HEALTH ECONOMICS ANALYSIS PLAN (HEAP) for FITNET-NHS

VERSION 1.0 (04/10/2021)

Contents

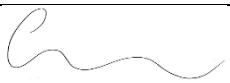
1. Administrative Information

1.1 HEAP Administrative Information

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?
Trial registration number; registry	ISRCTN registry: ISRCTN18020851
Source of funding	NIHR HTA Programme
Purpose of HEAP	The purpose of this HEAP is to describe the analysis and reporting procedure intended for the economic analyses to be undertaken. The analysis plan is designed to ensure that there is no conflict with the protocol and associated statistical analysis plan (SAP) and it should be read in conjunction with them.
Trial protocol version; date	This document is based on the published FITNET protocol (1) and the amendment to the published protocol (2). It is also based on the unpublished FITNET protocol v7.0, 2019-06-06.
Trial Statistical Analysis Plan (SAP) version, date	20210519_FITNETNHS_SAP_v1_0
Trial HEAP version, date	HEAP version 1.0, 04/10/2021
HEAP revisions	n/a
Roles and responsibilities	This HEAP was prepared by Dr Maddy Cochrane and approved by Professor Will Hollingworth. The trial health economists are responsible for conducting and reporting the economic evaluation in accordance with the HEAP.

APPROVALS

The following people have reviewed the Health Economics Analysis Plan and are in agreement with the contents.

Role	Name	Signature	Date
Author	Maddy Cochrane		14th July 2021
Lead Health Economist	Will Hollingworth		23rd July 2021
Chief Investigator	Esther Crawley		2nd October 2021

2. Trial Introduction & Background

2.1 Trial Background

2.1.1 Rationale

Chronic Fatigue Syndrome or Myalgic Encephalomyelitis (CFS/ME) is defined as generalised fatigue, causing disruption of daily life and persisting after routine tests and investigations (3, 4). Prevalence for CFS/ME amongst children in the UK is between 1-2.4% (5, 6). Children with CFS/ME are disabled (5,6) and use a significant amount of health care resources before accessing CFS/ME treatment (7). CFS/ME also impacts on the family, since parents often stop or reduce their time at work in order to care for their child (8).

Usual care for CFS/ME includes no treatment and treatment delivered by GPs or by therapists who do not specialise in CFS/ME. NICE recommends children with CFS/ ME are offered: Cognitive Behavioural Therapy (CBT) which uses strategies to change cognitive processes and resume activities; Graded Exercise Therapy (GET) where physical activity levels are stabilised before gradually increasing to manageable levels; or Activity Management, a goal-orientated and person-centred approach which establishes a baseline for all activity, including cognitive activities (school and homework), which is then increased (4).

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 around 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 (7). There is good evidence that CBT is effective in the treatment of paediatric CFS/ME (9). However, as most children in the UK are unable to access specialist CBT for CFS/ME delivered face to face, delivery of specialist CBT using the internet is an attractive option.

The original FITNET (Fatigue In Teenagers on the internet) trial, which was conducted in children with CFS/ME in the Netherlands(10), showed that internet-based CBT was effective compared to usual care at six months. Usual care in the original FITNET trial was not quantified but participants probably had access to therapy programmes provided by physical therapists who are often not specialists in CFS/ME. These therapy programmes include individual-or group-based rehabilitation programmes, CBT, GET, or both CBT and GET.

The FITNET-NHS (FITNET in the National Health Service) intervention evaluated in the present study has been developed, based on the Dutch FITNET (10) to deliver specialist CBT treatment over the internet for children and young adults with CFS/ME in the UK. Activity Management (delivered via telecare) represents usual care in this study, as it is the only NICE-recommended approach offered by some paediatricians (or equivalent specialist doctors) outside specialist services.

2.1.2 Co-morbidities: anxiety/ depression and CFS/ ME

More than 30% of children with CFS/ME also experience co-morbid anxiety and depression. Evidence from studies in adults indicate that CBT may be less effective in patients with co-morbid depression compared to those without depression (11). 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.

2.2 Aim of the trial

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 delivered over the internet for children with CFS/ME who do not have access to a local specialist CFS/ME service.

2.3 Objectives of the trial

2.3.1 Primary objective

- Estimate the effectiveness of FITNET-NHS compared to Activity Management in the NHS for paediatric CFS/ME where the primary outcome is disability at 6 months after randomisation, measured using the SF-36-PFS (Physical Function Scale) score.

2.3.2 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).

2.4 Trial population

2.4.1 Inclusion Criteria

1) Children aged 11 to 17 years.
2) Children with no local specialist CFS/ME service.
3) Children with CFS/ME defined using NICE guidance (4). Before being referred to the specialist service, children had to be assessed by a paediatrician (or equivalent specialist doctor) and have screening blood tests done to rule out other causes of fatigue, in accordance with NICE guidance(4). If there was no local specialised service (which is the case in approximately 90% of the UK), children were referred to the Bath Specialist CFS/ME Service where the specialist nurse determined if the child had CFS/ME by using questions on length of illness and other symptoms. Children who answer yes to these questions and therefore have 3 months of disabling fatigue plus one symptom (NICE guidance) were eligible. These included 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.

2.4.2 Exclusion Criteria

1) Children not disabled by fatigue.
2) Children whose fatigue is due to another cause.
3) Children or parents unable to complete videocalls due to limited internet access, or unwilling/unable to set up personal video call (e.g. Skype, Zoom) and email account.
4) Children or parents unable to complete FITNET-NHS modules (e.g. unable to read FITNET-NHS material, or significant development problems).
5) Children who report pregnancy at assessment.

2.5 Intervention and comparators

Bath Specialist CFS/ ME Service provided both treatment arms. Both interventions were delivered so that participants received treatment at home via the internet. For both groups, co-morbid mood disorder was identified via telephone/videocall at baseline by specialist nurses. The specialist nurses

used screening questions to identify co-morbid mood disorder including the Revised Children's Anxiety and Depression Scale (RCADS) questionnaire (Appendix A.2).

2.5.1 FITNET-NHS (Intervention)

2.5.1.1 Overview of FITNET and mode of delivery

FITNET (Fatigue In Teenagers on the interNET) NHS was an internet-delivered CBT programme delivered primarily by clinical psychologists (but also by a CBT therapist) from the Bath Specialist CFS/ME Service. The CBT programme comprised of 19 psycho-educational and CBT chapters for children and a parallel programme for parents. All care was provided by the therapists to the children and parents through email consultations (e-consultations). The total amount of care time scheduled for each family (inclusive of all child and parents' email exchanges) was 90 minutes and 60 minutes for the initial and follow up e-consultations, respectively. All e-consultations were recorded in the hospital's electronic medical records system (Millennium). Although, therapists scheduled 90- and 60-minute time slots per family for a specified date, there was flexibility on the actual date and time when the email exchange could take place. Children and parents who complete at least 80% of the chapters required, were considered to have adhered to treatment.

2.5.1.2 FITNET Materials

Children and their parents had separate e-consultations, FITNET platform accounts and log-ins. Children were asked to read through the FITNET chapters, answer questions and complete activity diaries online. The programme's chapters were based on CBT treatment specifically developed for children with CFS/ ME. For the children's programme, chapters 1 to 4 introduced CBT, explained the role of therapists, presented CFS/ ME as a multifactorial model with predisposing, precipitating, and maintaining factors, and discussed the role of the family. Chapter 4 focused on treatment goals including the goal of full-time education and chapter 5 focused on regulation of sleep-wake patterns. The CBT section was activated by a clinical psychologist once the child/ parent had completed the psycho-educational chapters. Chapters 6 to 19 focused on CBT strategies with instructions on exercises for identifying, challenging and changing cognitive processes that contribute to CFS/ME, and increasing self-efficacy with respect to fatigue, the ability to be active and work towards recovery. The 19 chapters for parents explored and addressed the parent's beliefs and behaviours towards their child with CFS/ME, focussing on their role as carers. In participants younger than 15 years, parents/ carers were supported to act as a coach for their child. In those older than 15 years, parents/ carers were encouraged to step back and support their child in taking responsibility for their treatment.

2.5.1.3 Schedule of key intervention components

2.5.1.3.1 Initial e-consultation

The first e-consultation comprised of supporting both children and parents to register on the FITNET-NHS platform. At this first consultation the therapist also explained the first few chapters of the programme. Therapists scheduled approximately 90 minutes per family (inclusive of all child and parents' email exchanges). Although each family was scheduled a 90-minute time slot, the actual date and time when the email exchanges took place could vary.

2.5.1.3.2 Follow up e-consultations

Following the initial e-consultation, the therapist provided ongoing support for the various chapters by scheduling follow up e-consultations every 1-3 weeks for a duration of approximately 6-12 months, with the frequency of the e-consultations decreasing over time. While participants were able to complete the chapters at their own pace, they were encouraged to work on, and complete, chapters before their next follow up e-consultation. The number of chapters worked on each week varied, with some chapters requiring several weeks and others being completed within one week. Children only completed the chapters which they needed, this meant they did not typically need to complete all chapters. Time allocated per chapter varied depending on a child's needs and whether they chose to have additional time to complete a chapter. Although each family was scheduled a 60-minute time slot for these ongoing e-consultations, the actual date and time when the email exchanges took place could vary. Some families required substantially more time per scheduled e-consultation. This additional support time was logged in the hospital's electronic medical records system by the therapists as an additional 30 minutes per family per scheduled e-consultation.

2.5.1.3.3 Further follow up e-consultations

After the 6-12 month intervention phase, all patients were offered a further follow up phase which involved the therapist sending e-consultations to the child and parent every three months (this was approximately 60-minute of the therapist's scheduled time per family). It was expected that most children would have completed the final chapters by the time they go onto this further follow-up phase. The further follow up phase was provided for an approximately six-month period before the therapist handed care back to the child's GP.

2.5.2 Activity Management (Comparator)

2.5.2.1 Overview of Activity Management and mode of delivery

Activity Management was delivered via videocall (i.e., Skype and Zoom) by various healthcare professionals (e.g. occupational therapist, physiotherapist, clinical psychologist) from the Bath

Specialist CFS/ME Service. Although both Activity Management and FITNET-NHS were delivered from the same site, no healthcare professionals delivered both FITNET and Activity Management. All children were offered up to six videocall appointments, these comprised: one initial assessment and up to five follow-up videocalls (children who took part in the pilot between 2016-2017 could only receive a total of three videocalls rather than up to six; the increased number of follow ups was introduced 23rd October 2017). Parents were not offered their own appointments with the therapist, although they could attend their child's appointment depending upon their child's preference.

2.5.2.2 Activity Management Materials

Children were sent information on CFS/ME, activity management, sleep and symptom management. Children were asked to record different types of activity – including cognitive activity (high concentration and low concentration) in paper diaries or via the iPhone/ iPad app "ActiveME". Recorded activity was used to help participants understand their baseline activity. Once the baseline activity was established, children were asked to record the total number of minutes spent each day doing high-energy cognitive activities (e.g. school work, home work, time on the computer and screens, reading and hobbies that require concentration and physical activity such as walking or PE). When children had managed their baseline activity for 1-2 weeks, they were asked to increase this amount by 10-20% each week (4, 11). Therapists discussed problems encountered by participants and provided possible solutions.

2.5.2.3 Schedule of key intervention components

2.5.2.3.1 Initial assessment videocall

At the initial assessment videocall (duration of around 90 minutes), the therapist discussed the different types of activity – including cognitive activity (high concentration and low concentration) – which varied according to age; carried out a detailed assessment of the individual's current activity levels; and collaboratively agreed a 'baseline', which was the average level of activity.

2.5.2.3.2 Follow up videocalls

The first follow up videocalls were scheduled to take place every 2-3 weeks over time the frequency of these follow ups reduced to every 4-6 weeks. During the follow-up videocalls (duration of approximately 60 minutes per follow up) the therapist reviewed activity and sleep and helped participants to problem-solve. Participants were encouraged to increase activity between sessions. Most children allocated to Activity Management receive all their initial and follow up videocalls within six months.

2.5.2.3.3 Further optional support from therapist to local clinician

After participants in the Activity Management arm had received all their follow up videocalls, therapists from the Royal United Hospitals (RUH) Bath NHS Foundation Trust's Specialist CFS/ME Service handed care over to a nominated clinician (e.g. GP, physiotherapist) who was local to the patient. The therapists offered the nominated clinician up to three telephone calls to advise the clinician on treatment options, overcoming barriers and symptom control for the child.

2.5.3 Medical Review (both arms)

Some children who required further support after completing the intervention, or after withdrawing from the intervention, were offered a medical review by a Clinical Psychologist at Bath Specialist CFS/ME Service. This medical review was for patients from both groups who could not be provided support by their local clinicians. Following the medical review, patients were typically offered further treatment such as CBT or GET by RUH Bath NHS Trust's Specialist CFS/ ME Service. Prior to the COVID-19 pandemic, the medical review was provided face-to-face. This meant uptake was relatively low due to the distance from the patient's home to Bath. Since the COVID-19 pandemic, RUH Bath NHS Trust's Specialist CFS/ME Service adjusted the delivery mode of their service and the medical reviews were provided via video consultation. It is anticipated that this change has led to higher uptake in medical reviews, for those coming to the end of treatment or withdrawing from the treatment they were allocated to.

2.6 Trial design

2.6.1 Randomisation

This study was an individually randomised RCT comparing FITNET-NHS with Activity Management in children with CFS/ME. An automated web randomisation service operated by the Bristol Randomised Trials Collaboration (BRTC) was used. Participants were randomised in a 1:1 ratio to receive either FITNET-NHS or Activity Management. Allocation used minimisation to facilitate balance by age (two categories, 11-14 and 15-17 years) and gender and retained a random component to prevent accurate prediction of allocation (i.e. preserve allocation concealment). Due to the nature of the interventions, it was not practical to blind either the child, parent or the clinical service to treatment allocation.

2.6.2 Sample size

The Minimum Clinically Important Difference (MCID) for the SF-36-PFS is 10 points (12) which is approximately 0.4 standard deviations (SD). In order to achieve 90% power at 5% significance to detect a 0.4 SD difference on the primary outcome (the SF-36-PFS), data on 266 children would be required. Attrition rates in September 2018 were at 15%, this meant 314 children would need to be recruited by the end of October 2020 (2).

The rate of co-morbid mood disorders in FITNET-NHS participants at baseline was investigated in October 2018. The rate (40%) was higher than the original estimates (30%). With the sample size target of 314 it was expected to be approximately 106 participants with co-morbid mood disorders (53 in each treatment group). This would give 53% power at 5% significance to detect a 0.4-SD difference on the primary outcome (SF-36-PFS) between treatment groups within this co-morbid subgroup.

2.6.3 Recruitment pathway

Young people were assessed by their GP, referred for local paediatric assessment and investigated using NICE guidance [4]. If a diagnosis of CFS/ME was made and there was no local specialist paediatric CFS/ME service (about 90% of UK cases), GPs were able to refer patients diagnosed with CFS/ME to the Bath specialist paediatric CFS/ME service. This was the standard referral pathway for out-of-area patients.

2.7 Trial start and end dates

Recruitment into the FITNET-NHS Trial began on 1 November 2016. Patients were recruited over a 48-month period up. The end of the trial for an individual participant and their parents/carers is 12 months after randomisation. The final follow up is therefore due by 11th November 2021.

2.7.1 Data collection schedule

2.7.1.1 Self-report data

Table 1 shows the schedule for the self-report data collection. The primary outcome was disability at 6 months after randomisation and was measured using the SF-36 physical function subscale questionnaire (SF-36-PFS) (13). Self-report secondary outcomes which were required for the economic evaluation were measured at four time points. At baseline and 3, 6 and 12 months after randomisation, children completed the Youth version of the EuroQoL health-related quality of life questionnaire (EQ-5D-Y) (14). At baseline and 3, 6 and 12 months after randomisation parents completed an adapted version of the Work Productivity and Activity Impairment Questionnaire

General Health V2.0 (WPAI:GH) (15). At 3, 6 and 12 months after randomisation parents completed a Healthcare Resource Use questionnaire on behalf of their child.

Table 1. Schedule of data collection.

	Data item	Baseline				Follow up		
		Referral letter	Eligibility assessment	Following recruitment	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			✓	✓	✓	✓

2.7.1.2 Routine data

Access to routinely collected medical records for children in the study was requested from national and local providers of primary (i.e. EMIS), secondary (i.e. NHS Digital and the RUH Millenium system) and mental health care data (i.e. NHS Digital). Only care received by the children in the 12 months after randomisation was included.

3. Economic Approach

3.1 Aims of economic evaluation

The aim of the economic evaluation is to evaluate whether an internet-delivered CBT package (FITNET-NHS) is cost-effective compared to Activity Management (delivered via videocall), and whether it should be offered by the NHS for treating children aged 11-17 years with CFS/ ME.

3.2 Objectives of economic evaluation

The primary objective is to answer the question: From the perspective of the NHS in the UK, what is the cost-effectiveness of an internet-delivered CBT package (FITNET-NHS) to treat children aged 11-17 years with CFS/ ME compared to Activity Management delivered via videocall, over a 12 month follow up period?

The secondary objectives will be to:

- Assess the cost-effectiveness of FITNET-NHS compared to Activity Management in children with and without co-morbid mood disorders.
- Examine cost-effectiveness from a wider perspective (including the patient and family/ carer costs, and impacts on education)

3.3 Overview of economic analysis

The within-trial cost-effectiveness analysis from the NHS and wider perspectives will use individual patient data from the FITNET-NHS trial. The primary economic analysis will be a cost-utility analysis (CUA) comparing the difference in costs to the NHS and the difference in quality-adjusted life years (QALYs).

3.4 Jurisdiction

The trial will be conducted in the UK where the health system is predominantly publicly funded and is free at the point of access.

3.5 Perspectives

The primary economic analysis will be from the NHS perspective which will include differences in resource use for primary and community care, secondary care and mental health services.

The wider perspective in this study wider perspective (including patient and family/ carer costs, and impacts on education).

3.6 Time horizon

All analyses will compare costs and outcomes over the first 12 months after randomisation. As CFS/ ME is a long-term condition, the positive impact of any successful therapy for CFS/ ME is likely to go beyond the 12-month time horizon. However, the research team have not been funded to conduct longer-term follow up including any extrapolation and evidence synthesis.

4. Economic Data Collection and Management

4.1 Statistical software use for health economic analysis

Stata version 16.1 or higher will be used for all health economic analyses.

4.2 Identification of resources

NHS resource use identified as relevant to the analysis are: (1) development of FITNET NHS platform; (2) staff training for FITNET NHS; (3) delivery of the interventions of interest; (4) primary and community care; other secondary care and mental health care use during follow up.

Patient/ carer and family resource use identified as relevant and important to include are: (1) out-of-pocket travel costs for health care visits; (2) over the counter medication costs; (3) loss in productivity; and (4) any other costs incurred due to the child's CFS/ ME.

4.3 Measurement of resource use

4.3.1 Development of FITNET NHS software

4.3.1.1 Planned and actual development of FITNET NHS software

Here we describe the development process of FITNET NHS software that occurred before the RCT and adaptations that would be needed for wider NHS roll-out, but we do not quantify the cost of this process or include it in our economic evaluation. We categorised it as a sunk cost which, if FITNET NHS is widely adopted, would be a cost which would be allocated across all patients who eventually use the system.

It had originally been intended that the FITNET NHS software would use an adapted version (largely similar but translated into English) of the software developed in the Dutch FITNET study. However, the software was not fit for purpose in terms of functionality and our PPI group did not feel the presentation was appropriate for UK adolescents. We therefore developed a new platform. This change required additional software to be developed so that the platform could be easily maintained, this included additional testing, deployment and monitoring functionality.

The FITNET NHS software was developed by staff at IT Services at the University of Bristol and an external contractor. Most of the staff and external contractor's time was allocated to development activities with just a small proportion of time allocated to planning, meeting and infrastructure activities. Development costs for the FITNET NHS software were funded by NIHR, the NHS and IT Services at the University of Bristol. As shown in Table 1, the main development costs were incurred near the beginning of the project in the financial year of 2016/17.

Table 1. Number of days developing FITNET NHS software

Financial year	**Effort in days***
2015/16	27
2016/17	109
2017/18	31
2018/19	49
2019/20	58
2021/21	24
Total days	**297**

*Inclusive of effort by staff at IT Services at University of Bristol and an external Contractor

4.3.1.2 Future developments

Although the FITNET NHS software developed for this study was reliable and robust, roll out of FITNET NHS as a long-term service would necessitate further development work so that the software can be used across multiple NHS trusts and information systems. The change in scope and bespoke nature of the FITNET NHS software in this study meant it did not include functionality to allow usage across multiple NHS Trusts. Adding such functionality is expected to require substantial changes to the software. In the short term, an alternative approach to wider implementation across multiple NHS Trusts would be to implement individual instances of the software at each Trust, however this would necessitate each Trust providing its own technical support, infrastructure and maintenance. Another

improvement to the FITNET NHS software would be to integrate the FITNET NHS platform data with NHS electronic medical records. The FITNET NHS software in this study used the participant's study identification numbers rather than NHS identifiers. It is expected that integration with electronic medical records in the future would require substantial information governance work and may also impact on the hosting requirements for the FITNET NHS application.

Future development work which could aim to provide a long-term service across multiple Trusts and information systems would be to re-platform the software rather than adapt the bespoke software used in this study. Re-platforming would allow for a new user experience and design phase as well as defining how the application should be hosted and integrated within NHS medical record systems. Further future work could also focus on how the application can be run and supported whilst in service and the size of the team required. Together, findings from this additional development work and learnings from the FITNET NHS study could be used to redevelop the FITNET NHS platform.

4.3.2 Intervention training and delivery costs

4.3.2.1 Staff training costs

Between November 2016 to January 2017, four clinical psychologists from Bath RUH Specialist CFS/ ME received four group face-to-face training days delivered by two external trainers on how to deliver FITNET NHS. Each training day involved around eight hours of the clinical psychologists' time which included preparatory work. In addition, the four clinical psychologists were provided with group supervision sessions which were delivered online by two external trainers. These group supervisory session were fortnightly across 2017 and were typically attended by around three of the four clinical psychologists.

Between 2017-2020, an additional six clinical psychologists and one CBT therapist received three group face-to-face training days delivered by an NHS clinical psychologist who had received training by the external trainers. In addition, staff trained in 2017 and 2018 received an additional group face-to-face training day to consolidate their learning and receive additional support from the external trainers.

Data on all face-to-face training sessions delivered between 2016-2020, were logged by a senior therapist at Bath RUH Specialist CFS/ ME service. Data logged included: dates when the training took place, and the number of clinicians and trainers who attended and provided the training, respectively. All staff were provided with a copy of a standard operating procedure (SOP) which outlined how to record FITNET-NHS e-consultations and contacts (made through the FITNET-NHS platform) in the RUH Bath NHS Trust electronic patient record system (Millennium).

4.3.2.2 Intervention delivery costs

The FITNET-NHS platform automatically recorded the number of times the child or their parent/carer logged onto the FITNET-NHS platform and the number of chapters the child or parent completed. Furthermore, the platform recorded the number of emails exchanged between the therapist and child or parent.

Patient-level data on the number and type of appointments was available for both the FITNET NHS and Activity Management interventions through RUH Bath NHS Trust's electronic patient record system (Millennium). The type of staff providing each appointment was also recorded in this system. Appointments were categorised as either initial or follow up appointments. One of the clinical psychologists who delivered the intervention was asked to allocate a standardised duration time to indicate the duration of a typical appointment type. The first appointment for both FITNET NHS and Activity Management were allocated a standardised time slot of 90 minutes. Follow up consultations including the medical reviews, for both intervention arms were allocated a 60-minute time slot per scheduled appointment. If a patient required substantially more support on a particular week, then an additional 30-minute time slot was logged in the Millennium system for that particular patient. Patients in the Activity Management arm who chose to have a clinician from RUH Bath NHS Trust provide telephone advice to a clinician in their local area had this activity recorded in their Millenium records. If a patient received another treatment option following their medical review the new treatment sessions were logged as face-to-face or Skype consultations.

4.3.3 Healthcare use

4.3.3.1 Routine data: primary care dataset

The FITNET-NHS trial intends to extract patient-level data from GP medical records to look at the primary care the child receives 12 months after randomisation (e.g. number of GP visits, tests undertaken, and medications prescribed). Patient-level primary care records will be requested as a bespoke extract from data extraction service provided by the EMIS Health GP IT system. The data extraction services at EMIS will link the primary care dataset with the FITNET NHS trial dataset using identifiable data for patient's involved in the FITNET NHS trial. These identifiers include: study ID number, NHS number, date of birth and postcode.

The FITNET NHS research team provided EMIS Health with a list of the GP practices where participants in the trial are registered at. The data extraction service was provided with each GP practice's unique identifier (NACS code) and/or customer number (CDB number) in order to identify which GP practices need to be sent a data sharing agreement. GP practices will then activate the

sharing agreement within their system so that patient-level records can be extracted. Data will only be extracted for participants who have provided consent for their medical records to be accessed and linked in this way, and from GP practices who have activated a data sharing agreement.

4.3.3.2 Routine data: secondary care and mental health datasets

Patient-level records will be requested as a bespoke extract from NHS Digital's Data Access Request Service (DARS). Hospital Episode Statistics (HES) datasets and the Emergency Care Data Set (ECDS) will be requested from NHS Digital for patient-level records on attendance at accident and emergency, admitted care and outpatient clinics at NHS hospitals in England in the 12 months after randomisation. In addition, the mental health dataset produced by NHS Digital will also be requested for patient-level records on use of NHS funded specialist secondary mental health care.

Bespoke data linkage will be carried out by NHS Digital. Data linkage involves linking NHS Digital's secondary care and mental health datasets with the FITNET NHS trial data. The University of Bristol will provide NHS Digital with identifiable data for the patient's involved in the FITNET NHS trial. These identifiers include: study ID number, NHS number, date of birth and postcode. Data will only be requested for participants who have provided consent for their medical records to be accessed and linked in this way. Examples of the data which will be extracted include: outpatient appointments, A&E attendances, admissions and discharges, elective emergency, operations, augmented care, diagnosis codes and healthcare resource group (HRG) codes.

4.3.3.3 Self-report data

Where routine data is available from the primary and secondary care electronic record, it will be used as the primary data source. Where routine data is not available (e.g. if linkage is not possible or a resource is not included in routine data), a resource use questionnaire (RUQ) (Appendices B.1-B.3), which had been piloted prior to the trial, was employed at 3, 6 and 12 months. The RUQ captured data from parent/carer(s) on their child's use of primary and community care, secondary care and mental health care.

Primary care questions included: (1) all types of GP surgery and telephone consultations with the GP and Practice Nurse/ Nurse Practitioner; (2) all types of GP home visits; and (3) all types of other primary and community-based contacts (e.g. walk-in centre visits, telephone calls to 111) (Question 4 in Appendix B.1-B.3). Medications include any prescribed medications as well as a list of specific medications (e.g. Amitriptyline, Melatonin, Paracetamol , Ibuprofen, Codeine, Other) (Question 5 in Appendix B.1-B.3). In addition, the RUQ captured secondary care use for the children as reported by

their parents/carers. Secondary care questions included outpatient, A&E, inpatient visits (Question 3 in Appendix B.1-B.3).

4.3.4 Wider costs: self-report data

4.3.4.1 Family out of pocket costs

The RUQ asked parent/ carer(s) to provide data on the costs they have incurred as a result of their child's CFS/ ME. Parents/carers were asked to report on out-of-pocket costs they incurred in the past three months at the 3 and 6 month follow up time point (Question 6 in Appendices B.1-B.2); and the past six months at the 12 month time point (Question 6, Appendix B.3): (1) cost of return journey to primary or community care centre, or hospital (for public transport this includes the cost of a return fare for the child and parent/ carer, for private vehicle this includes the cost of parking and fuel costs) (Questions 3 and 4 in Appendix B.1-B.3); (2) any over the counter medications purchased for their child (Question 5 in Appendix B.1-B.3); and (3) any other out of pocket expenses the parent/carer or the immediate family have incurred due to child's illness and (4) hours absent from work and regular activities due to child's health problems.

4.3.4.2 Parental productivity loss

Parents/ carers were also asked to report their productivity losses in the past seven days, using the adapted 6 item Work Productivity and Activity Impairment Questionnaire General Health V2.0 (WPAI:GH) (15). More specifically, they were asked to report about in the past seven days: (1) the amount of productivity lost at work due to child's health problems; and (2) the amount of daily activities (excluding work) impacted on due to child's health problems (Questions 1 and 2 in Appendix B.1-B.3).

4.3.4.3 Child educational costs

Parents were asked to report whether children had received support from a School counsellor in the past three months at the 3 and 6 month follow up time point (Question 4 in Appendices B.1-B.2) and the past six months at the 12 month time point (Question 4, Appendix B.3). At baseline, 3-, 6- and 12-month follow up, children were asked whether they are currently receiving home tuition (Question 3.2 and 2.2 in Appendices A.1 and C.1-C.3 respectively). In addition, in the follow up questionnaire children were asked to specify how many hours of home tuition they had received in the previous week (Question 2.3 in Appendices C.1-C.3). Children were also asked to report on the proportion of the week they typically attended school in the previous term (Question 3.1 and 2.1 in Appendices A.1 and C.1-C.3 respectively).

4.4 Valuation of resource use data

All primary and community healthcare resource use identified and measured will be valued in monetary terms using the latest Unit Cost series by the Personal Social Services Research Unit (PSSRU) (16). Secondary care and primary care tests (e.g. clinical biochemistry and haematology tests) will be valued using the latest NHS costs from the National Cost Collection (17). Prescribed medications will be assigned a unit cost from the British National Formulary (BNF) (18). When a unit cost is not available for the year of analysis, it will be inflated to current prices using the NHS cost inflation index (NHSCII) as published in the Unit Cost series (16). Actual prices reported by the patient's parent/carer(s) will be used for any out-of-pocket costs. Productivity costs will be derived from the Annual Survey of Hours and Earnings (19) using median pay per hour. Table 2 summaries how resource use to be measured and valued.

Table 2. Measurement and valuation methods for resource use items

Resource category	**Resource item**	**Measurement**	**Unit cost source**	**Unit cost (£2018/19)**	**Unit cost calculations/ assumptions**
Development costs	Number of days for development, meeting, planning and maintenance	• Timesheet records (2016-2021) by IT Services at University of Bristol	N/A	N/A	N/A
Intervention training costs	Number of sessions; Staff type attending and delivery training; Materials	• Training log sheets (2016-2019) • Health professional type and bands for NHS staff • Health professional type for external trainers (Dutch team)	NHS staff via Curtis and Burns 2019 Section 4, pages 143 & 150 (16); External trainers	Varies depending on staff type and band	Training took place in NHS locations and therefore capital costs are captured within the staff's unit costs- to check assumption
Intervention delivery costs	Number of appointments; Type of staff; Materials	• A standardised time for the initial and follow up consultations was assigned by the	NHS staff via Curtis and Burns 2019 Section 4,	Varies depending on staff type and band	For the primary analysis we will use the NHS provider perspective to cost the intervention. NHS provider perspective: this will be estimated using microcosting methods and use of

		Clinicians delivering the treatment and if a patient required additional time this was also recorded.; • Clinical IT system at Bath RUH (Millennium dataset)	pages 143 & 150 (16);		individual-level patient electronic health record data from the IT Millennium system.
Secondary healthcare	Number of A&E visits	• NHS Digital secondary care and mental health datasets; • RUQ Versions follow up only (no baseline) from 2017- 2021 (Question 3 in Appendix B.1-B.6)	National Cost Collection (17)	£168	Accident and Emergency outpatient visit
Secondary healthcare	Number of hospital outpatient visits	• NHS Digital secondary care and mental health datasets; • RUQ (Question 3 in Appendix B.1-B.3)	National Cost Collection (17)	Varies	Weighted average of outpatient visits

Secondary healthcare	Number of hospital inpatient admissions; Number of nights in hospital	• NHS Digital secondary care and mental health datasets; • RUQ (Question 3 in Appendix B.1-B.3)	National Cost Collection (17)	Varies	Estimated cost per night in hospital
Secondary healthcare	Other hospital appointments (e.g. mental health care)	• NHS Digital secondary care and mental health datasets; • RUQ (Question 3 in Appendix B.1-B.3)	National Cost Collection (17)	Varies	Estimated cost per night in hospital
Primary healthcare	Number of GP contacts at GP Surgery	• EMIS, SystmOne, Vision primary care datasets; • RUQ (Question 4 in Appendix B.1-B.3).	Curtis and Burns 2019, Section 2, page 119-120 (16)	£31	Cost per 9.22 minutes. GP face to face surgery costs including direct care staff costs but without qualification costs.
Primary healthcare	Number of GP contacts via telephone	• EMIS, SystmOne, Vision primary care datasets;	Curtis and Burns 2019 Section 2, 119-120 (16)	£23.90	Average telephone call of 7.1 minutes was taken from Curtis (2015).

		• RUQ (Question 4 in Appendix B.1-B.3).			
Primary healthcare	Number of GP contacts home visits	• EMIS, SystmOne, Vision primary care datasets; • RUQ (Question 4 in Appendix B.1-B.3).	Curtis and Burns 2019 Section 2, page 119-120 (16)	£71.30	Average travel time of 12 minutes was taken from Curtis (2015) and added to the average clinic consultation time of 9.22 minutes from Curtis and Burns (2018). It was therefore assumed the average time was 21.22 minutes.
Primary healthcare	Number of Practice Nurse/ Nurse Practitioner contacts at GP Surgery	• EMIS, SystmOne, Vision primary care datasets; • RUQ (Question 4 in Appendix B.1-B.3).	Curtis and Burns 2019 Section 2, page 118 (16)	£9.55	GP face to face surgery costs including direct care staff costs but without qualification costs. Assume telephone consultation is 15.5 minutes as reported in Curtis (2015).
Community/ primary care	Number of visits to walk in centre	• EMIS, SystmOne, Vision primary care datasets; • RUQ (Question 4 in Appendix B.1-B.3).	National Cost Collection (17)	Varies	Weighted average

Community/ primary care	Number of telephone calls to 111	• EMIS, SystmOne, Vision primary care datasets; • RUQ (Question 4 in Appendix B.1-B.3).	Pope et al. 2017 (20)	Adjust for price year	£12.26 per call (£2017)
Other community/ primary care contacts	Details of other contacts (free text)	• RUQ; • EMR	Curtis and Burns 2019 Section 2 (16)	Varies	Weighted average
Educational costs	Number of contacts with School Counsellor	• RUQ for the past 3 months at 3 and 6 month follow up time point (Question 4 in Appendices B.1-B.2) • RUQ for the past 6 months at the 12 month time point (Question 4, Appendix B.3).	Curtis and Burns 2019 Section 1 (16)	£94 per client-related hour	Assume the school is funding this service, based on Department for Education Report (2016) 'Counselling in schools: a blueprint for the future Departmental advice for school leaders and counsellors 2016' (21)
Educational costs	Hours of home tuition	• RUQ (Question 2.3 in Appendices C.1-C.3)	National Tutoring Programme (22)	£28 per hour for 2021	Assume private home tuition prices. The median for 2021 prices per hour was take from across five tutoring websites:

					• £22.03 per hour • https://tutorful.co.uk/blog/how-much-does-a-tutor-cost • £23 per hour for the average cost (2021 rates) • https://www.mytutor.co.uk/pricing/ • £28 per hour: • https://bristoltutors.co.uk/prices/ • £33 per hour: https://www.ashtutors.co.uk/pricing.html • £45 for hour (price ranged from £40-48 per hour for online and face to face): https://www.teacherstoyourhome.co.uk/process-and-prices
Primary care	Prescribed medication in the last 3 months as described on medication bottle/ packet	• EMIS, SystmOne, Vision primary care datasets; • RUQ (Question 5 in Appendix B.1-B.3).;	British National Formulary (BNF) (18)	Varies	Cost per quantity
Primary care	Number of tests	• EMIS, SystmOne, Vision primary care datasets;	National Cost Collection (17)	Varies	Cost per test

		• RUQ (Question 4 in Appendix B.1-B.3).			
Productivity	Absenteeism at work: Hours missed from work due to child's health problems	• RUQ (Questions 1 and 2 in Appendix B.1-B.3)	Annual Survey of Hours and Earnings (19)	£14.52 per hour.	Possible calculation: ONS average weekly earnings data in UK in 2018= £569 (median). Average hours worked per week were 39.2 hours (mean). ONS 2018. Hourly rate= £14.52 per hour.
Productivity	Presenteeism at work: Scale of impact (0-10) on productivity while working due to child's health problems	• RUQ (Questions 1 and 2 in Appendix B.1-B.3)	Annual Survey of Hours and Earnings (19)	£14.52 per hour at Zero on the scale of impact (0-10)	Apply proportionally. If the participant scores a 5 then we will assume this is 50% productivity. Hourly rate as described for Absenteeism data will be applied (Hourly rate= £14.52 per hour)
Productivity	Regular daily non-working activity: Scale of impact (0-10) on regular daily activities (excluding	• RUQ (Questions 1 and 2 in Appendix B.1-B.3)	Annual Survey of Hours and Earnings (19) ; Veerboy et al. 2018 (23)	£14 (€16)	Could apply the minimum wage or apply €16 per hour of unpaid/ leisure time lost for adults as suggested in Willingness to Accept study by Verboy et al. 2018

	work) due to child's health problems				
Family/ Carer costs	Out of pocket expenses	• RUQ recall for the past 3 months at the 3 and 6 month follow up (Question 6 in Appendices B.1-B.2); • RUQ recall for the past 6 months at the 12 month time point (Question 6, Appendix B.3):	Price reported by participant	Price reported by participant	

RUQ, Resource Use Questionnaire captures data on last 3 months at 3, 6 and 12 months post-randomisation; HES, Hospital Episode Statistics captures data on last 12 months at 12 months post-randomisation; EMR, Electronic Medical Records captures data at last 12 months at 12 months post-randomisation.

4.5 Identification of outcomes

The primary economic outcome measure was Quality Adjusted Life Years (QALYs) derived from utility scores, obtained using the EuroQoL health related quality of life questionnaire, Youth version (EQ-5D-Y). A secondary outcome relevant to the wider perspective is the child's foregone time in formal education.

4.6 Measurement of outcomes

The EQ-5D-Y (Baseline Questionnaire: Question 7.1 in Appendices A.1) and questions about time spent in education (Resource Use Questionnaire: Questions 3.1 and 2.1 in Appendices A.1 and C.1-C.3 respectively) were collected at baseline, 3, 6 and 12 months, using a participant self-completed questionnaire. At baseline the questionnaire was administered via post, at 3-, 6- and 12- month follow up it could be completed online. At 12 months, responses were included if they were received within three months after the final follow up timepoint.

4.7 Valuations of outcomes

At present, a UK value set for the EQ-5D-Y is not available and it is not recommended to use the adult value set as proxy value set for the EQ-5D-Y (24). If an appropriate EQ-5D-Y value set is available at the time of analysis patients' scores will be mapped to the value set in order to derive a utility score for each patient. The valuation set will enable a utility score to be calculated for each patient based on published UK population utility values. If no UK value set is available, we will consider using value sets recently derived in other European countries(25).

The area-under-the-curve approach will be used to transform utility scores into QALYs for the 12-month time horizon. Regression methods will be applied to generate appropriate estimates of differential mean QALYs and to control for any imbalance in baseline utility between arms. Controlling for baseline utility is necessary as previous literature has illustrated that a patient's baseline utility score is likely to be highly correlated with QALYs reported over the follow up period (26).

At present, there is a lack of valuation approaches for valuing a child's time foregone in formal education and so a monetary value will not be assigned for time lost education (27).

5. Economic Data Analysis

5.1 Analysis population

All patients who did not withdraw their consent to have their data used in the study will be analysed according to arm they were randomised to.

5.2 Timing of analyses

The final analysis will be conducted at the end of the trial.

5.3 Discount rates for costs and benefits

As costs and benefits will not be assessed beyond 12 months post randomisation discounting will not be required.

5.4 Cost-effectiveness threshold(s)

Adjusted mean costs and QALYs associated with each group will be combined through the Net Benefit (NB) framework. Cost-effectiveness will be evaluated using the NB framework over a range of values for the QALY, including the UK NICE recommended cost-effectiveness thresholds of £20,000-30,000 per QALY. We will use a threshold willingness-to-pay of £20,000 per QALY in the primary analysis.

5.5 Analysis of resource use and costs

Mean resource use will be estimated and presented by trial arm for each resource use category (e.g. outpatient visits, medication use, etc.). Standard deviations (SD) and the number of patients included in each category by arm will also be presented. Appropriate regression techniques will be used to estimate adjusted mean costs and the difference in adjusted mean costs (and their associated 95% confidence intervals) between the trial arms.

5.6 Analysis of outcomes

The primary economic outcome in the economic evaluation is Quality-Adjusted Life Years (QALYs). QALYs for each patient over the 12-month period will be calculated from the utility values using the area under the curve approach. Appropriate regression techniques will be used to estimate mean QALYs (adjusted for baseline utility scores) and the difference in adjusted mean QALYs (and their associated 95% confidence intervals) between the trial arms.

5.7 Data cleaning for analysis

Data variables not required for the economic analysis and duplicate data entries will be dropped from the dataset. Where there is uncertainty in the methodological choices made, these areas will be discussed between two health economists and where necessary a clinical expert will be consulted. In addition, face validity checks will be conducted on the data (e.g. to identify misspelt text and to check ranges of variables are appropriate) and queries will be checked against the original source documents. String and numerical values will be standardised and grouped for similar resource items to enable unit costing. All data cleaning will be documented in the Stata do files and log files.

5.8 Missing data

Missing data will be handled depending upon the prevalence and likely cause of the missingness. The mechanism of missingness will be assessed. For example, if the data is believed to be missing at random (MAR), then multiple imputation methods may be used (28).

5.9 Analysis of cost-effectiveness

Our primary analysis will combine cost and QALY data to calculate an incremental cost-effectiveness ratio (ICER) and net monetary benefit (NMB) statistic from the NHS perspective. Where missing data is believed to be substantial we will present imputed analyses as the primary analysis. More specifically, net benefit (NB) regression framework will be used to calculate each patient's incremental cost and effect together (29). The NB estimate will be used as the dependent variable in a regression equation where covariates (treatment allocation, age at recruitment, gender and baseline EQ-5D-Y) will also be accounted for. Regression model choice will be decided by inspecting the distribution of the data, covariates and correlation. If parametric methods are deemed inappropriate, then non-parametric methods such as bootstrapping may be used. In addition, the NB regression framework will be used to vary the willingness-to-pay (WTP) threshold and explore how the decision may change depending on the WTP value.

5.10 Sampling uncertainty

Uncertainty in the point estimates of NMB will be quantified using 95% confidence intervals estimated from the regression equations. NB regression equations estimated for various WTP values will also be used to indicate how sensitive the cost-effectiveness findings are at different WTP assumptions. Uncertainty will be characterised using cost-effectiveness acceptability curves (CEACs). The CEAC will illustrate the probability of FITNET-NHS being cost-effective compared to Activity Management across a range of WTP thresholds.

5.11 Subgroup analyses/Analysis of heterogeneity

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

5.12 Sensitivity Analyses

Uncertainty in the methodological choices made for the present economic evaluation will be assessed through a number of sensitivity analyses. This will involve making plausible changes to key methodological assumptions in order to understand how changes in the assumptions made impact on the cost-effectiveness result. Examples include:

- Assuming the fee per patient paid by the CCGs represent the intervention cost
- If applicable, different approaches to the handling of missing data e.g. complete case analysis

6. Reporting/Publishing

6.1 Reporting standards

The Consolidated Health Economic Evaluation Reporting Standards (CHEERS) guidelines will be followed when reporting the health economic evaluation, in a format appropriate to stakeholders and policy makers.

6.2 Reporting deviations from the HEAP

Prior to database lock and any comparative analysis of the final dataset, this HEAP will be finalised and published on the University of Bristol's research repository (PURE). Any deviation in the final analysis from the published HEAP will be documented and justified in the final published report.

7. Supplementary material

See supplementary materials: Appendix A-C.

8. References

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