Activity Management for the SF-36-PFS primary outcome only among participants allocated to FITNET-NHS who complete at least module 19, (complier-average causal effect: CACE analysis) by using the randomized allocation as an instrumental variable for treatment completion. We will conduct sensitivity analyses estimating the effectiveness of FITNET-NHS compared with Activity Management for the SF-36-PFS primary outcome only restricted to participants who fulfilled the CDC diagnostic criteria for CMS/ME at the time of recruitment to the trial (~80% of those recruited).

6.5 Analyses of effectiveness for those with co-morbid mood disorders

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.

6.6 Analyses of cost-effectiveness of FITNET-NHS compared to Activity Management

Our primary economic evaluation to assess the cost-effectiveness of FITNET-NHS compared to Activity Management will compare incremental costs and health gains, measured in Quality Adjusted Life Years (QALYs), in a cost utility analysis from an NHS perspective. We will use a threshold willingness-to-pay of £20,000 per QALY [51] to estimate the incremental net monetary benefits of FITNET-NHS. We will use non-parametric bootstrapping methods to calculate 95% confidence intervals and create a cost-effectiveness acceptability curve to estimate the probability that FITNET-NHS is cost-effective at varying willingness-to-pay thresholds. Between-group analyses of incremental costs, QALYs and net benefits will be adjusted for baseline values, age, gender, EQ-5D-Y score and for variables where there is a baseline imbalance.

Secondary analyses will examine the wider impact of treatment on parent/carer work, productivity, and other family expenses.

6.7 Analyses of cost-effectiveness for those with co-morbid mood disorders

We will use net benefit regression to explore the interaction between pre-morbid mood disorders and the cost-effectiveness of FITNET-NHS.

6.8 Analyses of differences in negative thinking between those with co-morbid mood disorders and those without

Descriptive analysis will be used to compare the cognitive styles between depressed and non-depressed adolescents. It is predicted that those who are depressed will differ significantly on the overgeneralising and selective abstraction subscales of the CNCEQ-R, and on the catastrophizing subscale of the CBRSQ. Logistic regression will be used to investigate outcome between groups.

7. PROJECT MANAGEMENT

The TMG, in collaboration with the BRTC, will be responsible for overall trial management, monitoring trial progress and quality, and ensuring that the study protocol is adhered to and that participants are safe. They will meet every 6 weeks. The chief investigator, a BRTC statistician, the research team, and co-applicants (as relevant) will join this meeting.

The TSC will ensure milestones are realistic and achieved. The TSC will be responsible for reviewing the internal pilot study and advising the NIHR HTA over implementation of trial stopping rules. The TSC will include a patient and a parent/carer, have an independent chair and include 2 clinicians and 4 methodologists. The TSC will meet prior to the start of the trial and then annually.

The DSMC will include 3 independent experts in CFS/ME, medical statistics and trials. The DSMC will meet at the start of the study, after recruitment has been running for 10-11 months (before a decision is made about continuing the trial) and then annually. The DSMC will have un-blinded access to data. DSMC meetings will be timed to provide reports to the TSC.

The trial is funded by the NIHR Health Technology Assessment Programme. The Sponsor for this trial is the University of Bristol. Indemnity for the study will be provided by the University of Bristol.

8. ETHICAL CONSIDERATIONS

Ethics review of the protocol and other trial related essential documents will be carried out by a UK Research Ethics Committee (REC). Any changes to these documents following a favourable ethical opinion will be submitted as an amendment to the REC prior to implementation.

8.1 Ethical issues

The main ethical issue in the FITNET-NHS trial is which comparator group should be used. The Board specified that the comparator group should receive a NICE-recommended treatment. We considered this carefully and decided to use Activity Management supported by a specialist clinician. Activity Management is used by some paediatricians (or equivalent specialist doctors) in general paediatric clinics throughout the UK. The Bath Specialist CFS/ME service currently offers limited Activity Management support to children referred from parts of the UK that do not have access to local specialist services.

The second ethical issue is that we need to be certain that this trial recruits children with CFS/ME and not with other disorders that present with fatigue. We believe that it is unethical to ask children who are unwell and disabled by fatigue to travel long distances for an assessment. We have therefore put in place rigorous assessments to ensure that other causes of fatigue are diagnosed and referred for appropriate treatment. Children will follow NICE guidance and will have an assessment with a local paediatrician (or equivalent specialist doctor) and screening blood tests to exclude other causes of fatigue. There is then further assessment to ensure that they have chronic disabling fatigue and that this is their

primary symptom. Children will complete the RCADS online and the research team will use this and other screening questions to exclude significant and dominant anxiety/depression and other mental health disorders as a cause of the fatigue.

Given the reported effectiveness of FITNET in the Netherlands, we have considered whether it is ethical to randomise children to FITNET-NHS in the UK, or whether it should be implemented without a trial. We do not know if FITNET-NHS will be effective, compared with Activity Management, within the NHS where children have access to different treatments and the referral pathway is different, compared to the Netherlands. Further, FITNET-NHS cannot be implemented in the NHS without knowing whether it is cost-effective.

8.2 Risks and benefits

8.2.1 Potential benefits to participants

Most children in the UK are unable to access treatment because there is no local specialist service. Children who take part in this this study will be offered treatment delivered by specialist CFS/ME therapists in both treatment arms (Activity Management over video call (e.g. Skype) or specialist CBT for CFS/ME delivered online). If FITNET-NHS is effective and cost-effective, its provision by the NHS has the potential to deliver substantial health gains for the large number of children suffering from CFS/ME.

8.2.2 Potential harms to participants

There is a small risk that the trial may recruit children that do not have CFS/ME but instead have other disorders that present with fatigue. To avoid this we have put in place rigorous assessments to ensure that other causes of fatigue are diagnosed and referred for appropriate treatment. Children will follow NICE guidance and will have an assessment with a local paediatrician (or equivalent specialist doctor) and screening blood tests to exclude other causes of fatigue. There is then further assessment to ensure that they have chronic disabling fatigue and that this is their primary symptom. Children will complete the RCADS online and the research team will use this and other screening questions to exclude significant and dominant anxiety/depression and other mental health disorders as a cause of the fatigue.

If children are recruited with fatigue and other disorders, the treatment approaches offered are sufficiently generic approaches to fatigue, they are likely to benefit to some extent.

8.2.3 Potential benefits to society

Health economic benefits: Children with CFS/ME use significant health care resources. Most mothers of children with CFS/ME reduce or stop work [10]. Effective treatment has the potential to reduce NHS and wider societal costs and improve school attendance and quality of life. The trial is needed now because ~90% of children with CFS/ME do not have access to treatment shown to be effective.

Attitudes and awareness: Approximately 90% of GPs and paediatricians in England do not have effective treatments for children with CFS/ME. The dissemination programme will increase awareness among the public, GPs and paediatricians. If FITNET-NHS is effective, it will change attitudes about paediatric CFS/ME being “untreatable” to being “treatable”.

This trial will provide useful information on the treatment of co-morbid mood disorders and what factors are important mediators in paediatric CFS/ME. This is likely to change the treatment offered by specialist CFS/ME services and will generate hypotheses for researchers. This trial aims to provide an intervention in the homes of children throughout England. If it is feasible this method could be used for other long term conditions where children do not have local specialist services. Results from the qualitative methods will tell us about how to improve these type of interventions. This is likely to benefit children from other conditions, their families, clinicians and the NHS.

9. DATA PROTECTION & PARTICIPANT CONFIDENTIALITY

Data will be managed according to the Data Management Plan. In brief, children and young people are allocated a unique 7 digit research identification number. This number is assigned to the patient and is used on clinical assessment forms prior to transfer of data so they are anonymised at source. A list of names and corresponding identification numbers are kept separately and securely on a password protected NHS server. This number will be used on screening logs and on all data collected. Personal information will be kept on consent forms which will have contact details. Consent forms will be password protected and stored on-line on secure University of Bristol servers.

Data will be entered into REDCap a secure system used by multiple institutions for large multicentre studies. Assessment data will be entered by the research team as this is collected prior to assessment. Participants are required to log in to the system and have to pass authentication before they can access their own data. There are several authentication methods available. The University of Bristol will use table-based authentication, which utilizes the storage of username/password pairs in a database table. In this system, the password in the database table is encrypted as a one-way hash of the password. Participants will be sent a web link to REDCap which will only allow access to their data. They will create a password which they will use each time they log in. REDCap also has an auto-log out system that will log participants out after 30 minutes if they have stopped using the database.

Audio-recordings will be encrypted, password protected and stored on a secure university server for five years. This is to enable us to check recordings if necessary while reports are being written. Transcripts will be anonymised and secure password protected university server.

All study documentation will be retained in a secure location during the conduct of the study and for 5 years after the end of the study, when all patient identifiable paper records will be destroyed by confidential means.

10. DISSEMINATION & OUTPUTS

The main outputs from the trial will be the findings on whether FITNET-NHS is effective and cost-effective, compared with Activity Management, for children with CFS/ME and for those children with additional co-morbid mood problems. Additional outputs will include: 1) Detailed knowledge of health care resource use for children with CFS/ME in primary and secondary care, before during and after access to specialist treatment. 2) Development of specialist internet-delivered CBT for a long term condition, with knowledge and expertise on delivering this intervention throughout the NHS. 3) Data on acceptability of remote access to specialist services using the Internet and telephone/videophone (e.g. Skype) for children with a long term condition. 4) A further the understanding of cognitive styles to explain why some adolescents with CFS/ME become depressed. These results will be important to researchers, clinicians (GPs and paediatricians), patients and the public.

We will disseminate the findings to researchers by publishing results in open access high impact journals. We will ensure that the trial outcome is known to clinicians by presenting research findings at national and international conferences and meetings. We will cascade information through clinical and research networks including: the British Association for CFS/ME, the UK CFS/ME Research Collaborative (CMRC) and the NIHR National School of Primary Care Research (SPCR). We have a robust plan to raise awareness of CFS/ME and this trial in the first 18 months of this study. At the end of the trial, we will work to further disseminate the findings through blogs, emails, podcasts, Twitter etc. to clinicians and GPs.

We will disseminate results to patients through the regional and national paediatric charity (Association of Young people with ME) and adult patient support groups that we work with

as well as liaising with other charities to ensure dissemination throughout the UK. We will write “research in progress” articles for newsletters/websites, and speak at their meetings.

We will communicate with the public by giving a public engagement lecture, an open academic lecture, press releasing every publication and giving interviews.

We will disseminate results to politicians and policy makers using the All Party Parliamentary Group for CFS/ME and members of parliament who are part of the CMRC. We will inform NICE of the trial results so that results can be included in updated guidance.

11. SUMMARY OF CHANGES TO THE PROTOCOL

Previous version of protocol	Date	New version of protocol	Date	Summary of changes
1.0	18/08/2016	2.0	21/09/2016	On request from REC: - Figure 2 has been incorporated and section 4.4 amended to clarify which tasks are part of normal clinical care pathway and which are part of the research pathway. - Updated typos in section 4.6.1 and 4.6.2
2.0	21/09/2016	3.0	10/10/2016	On request from HRA: - Removal of interviews with GPs and paediatricians (sections 4.7.1, 4.11.6, 4.12.2, 6.2)
3.0	10/10/2016	4.0	30/11/2016	-Correction of Lucy Beasant’s title from Dr to Miss -Clarification throughout that patients can be assessed by paediatricians or equivalent specialist doctors e.g. if they are 17 years of age this will be a consultant medic (or e.g. neurologist) as 17 year olds are not always seen by paediatricians - Clarification of the eligibility criteria in section 4.4.3. The diagnosis of CFS/ME can only be made if the answer to the following questions about fatigue is yes/true: i) debilitating persistent or relapsing fatigue for at least 3 months, but not life-long; ii) not the result of ongoing exertion and not substantially alleviated by rest; iii) post-exertional malaise; and iv) severe enough to cause substantial reduction in previous levels of occupational, educational, social or personal activities, one on length of illness and twelve on symptoms. This has always been part of the clinical assessment.
4.0	30/11/2016	5.0	01/08/2017	a) <u>Staff changes</u>: Simon Price and Mary-Jane Willows have now left and have been removed from the co-applicants list on the protocol. Sarah Baos has been replaced by Emma Anderson as Trial Manager

Previous version of protocol	Date	New version of protocol	Date	Summary of changes
				- Protocol section amended: 'Research Team Contact Details' (p1-2) b) Activity Management increased to six (rather than 3) sessions. - Protocol sections amended: Section 1. Summary; Section 4.2, Figure 2; Section 4.6.1 (activity management (comparator)) c) Clarified duration of initial Activity Management assessment - Protocol section amended: 4.6.1 'Activity Management (comparator)' d) The Activity Management treatment can be delivered by specialist clinicians from the Bath CFS/ME team that are from different professional backgrounds, not just Occupational Therapists. - Protocol sections amended: Section 1: Summary Section 4.6.1. Activity Management (Comparator) Every further instance where "Occupational Therapist" is stated as the Activity Management therapist has been changed to "clinician" or "specialist clinician" for clarity.
5.0	01/08/2017	6.0	25/06/2018	1. The University of Bristol department name has changed to Population Health Sciences. Protocol amended (page 1-2) 2. Staff changes: Harriet Downing, Simon Price and Kirsty Garland have left the trial. Protocol amended and Aideen Ahern has joined (page 1-2) 3. PIC site and patient poster/flyer information added to protocol as section 4.2.3 "Referral for treatment". (protocol page 11) 4. Screening blood tests updated in table 2 to be in line with NICE recommendations. (protocol page 13) 5. Screening bloods information in protocol amended to be more in line with clinical recommendations (protocol page 13) 6. References to a 'Chat' function within the FITNET-NHS platform have been removed from the protocol as patients and therapists did not use this feature, so it was deleted from the platform. (protocol page 16 and 23) 7. Duration of treatment (activity management) detailed in protocol amended to state 6 months in line with expected

Previous version of protocol	Date	New version of protocol	Date	Summary of changes
				clinical course. (protocol page 16) 8. Protocol amended to state that we now follow up enrolled families for baseline completion via email reminders and phone call. (protocol page 18) 9. Protocol amended to state that we record all recruitment consultations in the pilot phase, but can continue to record throughout trial as needed). (protocol page 21 and 22) 10. Safety information in protocol updated to include comorbid mood (anxiety/depression) symptoms, referral and prescriptions as expected (and therefore not adverse) events in this patient group, along with other routine medication prescribed within CFS/ME treatment (protocol page 22-23)

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