Online treatment of myalgic encephalomyelitis / chronic fatigue syndrome in adolescents: a parallel groups randomised controlled trial comparing specialist cognitive behaviour therapy to activity management

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As a UK NIHR HTA funded study, a monograph of the whole study has been published as part of the NIHR journals library. This report summarises the quantitative findings of the randomised controlled trial:

Crawley E, Anderson E, Cochrane M, Shirkey B, Parslow R, Hollingworth W, et al. Comparison of cognitive behaviour therapy versus activity management, both delivered remotely, to treat paediatric chronic fatigue syndrome / myalgic encephalomyelitis: the UK FITNET-NHS RCT. Health Technol Assess 2024; 28(70):1–134. doi: 10.3310/VLRW6701

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A summary of the health economic analysis was presented at the ISPOR Europe conference, Copenhagen, Denmark, in November 2023, and has been published in abstract form at doi.org/10.1016/j.jval.2023.09.506

What is known:

- Paediatric ME/CFS has disabling impacts on physical and cognitive function. Although CBT has been shown to improve fatigue, disability and school attendance, few adolescents in the UK have access to a local specialist treatment service.
- Online delivery of CBT has been shown to be acceptable to, and effective in the treatment of adolescents with ME/CFS. Online delivery has the potential to improve accessibility to specialist treatment.

What is new:

- Online delivery of specialist CBT was successfully integrated into a UK National Health Service clinic, allowing referrals to be accepted from across the UK.
- Delivered online, specialist CBT for paediatric ME/CFS led to faster improvement in physical function compared to AM, but is unlikely to be good value for money.

Abstract

Purpose: Online delivery may improve access to specialist treatment services for paediatric Myalgic Encephalomyelitis / Chronic Fatigue Syndrome (ME/CFS).

Methods: This parallel group randomised controlled trial, with no masking of allocated treatment, compared the clinical and cost-effectiveness of two interventions delivered online: specialist Cognitive Behavioural Therapy (CBT) and Activity Management (AM; self-monitoring to avoid peaks and troughs in physical activity). Adolescents aged 11-17 years with a diagnosis of ME/CFS were allocated 1:1 to online CBT or AM using a centralised randomisation system with minimisation of differences in age and sex. The primary outcome measure was the physical function subscale of the 36-item Short Form Health Survey, completed by participants at six months post-randomisation. Primary analyses were of the observed data between groups as allocated. Cost-effectiveness was assessed from an NHS and wider perspective.

Results: Between Nov 1, 2016 and Oct 31, 2020, 314 patients were allocated to CBT (n=155) or AM (n=159). The primary outcome measure was completed by 127 and 138 participants in the CBT and AM groups respectively. The CBT group reported greater improvement in physical function at six months (adjusted difference in means 8.2, [95% CI 2.7 to 13.6], p=0.003). By twelve months, both groups had achieved similar levels of improvement (adjusted difference in means 4.4, [95% CI –1.7 to 10.5], p=0.16). One or more adverse events were reported for 28 (18%) CBT group participants and 18 (11%) AM group participants. CBT was more expensive than AM from the NHS perspective (difference in means £1,048, [95% CI £625 to £1470]).

Conclusion: Delivered online, specialist CBT for paediatric ME/CFS led to faster improvement in physical function compared to AM, but is unlikely to be good value for money.

Trial registration: The study protocol was registered at www.isrctn.com (4th August 2016, ISRCTN 18020851) before the start of participant enrolment.

Introduction

Adolescents with ME/CFS are disabled, use significant health care resources, and have their lives and those of their families disrupted.(1-3) Co-morbid anxiety and depression are experienced by 30% of adolescents with ME/CFS.(4-6) Despite this, few areas in the UK have a local specialist paediatric ME/CFS service.

Evidence from randomised controlled trials supports the effectiveness of cognitive behavioural therapy (CBT) in the treatment of paediatric ME/CFS.(7-10) The Dutch FITNET trial demonstrated that CBT could be delivered online to adolescents with ME/CFS (aged 12 to 18 years), with greater effectiveness compared to usual care at six months in reducing fatigue, and improving physical function and school attendance.(9) If the FITNET intervention can be adapted to be delivered in the UK, the online format could improve access to specialist care for paediatric ME/CFS.

Consequently, this study aimed to adapt the FITNET CBT intervention to UK National Health Service (NHS) and compare its clinical and cost-effectiveness to that of AM, with both interventions delivered remotely.

Methods

Study design and participants

The study methods and interventions are described in detail elsewhere.(11, 12) In brief, we conducted a pragmatic parallel groups randomised controlled trial comparing CBT (FITNET-NHS) against AM, with both treatments delivered remotely. The study was based in a specialist NHS ME/CFS service in the South-West of England, with referrals accepted from across the UK.(11, 12) Patients were eligible if: aged between 11 and 17 years; diagnosed with ME/CFS according to the NICE 2007 guidance;(13) and not living within the catchment area of a specialist paediatric CFS/ME service. The latter criterion was relaxed following the onset of COVID-19 lockdowns which reduced the availability of face-to-face appointments. Patients were excluded if: not disabled by fatigue;

fatigue was due to an identified cause; unable to complete video calls or access intervention content; or if the patient reported being pregnant.

The study included integrated qualitative methods to optimise recruitment.(14)

Randomisation and Masking

Once registered as a study participant, patients were randomly allocated (1:1) to the CBT group or the AM group. An online randomisation service (Bristol Trials Centre) minimised differences in age (11 to 14 years or 15 to 17 years) and self-reported sex at birth (male or female) whilst retaining a random component to ensure allocation was concealed.

Due to the nature of the study interventions, it was not possible to mask participants, parents or clinicians to treatment allocation.

Interventions

Both interventions were manualized. AM was delivered in up to six video calls (one assessment and up to five follow-up sessions) by specialist therapists (e.g. occupational therapists, nurses) over approximately six months. It is a behavioural treatment, with cognitive therapy approaches prohibited by the protocol. A consistently manageable level of physical and cognitive activity would be agreed between the patient and their therapist, which would be maintained daily before increasing the overall level of activity at a pace the patient could manage.

FITNET-NHS adapted the Dutch FITNET online CBT programme for paediatric ME/CFS, to the UK NHS. Separate online modules for both the patients and their parents are included. Psycho-educational modules (19 in total) included causes of the ME/CFS; the relationship between ME/CFS, anxiety, depression and other illnesses; and approaches to the treatment of ME/CFS. The first five modules were made available to all participants, with the remainder selected by the therapist according to participant needs. There were separate CBT modules for patients and their parents, delivered by specialist clinical psychologists and which took place over six months. Parent modules addressed the

parents' beliefs and behaviours towards their child with ME/CFS, focussing on their role as carers. Patient modules were based on a multi-factorial model of the illness, aiming to identify, challenge and change fatigue perpetuating cognitive-behavioural factors. Therapists worked with patients and their parents separately, email consultations taking place with both, typically every two weeks with homework tasks in between.

Outcomes and resource use measures

The primary outcome was disability measured using the 36-item Short Form Health Survey Physical Function subscale (SF-36-PFS), completed six months after randomisation.(15) This subscale has 10 items and scoring ranges from 0-100 with higher scores indicating better physical function.

Secondary outcome measures assessed self-reported fatigue, measured by Chalder Fatigue Scale(16) and the Checklist Individual Strength (CIS) fatigue severity subscale,(17) school attendance as days per week attendance at school and/or receiving home tuition; mood, measured by the Revised Children's Anxiety and Depression Scale (RCADS),(18) and pain, measured using a visual analogue scale.(19) The Clinical Global Impression Scale asked participants to rate their overall improvement since recruitment on a seven-point scale, from very much worse (score = 7) to very much better (score = 1), at the 6 and 12-month assessments.(20)

For the cost-effectiveness evaluation, patients completed the EQ-5D-Y measure of quality of life.(21) Parents were asked to record the following on a resource use questionnaire: the child's primary and community care service use, medication use, and parents' out-of-pocket costs. Parents reported on productivity loss by completing the Work Productivity & Activity Impairment Questionnaire: General Health (WPAI:GH).(22) Participants self-reported days attending school or receiving home tuition.

Treatment training costs were captured via study records; treatment delivery costs were captured via patient-level records respectively collected from the specialist service's informatic system; Child's

hospital inpatient, outpatient and emergency care data were collected via Hospital Episode Statistics (available from digital.nhs.uk).

For each session, clinicians reported any deviations from the treatment protocol and, at discharge, reported each participant's treatment adherence on a 3 point scale: i) non-starter; ii) started then stopped; iii) 80%+ completion (majority of clinically relevant modules attended/completed).

A serious deterioration in health was identified as either: (A) clinician-reported serious deterioration in health, reported as an adverse event; (B) a decrease of ≥20 in SF-36-PFS between baseline and 3-, six or twelve months, or scores of "much" or "very much" worse on the Clinical Global Impression Scale; or (C) participant withdrawal from treatment because of feeling worse. Adverse events were collected during each participant's 12-month follow-up period, and were defined as any untoward medical occurrence which does not necessarily have a causal relationship with the treatment.

All data were collected on a REDCap database (projectredcap.org) hosted at the University of Bristol. Participants and parents completed questionnaire measures online at baseline, and at three, six and twelve months post-randomisation.

Statistical Analysis

The revised target was to randomise 314 participants, which under the assumption of 15% attrition would result in data being returned by 266 participants.(11) This sample size gives 90% power at 5% significance to detect a 10-point (approximately 0.4 SD difference) minimal clinically important difference for the primary outcome.(23)

The statistical analysis plan was made publicly available on 6th October 2021 (accessible at isrctn.com). Analyses were conducted using Stata (version 17.0) software. The primary analyses compared participants in their allocated treatment groups, and included those patients returning the outcome measure under consideration. Outcomes with a continuous scale of measurement were compared between allocated groups using linear regression, the difference in mean outcome

score being estimated as the coefficient of a binary variable distinguishing participants in the two allocated groups. The baseline measure of the outcome plus age and sex were included as additional covariates. The seven response categories of the Clinical Global Impression Scale were accommodated in an ordered logistic regression model.

The analysis of the primary outcome was extended to compare the relative treatment effect between pre-specified subgroups of participants with co-morbid anxiety or depression and those without this co-morbidity. Pre-specified sensitivity analyses were conducted for the primary outcome measure, these being a model including additional baseline measures which were observed to be imbalanced between the allocated groups, and a model further adjusting for any variation between allocated groups in the time from random allocation to the six month outcome assessment. Recognising the impact of school closures during the COVID-19 pandemic, we repeated the analysis having added a covariate that distinguished participants recruited during September 2019 onwards, and would be due to complete the primary outcome during pandemic restrictions. A further pre-specified analysis used a mean score method to explore the potential effect of missing outcome data on the study's conclusions, in the situation where the risk of a missing response is associated with the participant's outcome.(24) Finally, an exploratory analysis repeated the primary analysis having omitted the one participant for whom there was insufficient information to know if they met the new NICE diagnostic criteria for ME/CFS.(25)

Utility scores were valued using a proxy EQ-5D-Y value set from Germany.(26) Quality-adjusted life years (QALYs) were calculated from utility scores using the area under the curve approach. Whenever possible, national published unit costs were used to value resources with 2019/2020 prices. The primary economic analysis was a within-trial cost-utility analysis (CUA) conducted from an NHS perspective over a 12-month time horizon. Seemingly unrelated regression and multiple imputation by chained equations were used to estimate mean incremental differences in costs and QALYs. Incremental net monetary benefit (INMB) was calculated to estimate cost-effectiveness at

the UK's thresholds of £20,000 per QALY. Secondary health economic analyses included: a subgroup analysis to explore the interaction between co-morbid anxiety or depression disorder and cost-effectiveness of CBT compared to AM; and analyses testing missing data assumptions and including a wider perspective incorporating parental/carer and educational costs.

Results

The specialist paediatric ME/CFS service received 892 referrals between 1 November 2016 and 31 October 2020, of which 550 patients were eligible to participate (Figure 1). Of these, 314 (57% of eligible) patients were recruited into the trial. The most common reason for declining to participate was a preference to travel to the hospital for face-to-face treatment (114 of 236 decliners, 48%). Follow-up concluded as planned on 11 November 2021.

The typical participant was 14 years old, white British, and a little more likely to be female (Table 1). Participants joined the study around a year and a half after illness onset, with about half having a comorbid mood disorder and most having a reduced school timetable. At recruitment, participants were physically disabled with low mean scores on the SF-36-PFS.

The vast majority of participants started their allocated treatment, although for 14% of the CBT group and 26% of the AM group, treatment started more than 3-months following random allocation (Supplementary Table 1). Relatively few CBT group participants (37%) were considered by their therapist as having completed 80% or more of the expected intervention components, contrasting with the majority of AM group participants (78%) judged to have met this criterion.

There was greater improvement at six months, as measured by the primary outcome, for those allocated to CBT compared to AM (Table 2). The adjusted mean difference was 8.2 (95% CI 2.7, 13.6, p=0.003) in favour of CBT. The sensitivity analyses indicated that the primary analysis results are robust and unchanged to variations in the assumptions of the statistical analysis (Table 2).

The primary outcome measure was missing for 28 (18%) participants in the CBT group, and 21 (13%) in the AM group. These participants reported having poorer physical functioning at recruitment

compared with the study cohort as a whole (non-responders in the CBT group mean 45.0, SD 22.4; AM group mean 38.2, SD 23.1). Supplementary Table 2 presents a sensitivity analysis of the potential impact of the missing data on the observed results, where the risk of a response being missing is associated with the participant's outcome. These analyses indicate that our finding of a benefit of CBT compared to AM at six months is robust to quite substantial biases due to missing data.

Table 2 also presents the pre-specified subgroup analysis. At the 6-month assessment of the primary outcome, less of an advantage of CBT over AM is observed in the group with comorbid anxiety or depression, but this difference could have arisen by chance (interaction p-value = 0.38).

Participants in both groups continued to improve, and at twelve months there was no longer evidence of a difference in mean physical functioning (SF-36-PFS) between CBT and AM (Table 3).

Participants in both groups had less fatigue at both six and twelve months on both the CIS-fatigue scale and the Chalder Fatigue Scale (Table 3). Whilst the Chalder Fatigue Score indicated similar improvements in both allocated groups, the CIS Fatigue scale provided evidence of a greater improvement of fatigue symptoms in the CBT group compared to the AM group at six months (difference in means -3.9, 95% CI -6.8, -1.0). At twelve months, participants in both groups improved further but the advantage for the CBT group was maintained.

There was modest evidence of greater reduction in pain in the CBT group at six months, but with the AM Group having caught up most of that advantage by twelve months (Table 3). The CBT group was seen to recover time at school more rapidly, with just over half a day per week more at six and twelve months compared to AM. There was no clear evidence of differences in the degree of improvement between the two groups according to responses to the Clinical Global Impression scale at both six and twelve months (Supplementary Table 3).

One or more adverse events or serious adverse events were reported for 28 (18%) participants in the CBT group and 18 (11%) participants in the AM group. In contrast, participants meeting the pre-

defined criteria for a worsening condition on the SF-36-PFS or CGI were evenly distributed between the two groups, with a composite of these different measures indicating about one quarter of participants in each group experiencing a worsening condition at some point in the 12-month follow-up period (Supplementary Table 4).

CBT resulted in slightly higher mean QALYs (0.002, 95% CI -0.040 to 0.045) and substantially higher means costs (£1,048, 95% CI £625 to £1470) compared to AM (Table 4). The negative INMB (-£1,002, 95% CI -£2041 to £38) and the shape of the cost-effectiveness acceptability curve across a range of willingness-to-pay thresholds (Supplementary Figure 1) indicated FITNET-NHS CBT was unlikely to be cost-effective compared to AM. Just over two thirds of participants had some data missing over the 12-month follow-up. Nevertheless, the complete case analysis also found FITNET-NHS is unlikely to be cost-effective (Table 4). Similarly, results from sensitivity analyses assuming data are not missing at random (Supplementary Table 5), and including a wider perspective (Supplementary Table 6) did not change our interpretation. The probability that FITNET-NHS is more cost-effective than AM was higher in the subgroup of patients with comorbid anxiety/depression, but it did not exceed 0.5 at conventional willingness to pay thresholds (Supplementary Table 7 and Supplementary Figure 2).

Discussion

This study has shown that adolescents with ME/CFS are more likely to have better physical function at six months and attend more school at both six and twelve months after participating in CBT compared to AM, when delivery is online. By twelve months, similar levels of improvement in physical function were achieved in both groups. However, the FITNET-NHS delivery of online CBT is expensive and is unlikely to be cost-effective in comparison with AM over twelve months. There was no clear evidence that the relative treatment effects differed between participants with and without co-morbid depression and anxiety. A composite of the pre-defined measures of a worsening condition indicated that about one quarter of the participants in both groups experienced worsening

symptoms during the 12-month follow-up, consistent with the chronic and fluctuating nature of ME/CFS. All but one participant met the NICE 2021 diagnostic criteria.(25)

The results of this trial are consistent with previous randomised controlled trials that have shown that CBT for fatigue, delivered face-to-face with children and young people with ME/CFS, results in improved physical function and school attendance.(8-10) However, considering responses to the CIS-20 fatigue scale, we observed less improvement with FITNET-NHS than was observed in either the FITNET or usual care groups in the Dutch RCT.(9) Potential explanations for these contrasting findings include differences in the participants, and differences in the way treatment was delivered. In fact the participants were broadly comparable between the two trials, other than about 45% of participants in the present study having clinically significant depression, compared with less than 20% in the Dutch RCT.(9) This difference is unlikely to explain the contrasting findings however, as the findings of the present study do not suggest that the relative effectiveness of CBT and AM was moderated by comorbid depression or anxiety.

In terms of intervention delivery and uptake, face-to-face consultations were prohibited by the FITNET-NHS protocol, this contrasting with the Dutch FITNET programme for which the initial assessments were conducted face-to-face. The low proportion of participants completing their recommended FITNET-NHS modules may have limited the observed impact, although engagement with the interventions is difficult to compare between the studies due to very different measures employed.

The main strengths of the study included the randomised allocation of the intervention, pragmatic evaluation of the interventions as delivered in an NHS service receiving referrals from across the UK, the economic evaluation, and good retention for the primary outcome assessment. The main limitation was the inability to blind participants and their families to their intervention allocation, hence bias may affect the patient-reported primary outcome.

Further limitations include the very high proportion of participants from White-British backgrounds, which whilst broadly in line with referrals to the specialist paediatric ME/CFS service, severely limits what we can learn about the treatment of ME/CFS in other ethnic and racial groups. Although retention was good in terms of the primary outcome, half of participants had some missing data over the 12-month follow-up, affecting the economic analysis in particular. Whilst the cost-effectiveness analysis adds to a very limited evidence base for paediatric ME/CFS, the 12-month follow-up may be a limitation in failing to capture any longer term benefits of a faster return to usual activities.(27)

We present evidence that online delivery can be used to provide effective care to adolescents with ME/CFS who cannot access a local specialist service. However, as CBT costs more and the advantage over AM diminishes by twelve months, the FITNET-NHS programme was not cost-effective at conventional NHS thresholds. Policy-makers need to consider whether CBT can be delivered online as effectively but at lower cost.

Supplementary information

The online version contains supplementary material available at:

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Authors' contributions

EC was the chief investigator. EC, GB, DG, WH, DK, HK, JM,CM were responsible for the study design. EC, GB, WH, DK, HK, JM, CM, NM, SN, PS, EvdP were the grant holders. EC, JM, DK, PS, CM, NM, ML, EvdP were members of the trial management group. EA, MR, GTE co-ordinated the trial operations. BS, DG, CM planned and conducted the statistical analysis. AA, MC, WH planned and conducted the health economic analysis. NM, RP conducted the qualitative research and analysed the resulting data. GTE, EC, EA, MR, MC, WH, BS, CM, DK, JM contributed to the first draft of the manuscript. All authors had full access to data, collated data, interpreted data, edited, reviewed, and approved the final manuscript, and had final responsibility for the decision to submit for publication. All authors affirm that the manuscript is honest, accurate and transparent account of the study being reported; that no

important aspects of the study have been omitted; and that any discrepancies from the study as planned have been explained.

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Data availability

Given the nature of this dataset, access is controlled. Queries should be directed to the corresponding author. Access to data may be granted following review of the proposal and completion of a data sharing agreement.

Declarations

Ethical approval

This study was performed according to the principles of the Declaration of Helsinki. The study protocol and all associated documents were reviewed and approved by the South-West (Frenchay) Research Ethics Committee (reference 16/SW/0268), via the Integrated Research Application System (project ID 211202).

Consent for publication

Participants aged 11 to 15 years completed an assent form, while participants aged 16 to 17 years completed a consent form, with parents of all participants completing a consent form.

Disclaimer

This report describes independent research, and the views expressed in this publication are those of the authors and not necessarily those of the UK National Institute for Health and Care Research or the UK Department of Health and Social Care. The funder had no role in the collection, analysis, interpretation of data, writing of the report, or the decision to submit the article for publication, other than arranging review of the original funding application, and of the final report.

Competing interests

HK and GB received royalties from the publication and sale of a treatment manual for Cognitive Behaviour Therapy in ME/CFS in adults. The other authors have no conflict of interest to declare.

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Figure 1. CONSORT flow chart

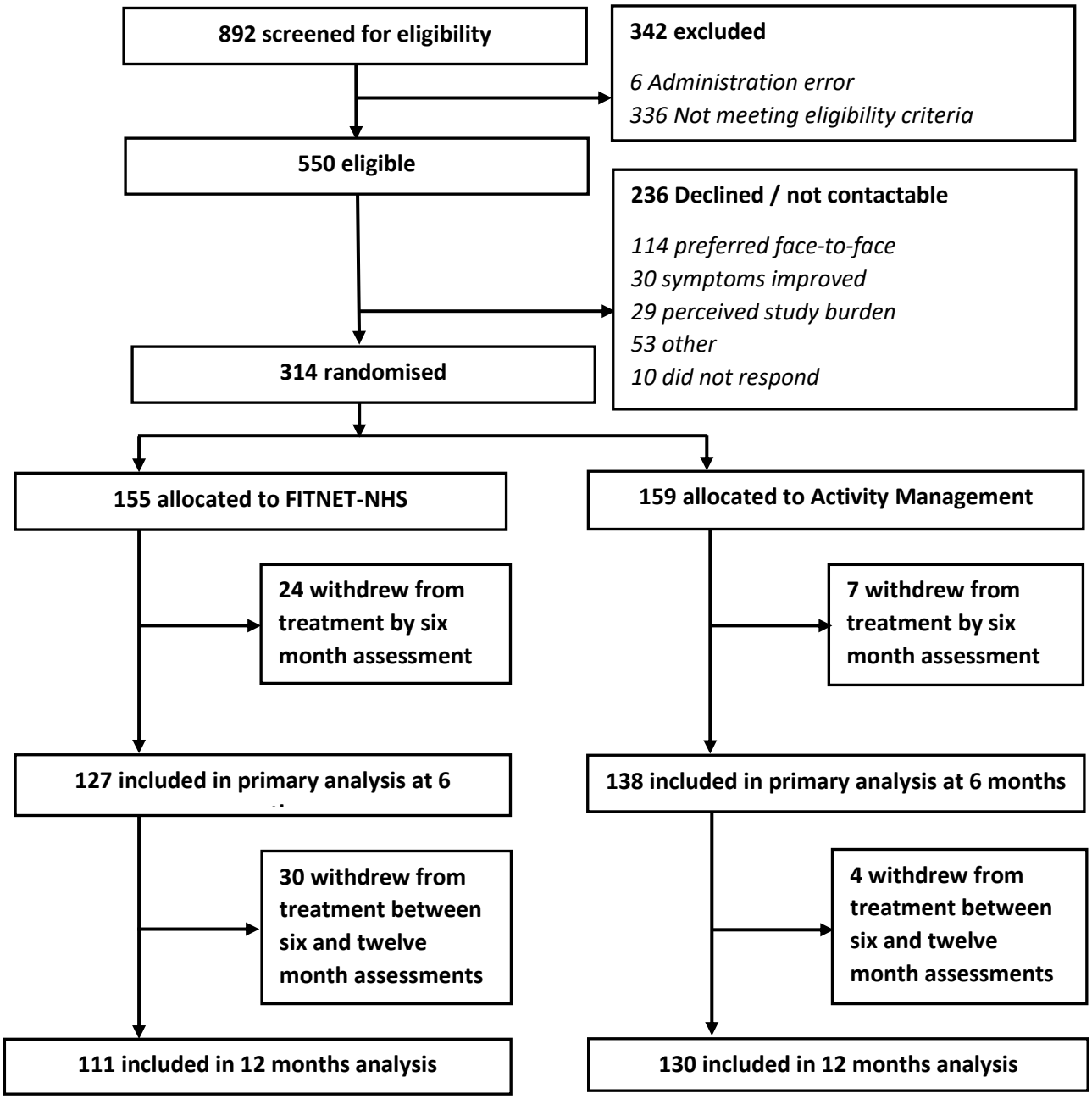

Table 1. Characteristics for the randomized participants at baseline

	FITNET-NHS (n=155)	**Activity Management** (n= 159)
Mean age in years (SD)	14 (1.6)	14 (1.8)
Number female (%)	98 (63%)	100 (63%)
Number White-British ethnicity (%)	142 / 150 (92%)	144 / 151 (91%)
Median months since illness onset (25^{th}, 75^{th} percentiles)	16 (9, 30)	18 (11, 30)
Number comorbid anxiety[1] (%)	15 (10%)	19 (12%)
Number comorbid depression[1] (%)	69 (45%)	76 (48%)
Number recruited during COVID-19 school closure (%)[2]	29 (19%)	33 (21%)
School attendance in the previous week		
None	35 (23%)	37 (23%)
About 10% to 40% (e.g. one half to two days)	43 (28%)	42 (26%)
About 60% to 80% (e.g. three to four days)	53 (34%)	53 (33%)
Full time (100%)	13 (8%)	14 (9%)
Not applicable (N/A)	6 (4%)	5 (3%)
Not answered	5 (3%)	8 (5%)

1. Determined clinically using the RCADS
2. Randomized after March 18, 2020, date of school closure due to the COVID-19 pandemic

Table 2. Summary statistics and treatment effect estimates for the Short Form 36 Physical Function at the 6-month assessment point (primary outcome measure, higher scores better functioning)

	FITNET-NHS	**Activity Management**		
	Mean (SD), N	Mean (SD), N	Difference in means (95% CI)	p-value
Baseline measurement	49.8 (21.9), 150	47.1 (23.6), 151		
Primary outcome at 6 months	60.5 (29.5), 127	50.3 (26.5), 138	8.2 (2.7, 13.6)	0.003
Sensitivity analyses:				
Covariate added: days after randomisation outcome completed[1]	60.5 (29.5), 127	50.3 (26.5), 138	8.6 (3.2, 14.1)	0.002
Covariate added: randomized before / after 1st September 2019	60.5 (29.5), 127	50.3 (26.5), 138	8.2 (2.7, 13.6)	0.003
6 or 12 months assessment used according to when intervention started	59.5 (29.6), 131	50.6 (27.2), 141	7.2 (1.8, 12.5)	0.009
Participants included if attending 1+ sessions	60.9 (29.3), 126	50.7 (26.0), 134	8.5 (3.1, 14.0)	0.002
Post-hoc sensitivity analyses new definition ME/CFS (NICE 2021)	60.5 (29.5), 127	50.5 (26.4), 137	8.0 (2.5, 13.4)	0.004
Subgroup analysis				
Baseline assessment:				
Co-morbid anxiety or depression	43.8 (20.1), 69	42.1 (21.0), 73		
No co-morbid anxiety or depression	54.8 (22.2), 81	51.7 (25.0), 78		
6 month assessment:				
Co-morbid anxiety or depression	52.1 (30.3), 55	45.3 (25.3), 64		
No co-morbid anxiety or depression	67.0 (27.3), 72	54.5 (27.0), 74		
Interaction effect [2]			-4.9 (-15.9, 6.1)	0.38

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

Table 3. Summary statistics and treatment effect estimates for the secondary outcome questionnaire measures at 6 and 12 months

	FITNET-NHS	**Activity Management**	Difference in means (95% CI)	p-value
	Mean (SD), N	Mean (SD), N		
SF-36 PFS 12 months	62.9 (29.1), 111	57.8 (27.9), 130	4.4 (-1.7, 10.5)	0.16
Chalder Fatigue: score range 0 to 33, high scores = greater fatigue				
Baseline	25.4 (4.6), 150	24.7 (5.3), 150		
6 months	20.1 (7.7), 118	20.0 (7.6), 132	-0.5 (-2.2, 1.3)	0.60
12 months	19.3 (8.0), 105	19.5 (8.1), 124	-0.8 (-2.7, 1.2)	0.44
CIS Subjective Fatigue 8-item Subscale: score range 8 to 56, high scores = greater fatigue				
Baseline	48.8 (6.4) 150	47.7 (7.6) 151		
6 months	41.2 (12.6) 77	43.7 (9.4) 101	-3.9 (-6.8, -1.0)	0.009
12 months	37.6 (13.2) 74	40.7 (11.0) 88	-3.9 (-7.4, -0.4)	0.029
Pain VAS: score range from 0 to 100, high scores = greater pain intensity				
Baseline	47.5 (28.1), 150	49.5 (27.1), 151		
6 months	35.3 (27.9), 81	43.8 (26.7), 102	-5.9 (-12.2, 0.5)	0.072
12 months	35.2 (29.1), 74	37.8 (27.3), 88	-0.4 (-7.9, 7.2)	0.92
School attendance: as a percentage of full-time, high scores = greater school attendance				
Baseline	42.6 (34.9), 144	42.6 (35.1), 146		
6 months	52.2 (37.4), 116	41.8 (36.5), 121	12.0 (4.9, 19.0)	<0.001
12 months	56.7 (38.8), 97	46.7 (39.8), 111	12.4 (3.3, 21.5)	0.008

Table 4. Primary Health Economic analysis and complete case sensitivity analysis for missing data

		Adjusted[1], mean (95% Confidence Interval)		**Incremental adjusted[1] mean (95% Confidence Interval)**			
Trial group	**n**	**Costs (£)**	**QALYs**	**Costs (£)**	**QALYs**	**ICER (£/QALY)**	**iNMB at £20,000 / QALY (95% CI)**
Primary analysis: SUR with MI and MAR assumption							
FITNET-NHS	155	£2826	0.532	£1048	0.002	£457721	-£1002
		(£2525 to £3126)	(0.501 to 0.564)	(£625 to £1470)	(-0.041 to 0.045)		(-£2041 to £38)
Activity Management	159	£1778 (£1481 to £2075)	0.530 (0.501 to 0.558)				
Sensitivity analysis: SUR with Complete Case and MCAR assumption							
FITNET-NHS	39	£2912	0.582	£1287	0.020	£63768	-£884
		(£2490 to £3333)	(0.529 to 0.636)	(£731 to £1844)	(-0.051 to 0.091)		(-£2477 to £710)
Activity Management	53	£1624 (£1263 to £1985)	0.562 (0.516 to 0.608)				

1. Adjusted for age and gender for both costs and QALYs. In addition, QALYs were adjusted for baseline utility; SUR= Seemingly Unrelated Regression; MI= Multiple Imputation; MAR=Missing At Random; MNAR=Missing Not At Random; CI= confidence interval; iNMB= incremental net monetary benefit

Supplementary Material for:

Online treatment of myalgic encephalomyelitis / chronic fatigue syndrome in adolescents: a parallel groups randomised controlled trial comparing specialist cognitive behaviour therapy to activity management

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Supplementary Table 1. Treatment Fidelity and Adherence

	FITNET-NHS (n=155)	Activity Management (n=159)
Number not starting allocated treatment (%)	3 (2%)	9 (6%)
Number completing 80% or more of expected modules / sessions of allocated treatment (%) (therapist judgement)	58 (37%)	124 (78%)
Number starting allocated treatment more than three months after allocation (%)	22 (14%)	42 (26%)

Supplementary Table 2. Sensitivity analyses under different assumptions about the missing primary outcome data in the CBT group. In each case non-response in the AM group is assumed to be missing at random. A positive difference in means indicates an benefit of CBT compared with AM.

	Difference in mean physical function	95% confidence interval
Primary analysis – complete case estimate (From Table 2)	8.2	(2.7, 13.6)
Non-respondents on average 5 points lower (A lower level of improvement in non-responders)	7.2	(1.8, 12.7)
Non-respondents on average 10 points lower (No change from baseline in non-responders)	6.3	(0.9, 11.76)
Non-respondents on average 15 points lower (A deterioration compared to baseline in non-responders)	5.4	(-0.12, 10.9)

Supplementary Table 3. Participant-rated Clinical Global Impression Scale of change in overall health from baseline

	FITNET-NHS	**Activity Management**	**Odds ratio (95% CI)**	**p-value**
Change from baseline (6 months)				
Much better or very much better (%)	40 (33%[2])	38 (30%)		
Minimal change (%)[1]	69 (57%)	85 (64%)		
Much worse or very much worse (%)	12 (10%)	9 (7%)	1.13 (0.73,1.77)	0.58
Missing	*34*	*27*		
Change from baseline (12 months)				
Much better or very much better (%)	47 (43%)	44 (34%)		
Minimal change (%)[1]	54 (50%)	74 (58%)		
Much worse or very much worse (%)	8 (7%)	10 (8%)	1.15 (0.73,1.83)	0.54
Missing	*46*	*31*		

1. Includes the responses “no change”, “a little better”, and “a little worse”. Categories are not combined when estimating the odds ratio
2. Percentages are out of non-missing answers.

Supplementary Table 4. Safety measures

	FITNET-NHS (n= 155)	**Activity Management (n=159)**
Number of participants with clinician report of worsening condition (%)	3(2)	1(1)
Number of participants reporting worsening condition on withdrawing from treatment (%)	7(5)	0
Number of participants with evidence of worsening condition from SF-36 Physical Function or the Clinical Global Impression scale (%)[1]	36 (23%)	41 (26%)
Number of participants with any evidence of worsening condition – one or more of the above (%)	39 (25%)	42(26%)

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

Supplementary Table 5. Cost-effectiveness of FITNET-NHS compared to Activity Management under different MNAR assumptions for missing health-related quality-of-life data

Scenario number	MNAR rescaling parameters[1]		Incremental cost[2] (£) (95% CI)	Incremental QALYs (95% CI)	INMB[3] (£) (95% CI)	Probability cost-effective (%)
	AM	FITNET-NHS				
MAR	1	1	£1048 (£624 to £1470)	0.002 (-0.041 to 0.045)	-£1002 (-£2041 to £38)	2.95
1	1	0.95	£1048 (£624 to £1470)	-0.002 (-0.045 to 0.040)	-£1097 (-£2128 to -£65)	1.86
2	0.95	1	£1048 (£624 to £1470)	0.006 (-0.037 to 0.049)	-£930 (-£1967 to £107)	3.94
3	0.95	0.95	£1048 (£624 to £1470)	0.001 (-0.041 to 0.044)	-£1025 (-£2054 to £4)	2.54
4	0.95	0.90	£1048 (£624 to £1470)	-0.004 (-0.046 to 0.039)	-£1120 (-£2142 to -£98)	1.59
5	0.90	0.95	£1048 (£624 to £1470)	0.005 (-0.038 to 0.047)	-£953 (-£1981 to £74)	3.45
6	0.90	0.90	£1048 (£624 to £1470)	-0.000 (-0.042 to 0.042)	-£1048 (-£2069 to -£28)	2.20

1. For example FITNET-NHS= 0.9 means that all imputed quality-of-life values in the FITNET-NHS group have been reduced by 10%.
2. Missing costs were assumed to be MAR in all scenarios.
3. At a cost-effectiveness threshold of £20,000 per QALY. AM= Activity Management, CI= confidence interval, INMB= incremental net monetary benefit, MAR= missing at random, MNAR= missing not at random, QALY= quality-adjusted life year.

Supplementary Table 6. Health Economic additional analyses

Trial group	n	Adjusted[1], mean (95% CI) Costs (£)	QALYs	Incremental adjusted[1] mean (95% CI) Costs (£)	QALYs	ICER (£/QALY)	iNMB at £20,000 /QALY (95% CI)
Wider perspective[2]							
FITNET-NHS	155	£8458 (£7338 to £9578)	0.536 (0.506 to 0.566)	£1214 (-£260 to £2688)	0.006 (-0.037 to 0.048)	£215276	-£1101 (-£2910 to £708)
Activity management	159	£7244 (£6242 to £8247)	0.530 (0.501 to 0.566)				
Sensitivity analysis: Assuming the fee per patient paid by the CCGs represents the intervention cost							
FITNET-NHS	155	£4546 (£4214 to £4878)	0.535 (0.504 to 0.565)	£2080 (£1613 to £2546)	0.005** (-0.036 to 0.049)	£355656	-£1963 (-£3006 to -£919)
Activity management	159	£2466 (£2138 to £2794)	0.529 (0.499 to 0.559)				
Sensitivity analysis: Excluding FITNET-NHS training costs							
FITNET-NHS	155	£2496 (£2195 to £2796)	0.532 (0.500 to 0.564)	£717 (£295 to £1140)	0.002 (-0.041 to 0.045)	£313489	-£672 (-£1711 to £368)
Activity management	159	£1778 (£1481 to £2075)	0.530 (0.501 to 0.558)				
Sensitivity analysis: FITNET-NHS delivered by Band 6 clinicians							
FITNET-NHS	155	£2653 (£2354 to £2953)	0.533 (0.502 to 0.564)	£875 (£454 to £1296)	0.003** (-0.038 to 0.046)	£258839	-£807 (-£1837 to £222)
Activity management	159	£1778 (£1483 to £2074)	0.530 (0.501to 0.558)				

Supplementary Table 6. Continued.

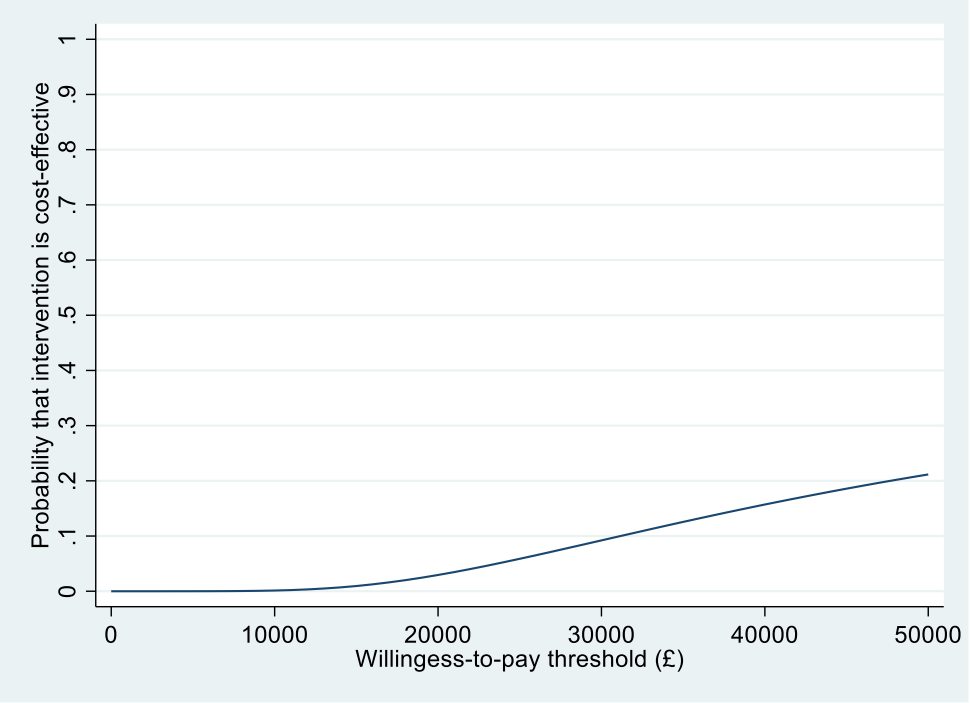
Trial group	n	Adjusted[1], mean (95% CI) Costs (£)	QALYs	Incremental adjusted[1] mean (95% CI) Costs (£)	QALYs	ICER (£/QALY)	iNMB at £20,000 /QALY (95% CI)
Sensitivity analysis: Value set from Spain							
FITNET-NHS	155	£2822 (£2521 to £3123)	0.410 (0.373 to 0 .448)	£1047 (£624 to £1471)	0.010 (-0.041 to 0.061)	£100805	-£840 (-£2024 to £345)
Activity management	159	£1775 (£1476 to £2073)	0.400 (0.365 to 0.435)				

1. Adjusted for age and gender for both costs and QALYs.
2. The slight difference in incremental QALYs observed for this analysis when compared to the primary analysis, is due to training costs being a fully observed variable in our multiple imputation model. In addition, QALYs were adjusted for baseline utility; iNMB= Incremental Net Monetary Benefit; CCGs= Clinical Commissioning Groups; SUR= seemingly unrelated regression; CI= Confidence Interval; ICER= incremental cost-effectiveness ratio; QALYs= quality-adjusted life years.

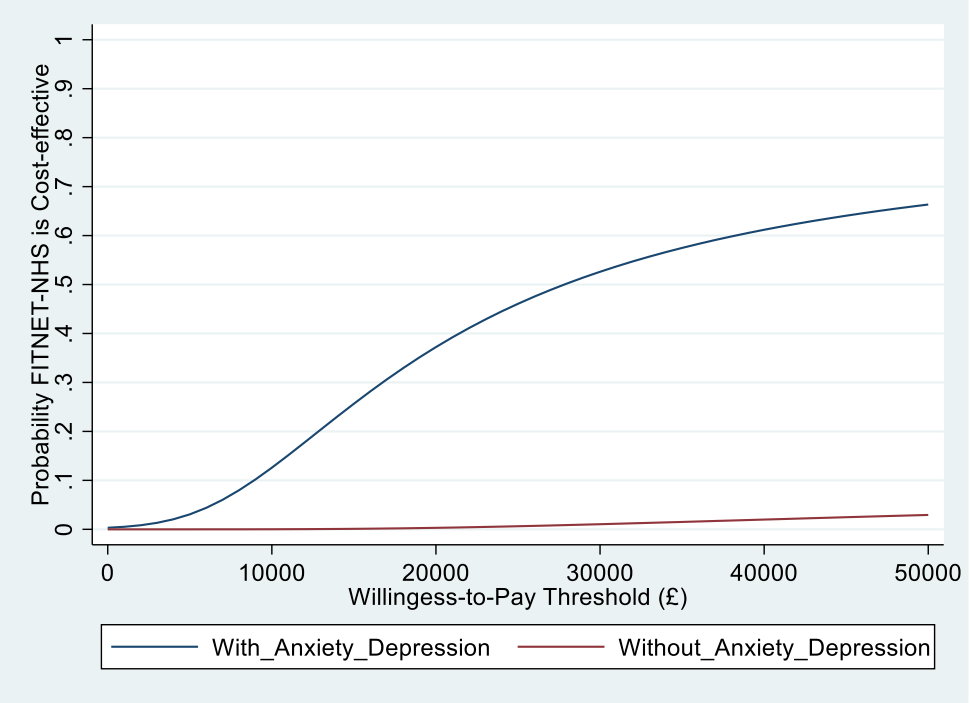
Supplementary Table 7. Subgroup analysis for comorbid anxiety/ depression

		Adjusted[1], mean (95% CI)		Incremental adjusted[1] mean (95% CI)			
Trial group	**n**	**Costs (£)**	**QALYs**	**Costs (£)**	**QALYs**	**ICER (£/QALY)**	**iNMB at £20,000 /QALY (95% CI)**
Subgroup analysis: Patients with comorbid anxiety/ depression							
FITNET-NHS	69	£2973 (£2475 to £3470)	0.464 (0.415 to 0.514)	£950 (£265 to £1634)	0.034 (-0.032 to 0.101)	£27822	-£267 (-£1873 to £1339)
Activity management	78	£2023 (£1554 to £2493)	0.430 (0.386 to 0.474)				
Subgroup analysis: Patients without comorbid anxiety/ depression							
FITNET-NHS	86	£2720 (£2364 to £3076)	0.590 (0.585 to 0.657)	£1191 (£678 to £1704)	-0.031 (-0.083 to 0.022)	-£38995	-£1802 (-£3091 to -£512)
Activity management	81	£1529 (£1162 to £1897)	0.621 (0.585 to 0.657)				

1. Adjusted for age and gender for both costs and QALYs. In addition, QALYs were adjusted for baseline utility; CI= confidence interval; iNMB= incremental net monetary benefit.



Supplementary Figure 1. Primary analysis: NHS Perspective with multiple imputation (n=314)



Supplementary Figure 2. Subgroup analysis with and without comorbid anxiety/ depression