



Synopsis

Methylphenidate versus placebo for fatigue in patients with advanced cancer: the MePFAC randomised controlled trial

Patrick Stone¹, Ollie Minton^{2*}, Alison Richardson³, Peter Buckle⁴,
Zinat E Enayat⁴, Louise Marston⁵ and Nick Freemantle⁶

¹Marie Curie Palliative Care Research Department, Division of Psychiatry, University College London, London, UK

²University Hospitals Sussex NHS Foundation Trust, Worthing Hospital, Worthing, UK

³University of Southampton & University Hospital Southampton NHS Foundation Trust, Southampton General Hospital, Southampton, UK

⁴Marie Curie Palliative Care Research Department, Division of Psychiatry, University College London, London, UK

⁵Department of Primary Care and Population Health, Institute of Epidemiology & Health Care, Faculty of Population Health Sciences, University College London, London, UK

⁶Comprehensive Clinical Trials Unit, University College London, London, UK

*Corresponding author Ollie.minton@nhs.net

Published July 2025

DOI: 10.3310/GJPS6321

Volume 29 • Issue 36

Abstract

Background: Previous meta-analyses suggested methylphenidate may be effective for cancer-related fatigue.

Trial design: Phase III, parallel-group, randomised, double-blind, placebo-controlled trial.

Methods: Participants were adults with advanced cancer with cancer-related fatigue receiving palliative care at 17 palliative care services in England between June 2018 and April 2023.

Principal exclusions: Pregnancy; glaucoma; pheochromocytoma; planned general anaesthesia; hyperthyroidism; severe psychiatric disorders; hypertension; severe cardiovascular disorders; cerebrovascular disorders; anaemia; thrombocytopenia; leucopenia; infection; renal or liver impairment; concomitant clonidine, warfarin, monoamine oxidase inhibitors or modafinil; alcohol or drug dependency; epilepsy.

Interventions: Methylphenidate 5 mg tablets or matching placebo. Starting at 1 tablet twice daily, titrated over 6 weeks to a maximum of 12 tablets/day.

Objective: To estimate clinical effectiveness of methylphenidate versus placebo for cancer-related fatigue in patients receiving palliative care.

Primary outcome: Fatigue at 6 (\pm 2) weeks measured using the Functional Assessment of Chronic Illness Therapy – Fatigue Scale score. Secondary outcomes were fatigue at other time points; quality of life, adverse events, activities of daily living; appetite; anxiety; depression; patient satisfaction; survival and need for other medication.

Randomisation: Computer-generated 1 : 1 randomisation, stratified by centre, concomitant treatment, depression and initial fatigue score.

Blinding: Participants and outcome assessors were blinded to group assignment.

Results: *Numbers randomised:* Eighty-four were allocated to methylphenidate and 78 to placebo.

Recruitment: Study completed.

Numbers analysed: Seventy-five in methylphenidate group and 72 in placebo group were included in analysis of primary outcome.

Outcome: There was no statistically or clinically significant difference in primary outcome between groups. Functional Assessment of Chronic Illness Therapy – Fatigue Scale scores were 1.97 points (95% confidence interval –0.95 to 4.90; $p = 0.186$) higher (better) on methylphenidate than placebo. Functional Assessment of Chronic Illness Therapy – Fatigue Scale score was nominally statistically significantly higher (better) in methylphenidate group across

duration of study [Diff 2.20 (95% confidence interval 0.39 to 4.01)] but did not reach the minimal clinically important difference (5 points). At 6 weeks, there were no statistically significant differences in quality-of-life or symptom domains except for depression scores [nominally statistically significantly reduced in methylphenidate group: Diff -1.35 (95% confidence interval -2.41 to -0.30)].

Harms: There were 25 serious adverse events in 20 participants receiving methylphenidate and 25 serious adverse events among 16 participants receiving placebo. There were no suspected unexpected serious adverse reactions. There were no statistically significant differences in deaths occurring within 75 days of randomisation (2 participants in placebo group and 6 participants in the methylphenidate group; Fisher's exact *p*-value 0.278). Adverse events were similar in the two groups, with no pattern to suggest increased harm with methylphenidate.

Limitations: Participants were highly selected due to multiple exclusion criteria. The choice of 5-point difference in Functional Assessment of Chronic Illness Therapy – Fatigue Scale score as clinically significant primary outcome may be debated.

Conclusions: Methylphenidate did not reduce fatigue severity in patients with advanced cancer at 6 (\pm 2) weeks but was safe and well tolerated.

Future work: Further trials of methylphenidate for fatigue in patients with advanced cancer receiving palliative care are not recommended. There may be scope for further studies in different populations or for different indications.

Funding: This synopsis presents independent research funded by the National Institute for Health and Care Research (NIHR) Health Technology Assessment programme as award number 15/46/02.

A plain language summary of this synopsis is available on the NIHR Journals Library Website (<https://doi.org/10.3310/GJPS6321>).

Synopsis

Some text in this manuscript has been reproduced from Stone *et al.*¹ This is an Open Access article distributed in accordance with the terms of the Creative Commons Attribution (CC BY 4.0) licence, which permits others to distribute, remix, adapt and build upon this work, for commercial use, provided the original work is properly cited. See: <https://creativecommons.org/licenses/by/4.0/>. The text below includes minor additions and formatting changes to the original text.

Rationale and background

Fatigue is a common problem in patients with advanced cancer receiving palliative care.² It has major effects on quality of life (QoL),³ and patients report that it affects them more than other symptoms, such as pain or nausea.⁴ The causes of cancer-related fatigue are multifactorial.⁵ Occasionally, treatment directed at a clearly identified underlying problem can alleviate the fatigue (e.g. blood transfusions for anaemia⁶). For the majority of patients, no underlying cause is clearly identified and management has to be symptom-directed.⁷ There is some evidence that exercise^{8,9} and (to a lesser extent) psychological therapies^{10,11} can help to alleviate fatigue in these circumstances. However, these therapies are not always appropriate or effective in patients with advanced cancer. Methylphenidate (MPH) is a psychostimulant drug that is widely used as part of the management of people with attention deficit hyperactivity disorder.^{12,13} It has also been evaluated as a potential treatment for cancer-related fatigue. Some trials and meta-analyses have suggested

that this medication may be effective,¹⁴⁻¹⁸ but the evidence is mixed with many trials showing no benefit.¹⁹⁻²⁵ In the context of ongoing uncertainty about its role, this research was conducted in response to a commissioned call by the NIHR (HTA no 15/46/02). This synopsis summarises the work we undertook to address the commissioning brief; the main findings have been published in the *Journal of Clinical Oncology*.¹

Objective

To estimate clinical effectiveness of MPH versus placebo for cancer-related fatigue in patients receiving palliative care.

Primary aim

To compare Functional Assessment of Chronic Illness Therapy – Fatigue Scale (FACIT-F) score in patients with advanced cancer receiving individually titrated doses of MPH with patients receiving placebo after 6 weeks' treatment.

Secondary aims

To compare secondary outcomes [other measures of QoL, adverse events (AEs), activities of daily living, appetite, anxiety, depression, satisfaction of patients, survival and need for other medication] between patients receiving MPH and placebo. To compare adverse effects in patients receiving MPH and placebo.

Methods

The study methods are summarised below. The Study Protocol is available as Supplementary Information

([Report Supplementary Material 1](#)). A summary of the major amendments to the protocol and the rationale for the changes are shown in [Appendix 1, Table 4](#).

Design

This was a prospective, double-blind, 1 : 1 randomised, parallel-group, placebo-controlled, multicentre trial.

Participants

Participants were adults with advanced incurable cancer (all types), receiving generalist or specialist palliative care with moderate or severe fatigue [$> 3/10$ on a numerical rating scale (NRS)]. Exclusion criteria were: pregnancy; breastfeeding; sensitivity to MPH; glaucoma; pheochromocytoma; planned general anaesthesia; concomitant treatment with psychostimulants, clonidine, warfarin, monoamine oxidase inhibitors or modafinil; severe mood disorders; psychosis; hypertension ($> 160/100$ mmHg); uncontrolled heart failure or angina; arterial occlusive disease; congenital heart disease; cardiomyopathies; myocardial infarction (MI) or stroke (within last year); life-threatening arrhythmias and channelopathies; cerebral aneurysm; cerebrovascular abnormalities; seizures; hyperthyroidism; haemoglobin < 80 g/l; platelets $< 50 \times 10^3/\mu\text{l}$; white blood count $< 1.5 \times 10^9/\text{l}$; estimated glomerular filtration rate (eGFR) < 45 ml/minute/ 1.73 m^2 ; alanine aminotransferase (ALT) > 2 or bilirubin $> 1.5 \times$ upper limit of normal; infection; substance/alcohol dependency; participation in another study; insufficient English-language skills; or inability to swallow medication.

Settings

Participants were recruited from hospital, community and hospice palliative care services in England.

Study intervention

Initially, participants were prescribed 1 tablet twice daily (=MPH 10 mg/day) or matching placebo. Participants were contacted every week, and the dose of medication was adjusted (either up or down) over the course of the first 6 weeks of the study (dose titration phase), up to a maximum of 12 tablets/day (= 60 mg/day). Thereafter, for the next 2 weeks (dose maintenance phase), the dose of medication was not increased any further (although it could be reduced in response to adverse effects). During the next week (dose tapering phase), the dose was reduced and then the medication was stopped completely for the last week of the trial.

Dose titration schedule

During each of the first 6 weeks of the study, principal investigators (PIs) were permitted to increase (by up to

10 mg/day) the dose of study medication if the participant did not feel fatigue was 'adequately controlled', provided there were no dose-limiting AEs (see below). In the presence of dose-limiting AEs, the dose of medication either remained stable or was decreased (depending on the clinical judgement of the PI). If participants reported that fatigue was 'adequately controlled', then the dose of study medication was not changed.

Study procedures

After obtaining written informed consent, participants were randomised to receive either MPH or matching placebo tablets in a double-blind fashion. Participants were contacted every week either in person or by telephone. Initially, the assessments at baseline, week 3, week 6 and week 10 occurred face to face, with the other assessments occurring by telephone. However, in response to the COVID pandemic, the trial was modified to permit all assessments, after the baseline visit, to occur remotely if necessary. A flow diagram to summarise the assessments undertaken at each week is shown in [Figure 1](#).

Primary outcome assessment

The 40-item FACIT-F questionnaire consists of a 27-item FACIT-General QoL questionnaire and a standalone 13-item fatigue questionnaire, known as FACIT-F.²⁶ The primary outcome of this study was fatigue at 6 weeks (± 2 weeks) measured using the FACIT-F score. Each of the 13 items on this questionnaire can be answered on a 5-point scale: 'Not at all', 'A little bit', 'Somewhat', 'Quite a bit', 'Very much'. Scores can range between 0 and 52, with higher scores representing lower fatigue levels. FACIT-F scores were measured at baseline and every week of the study. FACIT-F scores were completed by patients themselves (paper records) at face-to-face visits or responses were collected over the telephone for remote assessments. If FACIT-F scores were not available at week 6, then the scores at weeks 7, 8, 5 or 4 (in that order) were used instead for the primary outcome assessment.

Secondary outcome assessments

Other measures of fatigue FACIT-F scores were obtained at each study week, and all such measures, except those obtained at week 6 (± 2 weeks), were regarded as secondary outcomes. Fatigue as a secondary outcome was also assessed using the fatigue subscale of the European Organisation for Research and Treatment of Cancer Quality of Life Core 15 Palliative Care (EORTC QLQ-C15-PAL)²⁷ described in more detail below. Scores were obtained at baseline and at weeks 3, 6 and 10.

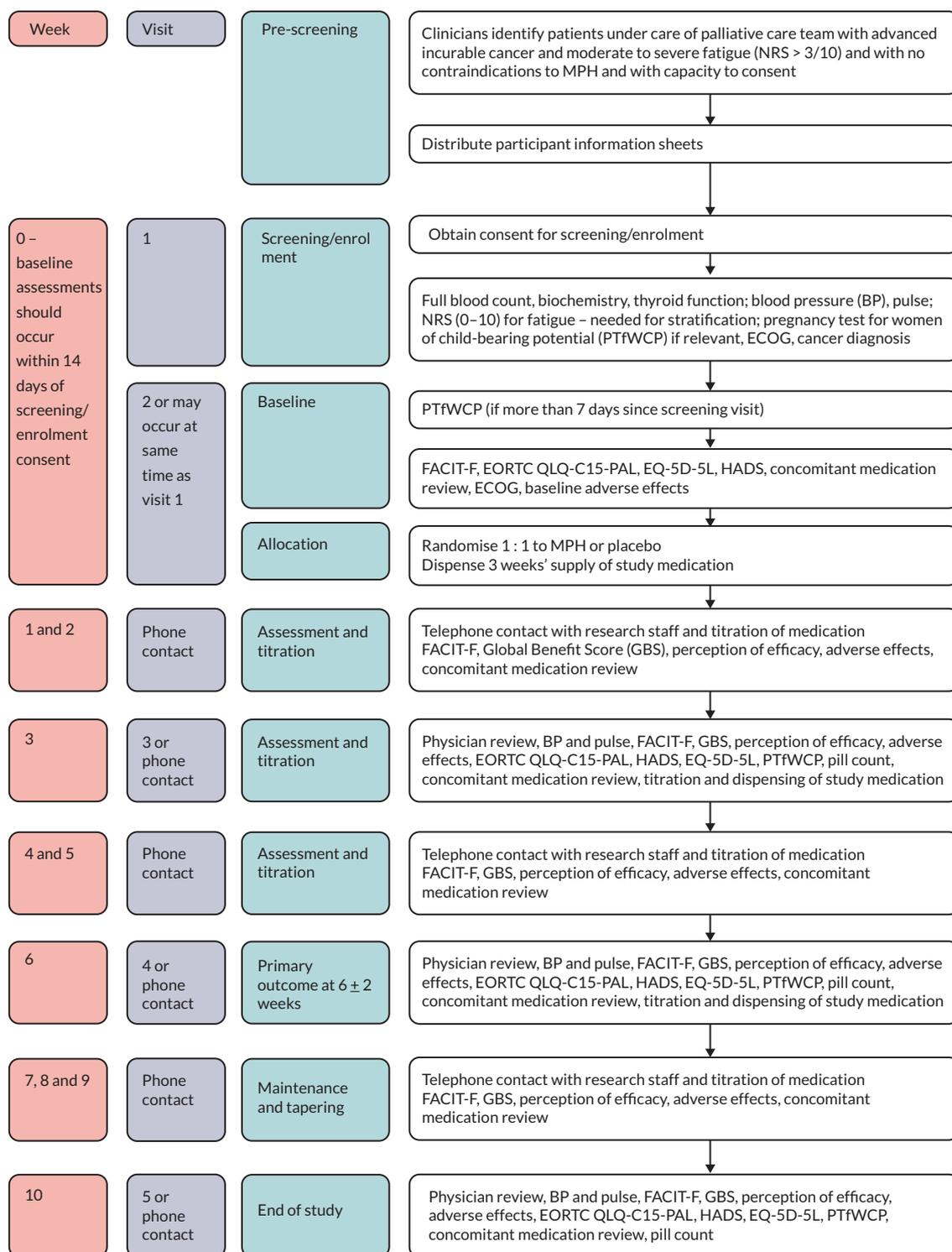


FIGURE 1 Methylphenidate versus placebo for fatigue in advanced cancer flow diagram of study assessments. ECOG, Eastern Cooperative Oncology Group; EORTC QLQ-C15-PAL, European Organisation for Research and Treatment of Cancer Quality of Life Core 15 Palliative Care; EQ-5D-5L, EuroQol-5 Dimensions, five-level version; HADS, Hospital Anxiety and Depression Scale.

Quality of life Quality of life was assessed using the EORTC QLQ-C15-PAL²⁷ and the EuroQol-5 Dimensions, five-level version (EQ-5D-5L).²⁸ The EORTC QLQ-C15-PAL is a 15-item core QoL questionnaire which provides a global QoL score (1 item), a physical functioning (3

items) and emotional functioning (2 items) score; and symptom scores for fatigue (2 items), pain (2 items), nausea (1 item), anorexia (1 item), dyspnoea (1 item), constipation (1 item) and insomnia (1 item). Each item has four possible responses: 'Not at all'; 'A little'; 'Quite

a bit' and 'Very much'. On QoL and functional scales, higher scores represent better levels of functioning, and on symptom scales, higher scores represent greater severity.

The EQ-5D-5L²⁸ measure provides a simple descriptive profile and a single preference-based index value for health status. It assesses five dimensions of QoL (mobility, self-care, usual activities, pain/discomfort and anxiety/depression), each of which can be scored on a 5-point scale ranging from no problems to inability to do an activity or extreme severity of symptoms. The second part of the measure is a vertical visual analogue scale (VAS) numbered 0–100, with 0 representing 'The worst health you can imagine' and 100 representing 'The best health you can imagine'.

Scores on both scales were obtained at baseline and at weeks 3, 6 and 10.

Activities of daily living Activities of daily living were assessed using the physical functioning subscale of the EORTC QLQ-C15-PAL (see above) at baseline and at weeks 3, 6 and 10.

Appetite Appetite was assessed using the anorexia item on the EORTC QLQ-C15-PAL (see above) at baseline and at weeks 3, 6 and 10.

Anxiety and depression Anxiety and depression were assessed using Hospital Anxiety and Depression Scale (HADS).²⁹ This is a 14-item screening tool consisting of separate 7-item scales for anxiety [Hospital Anxiety and Depression Scale – Anxiety subscale (HADS-A)] and depression [Hospital Anxiety and Depression Scale – Depression subscale (HADS-D)]. Scores on each scale can vary between 0 and 21, with higher scores representing more severe symptoms. HADS scores were assessed at baseline and at weeks 3, 6 and 10.

Satisfaction of patients Satisfaction of patients was assessed using a study-specific 5-point global benefit score (GBS) and assessed weekly. Respondents were asked to rate their degree of satisfaction by choosing a response to the statement, 'Overall with regard to fatigue, during the last week, I found that . . .'. Responses were 'Things have got much better', 'Things have got a little better', 'There has been no change', 'Things have got a little worse' and 'Things have got a lot worse'.

Need for other medication Participants' use of other medication (specifically steroids, antidepressants, anxiolytics and analgesics) was recorded weekly.

Survival Survival of participants was recorded up until the end of the study period (and until at least 75 days after the patient had been randomised).

Blood pressure and pulse Blood pressure (BP) and pulse were measured at baseline and at weeks 3, 6 and 10.

Adverse events Adverse events were actively sought by asking participants about the presence or absence of the following known potential side effects of MPH: cough, sore throat, other airway symptoms, abdominal pain, diarrhoea, nausea, vomiting, dry mouth, other gastrointestinal (GI) symptoms, anxiety, depression, irritability, aggression, mood swings, abnormal behaviour, other mood and mental state symptoms, hair loss, itch, skin rashes, other skin and hair symptoms, loss of appetite, loss of weight, feeling heart racing, awareness of abnormal rhythms, headaches, dizziness, drowsiness, difficulty sleeping, abnormal muscle movements (twitching), abnormal activity levels (pacing), joint pain, fever, cold or flu-like symptoms, other symptoms.

Participants were asked to rate whether the AEs were mild, moderate or severe, and PIs were asked to determine whether or not any reported AEs should be regarded as dose-limiting. A dose-limiting AE was defined as one which prevented an increase (or necessitated a reduction) in the dose of MPH. Non-serious adverse events (non-SAEs) were recorded weekly and assessed for severity. SAEs and suspected unexpected serious adverse reactions (SUSARs) were additionally assessed for causality and expectedness and were reported to the sponsor within 24 hours.

Patient satisfaction Patient satisfaction was measured on a weekly basis using the 5-point GBS^{30,31} described above.

Statistical methods

The statistical methods are summarised below. The full statistical analysis plan is available as Supplementary Information (see [Report Supplementary Material 2](#)). For clarity of presentation, for secondary outcomes only, we have described results which would conventionally be regarded as statistically significant, as being 'nominally statistically significant'. This is to reflect the issue that although such findings may have reached a conventional level of statistical significance, they were not the primary outcome, and it would therefore be potentially misleading to describe such results as 'statistically significant' without further qualification.

Sample size

Randomising 162–230 participants and attaining 130–172 evaluable patients (20–25% attrition) would result in this study having 80–90% power to detect a difference of 5

points on FACIT-F score (effect size 0.5) at 6 (\pm 2) weeks between groups at 5% significance (two-sided). This was regarded as representing a minimal clinically important difference (MCID).

Randomisation and concealment

Randomisation (1 : 1) was online with random permuted blocks, stratified by: site, receipt of palliative treatment, high depression score (> 10 on HADS-D) and severity of fatigue (> 7/10 on NRS). Randomisation was performed by the PI and undertaken using an independent data management company ('Sealed Envelope'). Following randomisation, PIs were provided with a randomisation code. Site pharmacies held the randomisation code list which was required to dispense the correct study medication bottles. The study medication bottles' main labels were blinded; however, they had a tear-off unblinded portion of the label which stated either active investigational medicinal product (IMP) or placebo. Prior to dispensing, the site pharmacy removed the unblinded portion of the tear-off label and filed this in the pharmacy file so that the bottles dispensed were fully blinded. The research team did not have access to the pharmacy file containing the randomisation code list. Other than the dispensing pharmacist, all staff and participants were blind to study allocation. Data were analysed blind to allocation.

Analysis

The trial was analysed by intention to treat. Analysis of the primary outcome used a mixed-effects linear model. Each participant provided two values, one for baseline and one for follow-up, with random intercepts for participant. Fixed effects were time point (baseline or follow-up), randomised treatment and the stratification factors (except site and fatigue severity). Secondary outcomes were analysed in a similar way using mixed-effects linear regression. The GBS, categorised as 'stayed the same' or 'got worse' versus 'got better', was analysed using logistic regression, including randomised group only, because of lack of power. Survival of participants was analysed using Cox proportional hazards regression controlling for receipt of palliative treatment, high depression score (stratification factors). Kaplan–Meier survival curves were generated to display survival from date of randomisation in the two study arms. Frequency and percentage of SAEs, severe and other AEs were analysed descriptively. We examined the sensitivity of the primary outcome to the allocation of any participants who were randomised in error, repeating the primary analysis, including them in the group they were allocated. In addition, we undertook a threshold analysis, in which participants with missing data in the MPH group were attributed a score at the highest 10% of placebo values, and participants with missing data in the placebo group were attributed the median value for the

placebo participants. We undertook subgroup analyses with the primary outcome; we first analysed data with an interaction between randomised group and stratification factors (except site) separately. Then we analysed data from each subgroup separately to determine the effect of randomisation on the participants in the given subgroup.

Results

The main results have previously been presented in our linked publication in the *Journal of Clinical Oncology*.¹

The sites at which participants were recruited and the PIs at each site are shown in [Appendix 2, Table 5](#). Across the 17 active sites, 162 participants were randomised {73 men; mean 65.8 [standard deviation (SD) 10.3] years}. The first patient was enrolled on 29 June 2018, and the last patient was randomised on 27 April 2023. The last visit for the last patient was 3 July 2023, which is when the trial ended.

The Consolidated Standards of Reporting Trials diagram to show the flow of participants through the trial is shown in [Figure 2](#). Three participants were excluded from analysis (two patients in the methylphenidate group were randomised in error, and one participant in the placebo group never took the allocated pills). Seventy-seven were allocated and received placebo [baseline FACIT-F score = 22 (SD 10)]; and 82 were allocated and received MPH [FACIT-F score = 20 (SD 9)]. After 6 weeks, the median daily dose of MPH/placebo was six tablets (=MPH 30 mg).

Data for analysis of the primary outcome [FACIT-F score at 6 (\pm 2) weeks] were available for 75 in the MPH group and 72 in the placebo group. Three participants in the MPH group did not have FACIT-F score outcome data at week 6 but were nonetheless included in the analysis of the primary outcome (1 provided usable data at week 5; 2 provided usable data at week 4; no additional data were used at week 7 or 8). Five participants in the placebo group did not have FACIT-F score outcome data at week 6 but were nonetheless included in the analysis of the primary outcome (1 provided usable data at week 5; 4 provided usable data at week 4; no additional data were used at week 7 or 8).

Baseline characteristics

The screening/baseline characteristics of participants are shown in [Table 1](#). The participants in the randomised groups were balanced for key characteristics. Of those participants for whom performance status data were available, the majority in both groups had ECOG status 1 (ambulatory and able to carry out work of a light or sedentary nature) or 2 (unable to carry out any work activities; up and about more than 50% of waking hours). The participants in the MPH arm were slightly more fatigued at baseline than those in the placebo arm.

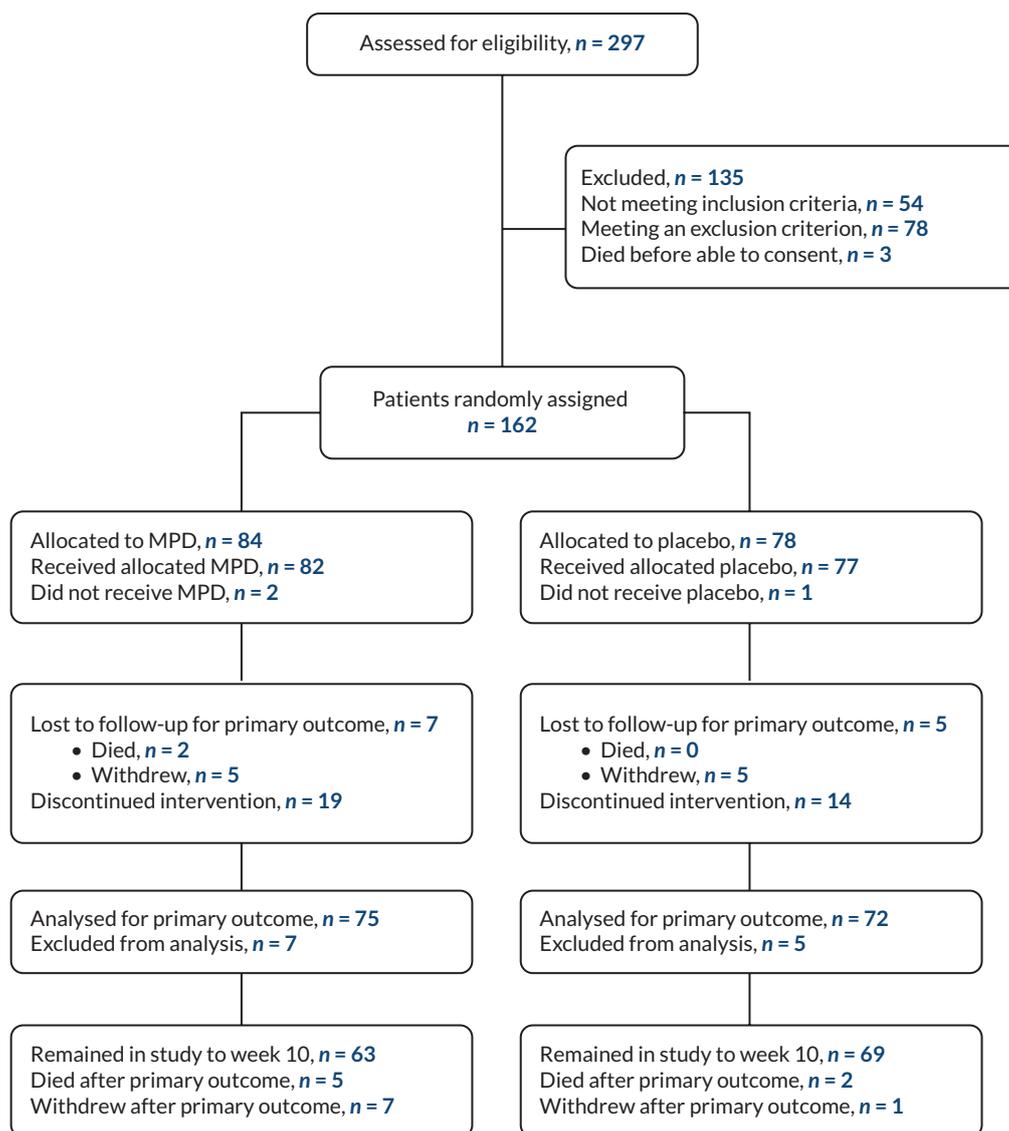


FIGURE 2 Consolidated Standards of Reporting Trials diagram showing flow of study participants. Reproduced from Stone *et al.*¹ This is an Open Access article distributed in accordance with the terms of the Creative Commons Attribution (CC BY 4.0) licence, which permits others to distribute, remix, adapt and build upon this work, for commercial use, provided the original work is properly cited. See: <https://creativecommons.org/licenses/by/4.0/>. The figure includes minor additions and formatting changes to the original text.

Primary outcome

The results of the statistical analyses for the primary outcome are shown in [Table 2](#). There was no statistically or clinically significant difference in primary outcome between groups. After $6 (\pm 2)$ weeks, FACIT-F scores were 1.97 points [95% confidence interval (CI) -0.95 to 4.90 ; $p = 0.186$] higher (better) on MPH than placebo. A sensitivity analysis (including the two participants randomised in error) similarly showed a non-significant difference between groups (FACIT-F score coefficient 2.05, 95% CI -0.85 to 4.95 ; $n = 161$).

The predictors of missingness for study data are shown in [Supplementary Information](#) (see [Report Supplementary Material 3](#)). Patients with lung cancer were more likely to

have missing data than other participants, but including predictors of missingness in the statistical modelling did not significantly affect the results of the statistical modelling for the primary outcome. A threshold analysis, in which participants with missing data in the MPH group were assumed to have low levels of fatigue and participants with missing data in the placebo arm were assumed to have average levels of fatigue, was nominally significant (FACIT-F score coefficient 3.15, 95% CI 0.26 to 6.04; $n = 159$).

Interaction between stratification factors and randomised group

None of the subgroups based on the stratification factors (high/low baseline fatigue; high/low baseline depression;

TABLE 1 Screening and baseline data of analysed participants

Characteristic	Placebo		MPH	
	n/N or mean	% or (SD)	n/N or mean	% or (SD)
<i>Screening data</i>				
Male	35/77	45	38/82	46
Age at randomisation	62.6	(11.8)	64.7	(11.9)
<i>ECOG performance status</i>				
0	3	4	3	4
1	30	39	38	46
2	27	3	21	26
3	3	4	5	6
4	0	0	0	0
Missing data	14	18	15	18
<i>Primary diagnosis</i>				
Breast	20	26	21	26
Lung	15	20	11	14
Prostate	14	18	9	11
Lower GI	7	9	11	14
Urogenital	5	7	5	6
Upper GI	4	5	5	6
Other	3	4	3	4
Haematological	2	3	6	7
Gynaecological	2	3	5	6
Head and neck	0	0	1	1
Neurological	1	1	1	1
Unknown primary	1	1	0	0
Two primary diagnoses	1	1	3	4
Rare tumour groups	0	0	0	0
Missing data	2	3	1	1
<i>Sites of metastases</i>				
Bone	32	42	31	38
Lung	23	30	20	25
Nodal	17	22	17	21
Liver	12	16	16	20
Other	11	14	15	19
None	6	8	6	7
Adrenal	2	3	3	4
Malignant pleural effusion	2	3	1	1

TABLE 1 Screening and baseline data of analysed participants (continued)

Characteristic	Placebo		MPH	
	n/N or mean	% or (SD)	n/N or mean	% or (SD)
Renal	1	1	2	2
Brain	1	1	2	2
Malignant ascites	0	0	1	1
Unknown	0	0	1	1
Missing data	1	1	1	1
<i>Blood results</i>				
Thyroxine (pmol/l)	14.7	(2.9)	15.1	(3.2)
Thyroid-stimulating hormone (mU/l)	1.7	(1.1–2.5)	1.8	(1.3–3.0)
Haemoglobin (g/l)	121	(17)	123	(15)
Platelets median ($\times 10^9/l$)	237	(189–310)	248	(206–298)
White blood count ($\times 10^9/l$)	6.2	(4.6–7.9)	5.8	(4.4–7.3)
eGFR (ml/minute/1.73 m ²)	72	(60–90)	69	(60–90)
ALT (U/l)	16	(12–31)	18	(13–29)
Bilirubin ($\mu\text{mol/l}$)	7	(5–9)	6	(5–10)
<i>Stratification factors</i>				
Current, recent or scheduled disease-modifying treatment	62	81	62	76
Depression > 10 on HADS-D	17	22	25	30
Fatigue > 7/10 on NRS	26	34	30	37
<i>Baseline data</i>				
FACIT-F score	22	(10)	20	(9)
HADS depression score median (IQR)	6	(4–9)	7	(5–11)
HADS anxiety score median (IQR)	4	(2–9)	6	(3–9)
<i>EORTC QLQ-C15-PAL</i>				
Pain	53	(20)	52	(19)
Physical functioning	50	(17)	50	(18)
Emotional functioning	42	(17)	44	(17)
Fatigue	72	(18)	74	(15)
QoL	31	(14)	30	(13)
Nausea	39	(22)	44	(22)
Loss of appetite	52	(26)	52	(25)
Shortness of breath	53	(24)	52	(21)
Constipation	41	(21)	47	(24)
Sleep	51	(27)	56	(25)
EQ-5D-5L utility	0.65	(0.18)	0.62	(0.21)

continued

TABLE 1 Screening and baseline data of analysed participants (continued)

Characteristic	Placebo		MPH	
	n/N or mean	% or (SD)	n/N or mean	% or (SD)
Systolic blood pressure (SBP)	126	(16)	130	(16)
Diastolic blood pressure (DBP)	76	(10)	77	(10)
Pulse rate	81	(13)	83	(13)
<i>Concomitant medication</i>				
Strong opioids	31	40	31	38
Other analgesia	39	51	34	41
Benzodiazepines	5	6	4	5
Antidepressants	22	29	32	39
Steroids	16	21	21	26
None of the above	4	5	2	2

IQR, interquartile range.

Note

Reproduced from Stone *et al.*¹ This is an Open Access article distributed in accordance with the terms of the Creative Commons Attribution (CC BY 4.0) licence, which permits others to distribute, remix, adapt and build upon this work, for commercial use, provided the original work is properly cited. See: <https://creativecommons.org/licenses/by/4.0/>. The table includes minor additions and formatting changes to the original text.

or disease-modifying therapies yes/no) showed significant improvements in FACIT-F score (see [Table 2](#)). There was, however, a nominally significant interaction between disease-modifying treatment and primary outcome, with participants who were in receipt of disease-modifying therapy having higher fatigue levels (lower FACIT-F scores) than participants who were not in receipt of such therapy.

Secondary outcomes

Summary data for the primary and secondary outcomes for each week of the study (by randomised group) are shown in [Appendix 3, Tables 6–15](#). Statistical modelling results for secondary outcome data are shown in [Table 2](#).

Other measures of fatigue

There were nominally statistically significant increases in FACIT-F score (lower fatigue) at all study weeks, except for week 1, week 7 (first week of maintenance), week 9 (dose tapering) and week 10 (off study medication). There was also a nominally significant reduction in fatigue across the whole 10-week period (2.20, 95% CI 0.39 to 4.01). There were no significant differences in EORTC-QLQ-C15-PAL-fatigue scores at weeks 3, 6 or 10.

Quality of life

There were no significant differences in EORTC-QLQ-C15-PAL-QoL or EQ-5D-5L utility scores at weeks 3, 6 or 10.

Activities of daily living

There were no significant differences in EORTC-QLQ-C15-PAL-physical functioning scores at weeks 3, 6 or 10.

Appetite

There were no significant differences in EORTC-QLQ-C15-PAL-anorexia scores at weeks 3, 6 or 10.

Anxiety and depression

There was a nominally significant reduction in HADS-D scores at week 6 (–1.35, 95% CI –2.41 to –0.31) but not at week 3 (–0.73, 95% CI –1.65 to 0.19) or week 10 (–0.39, 95% CI –1.45 to 0.66). There were no significant differences in HADS-A scores at weeks 3, 6 or 10.

Patient satisfaction

There were no significant differences in the ORs (stayed the same/got worse vs. got better) for GBSs at any week of the study.

Need for other medication

There were no differences between the groups at week 6 with regard to the likelihood that they needed to start a new concomitant medication (opioid, other analgesic, benzodiazepine, antidepressant or other), or to have the dose of an existing such medication increased (see [Table 2](#)).

TABLE 2 Statistical analyses for primary and secondary outcomes

Outcome	Estimate	95% CI
Primary outcome		
Week 6 (± 2) (n = 159)	1.97	(-0.95 to 4.90)
Including predictors of missingness (n = 157)	1.89	(-1.05 to 4.84)
Including those randomised in error (n = 161)	2.05	(-0.85 to 5.95)
Threshold analysis (n = 159)	3.15	(0.26 to 6.04)
Stratification factors		
Disease-modifying treatment - yes (n = 35)	0.12	(-6.20 to 6.43)
Disease-modifying treatment - no (n = 124)	2.40	(-0.77 to 5.58)
p-value for interaction	0.002	
Baseline HADS-D > 10 (n = 117)	2.31	(-1.05 to 5.67)
Baseline HADS-D \leq 10 (n = 42)	0.76	(-5.42 to 6.95)
p-value for interaction	0.552	
Fatigue > 7/10 on NRS (n = 56)	1.28	(-4.12 to 6.67)
Fatigue \leq 7/10 on NRS (n = 103)	2.32	(-1.01 to 5.66)
p-value for interaction	0.067	
Secondary outcomes		
FACIT-F score (coefficient) (n = 159)		
Week 1	0.06	(-2.41 to 2.53)
Week 2	3.25	(0.53 to 5.97)
Week 3	3.24	(0.37 to 6.11)
Week 4	3.16	(0.16 to 6.16)
Week 5	3.18	(0.21 to 6.15)
Week 6	3.11	(0.16 to 6.05)
Week 7	2.72	(-0.51 to 5.94)
Week 8	3.47	(0.40 to 6.54)
Week 9	1.91	(-1.12 to 4.95)
Week 10	-0.55	(-3.56 to 2.47)
All weeks	2.20	(0.39 to 4.01)
EORTC QLQ-C15-PAL (coefficients)		
Pain (n = 159)		
Week 3	0.19	(-4.85 to 5.24)
Week 6	1.63	(-3.66 to 6.93)
Week 10	1.77	(-3.96 to 7.50)
Physical functioning (n = 159)		
Week 3	-0.31	(-4.05 to 3.44)

continued

TABLE 2 Statistical analyses for primary and secondary outcomes (continued)

Outcome	Estimate	95% CI
Week 6	-2.67	(-7.28 to 1.94)
Week 10	1.70	(-2.93 to 6.34)
<i>Emotional functioning (n = 158)</i>		
Week 3	0.75	(-3.97 to 5.48)
Week 6	1.71	(-3.18 to 6.59)
Week 10	3.40	(-2.04 to 8.84)
<i>Fatigue (n = 159)</i>		
Week 3	-4.74	(-9.78 to 0.29)
Week 6	-2.50	(-7.79 to 2.80)
Week 10	2.86	(-2.69 to 8.41)
<i>QoL (n = 159)</i>		
Week 3	0.71	(-2.87 to 4.30)
Week 6	-2.09	(-5.91 to 1.74)
Week 10	-0.25	(-4.20 to 3.69)
<i>Nausea (n = 159)</i>		
Week 3	4.05	(-2.22 to 10.31)
Week 6	4.30	(-2.07 to 10.66)
Week 10	6.14	(-0.53 to 12.82)
<i>Appetite (n = 159)</i>		
Week 3	0.85	(-7.72 to 6.03)
Week 6	6.71	(-0.59 to 14.00)
Week 10	4.04	(-3.61 to 11.68)
<i>Shortness of breath (n = 159)</i>		
Week 3	0.03	(-6.06 to 6.11)
Week 6	-6.17	(-12.78 to 0.44)
Week 10	-4.71	(-11.59 to 2.17)
<i>Constipation (n = 158)</i>		
Week 3	3.24	(-3.25 to 9.74)
Week 6	4.64	(-2.02 to 11.29)
Week 10	0.41	(-6.36 to 7.18)
<i>Sleep (n = 159)</i>		
Week 3	-6.55	(-13.74 to 0.64)
Week 6	-5.49	(-12.96 to 1.98)
Week 10	-6.85	(-13.97 to 0.28)

TABLE 2 Statistical analyses for primary and secondary outcomes (continued)

Outcome	Estimate	95% CI
<i>EQ-5D-5L utility (coefficient)</i>		
Week 3 (n = 147)	0.025	(-0.027 to 0.076)
Week 6 (n = 138)	0.028	(-0.031 to 0.086)
Week 10 (n = 130)	0.001	(-0.052 to 0.055)
Overall difference in quality-adjusted life-years (n = 159)	0.009	(-0.006 to 0.024)
<i>HADS anxiety (coefficient) (n = 159)</i>		
Week 3	-0.70	(-1.61 to 0.22)
Week 6	-0.39	(-1.40 to 0.62)
Week 10	-0.32	(-1.42 to 0.77)
<i>HADS depression (coefficient) (n = 159)</i>		
Week 3	-0.73	(-1.65 to 0.19)
Week 6	-1.35	(-2.41 to -0.30)
Week 10	-0.39	(-1.45 to 0.66)
<i>GBS (OR)</i>		
Week 1 (n = 157)	0.68	(0.34 to 1.34)
Week 2 (n = 152)	0.77	(0.41 to 1.45)
Week 3 (n = 147)	0.80	(0.42 to 1.55)
Week 4 (n = 147)	0.66	(0.34 to 1.26)
Week 5 (n = 140)	1.48	(0.76 to 2.88)
Week 6 (n = 139)	1.27	(0.64 to 2.51)
Week 7 (n = 135)	1.06	(0.53 to 2.12)
Week 8 (n = 134)	1.31	(0.64 to 2.70)
Week 9 (n = 129)	1.29	(0.62 to 2.70)
Week 10 (n = 132)	2.11	(0.96 to 4.61)
Died at any time (OR) (n = 159)	0.86	(0.45 to 1.61)
Time to death (HR) (n = 159)	0.98	(0.66 to 1.47)
<i>Increased or started between baseline and 6 weeks (OR)</i>		
Strong opioids (n = 158)	0.50	(0.18 to 1.34)
Other analgesia (n = 159)	1.70	(0.48 to 6.07)
Benzodiazepines (n = 157)	0.46	(0.04 to 5.21)
Antidepressants (n = 158)	1.95	(0.35 to 10.95)
Steroids (n = 158)	0.48	(0.15 to 1.51)

HR, hazard ratio; OR, odds ratio.

Note

Reproduced from Stone *et al.*¹ This is an Open Access article distributed in accordance with the terms of the Creative Commons Attribution (CC BY 4.0) licence, which permits others to distribute, remix, adapt and build upon this work, for commercial use, provided the original work is properly cited. See: <https://creativecommons.org/licenses/by/4.0/>. The table includes minor additions and formatting changes to the original text.

Survival

There were no significant differences in the number of participants dying, nor in the time to death. The Kaplan–Meier survival curves are shown in the Supplementary Information (see [Report Supplementary Material 4](#)).

Blood pressure and pulse

Mean BP and pulse rates were similar in MPH (BP 128/77 mmHg; pulse 82 b.p.m.) and placebo (BP 124/75 mmHg; pulse 84 b.p.m.) groups at week 6.

Adverse events

There were 25 SAEs in 20 participants receiving MPH and 25 SAEs among 16 participants receiving placebo. There were no SUSARs. Six participants receiving MPH and two receiving placebo died within 75 days of randomisation (Fisher's exact *p*-value 0.278).

Adverse events in each group at each week of the study are shown in [Appendix 4, Tables 16–22](#). There was no pattern to suggest consistent differences in adverse effects between groups.

Discussion

Principal findings

We found that MPH, at a dose individually tailored to each person according to perceived benefits and side effects, was not superior to placebo at relieving fatigue after 6 (± 2) weeks' treatment. Although we detected some improvement in fatigue (over that offered by placebo) at most times during the study, none of these improvements reached a level that was considered to be clinically important (i.e. enough to be noticeable by patients and to make a significant impact on their QoL), and given the neutral primary outcome, the findings on secondary outcomes must be considered nominal/exploratory. This conclusion is supported by the finding that after 6 weeks' treatment, participants receiving MPH did not report statistically significant improvements in QoL or health status and were as likely to state that they considered MPH to be effective (MPH 27/72, 37.5%) as placebo (23/67, 34%).

In addition to evaluating the effectiveness of MPH, our study also paid close attention to monitoring potential AEs. We did this because we were aware that, even if MPH had been found to be effective as a treatment for fatigue, its usefulness may have been limited by toxicity. In fact, we found that MPH was neither very good at relieving fatigue nor did it cause any great increase in adverse effects. This suggests that while MPH cannot be recommended as a

treatment for cancer-related fatigue, it would be safe to continue to explore this medication as a therapy for other symptoms in patients with advanced cancer (such as low mood or opioid-related drowsiness).

Contribution to existing knowledge

Prior to our study, there was contradictory evidence about the benefits or otherwise of MPH for fatigue in patients with advanced cancer. [Table 3](#) summarises the main features of, and results from, previous studies. There have been major variations in key study design features in previous studies. In particular, with respect to: choice of patient population, formulation and dose of MPH, use of as required or regular dosing, fixed-dose or individually titrated dosing schedules, length of study and choice and timing of primary outcome measures.

Our findings support the conclusions of previous systematic reviews and meta-analyses^{14,32,33} that psychostimulant medications appear to be safe when used in patients with cancer for the attempted relief of fatigue. Gong and colleagues³² systematic review reported that adverse effects were described in 4.9% of participants (from five included studies) receiving MPH versus 1.6% of participants receiving placebo. The difference in frequency of adverse effects was not statistically significant. The most commonly reported adverse effects (compared to those reported by patients on placebo) were vertigo, anxiety, anorexia and nausea. In Minton and colleagues' systematic review,³³ it was reported that there was no increased risk of SAEs in trial participants receiving MPH versus placebo. In our own study, we similarly found no increase in SAEs or in mortality among participants receiving MPH. We collected frequent and wide-ranging data regarding potential adverse effects of MPH throughout the 10 weeks of the study generally found that the treatment was well-tolerated. The following mild, moderate or severe AEs were reported with a frequency ≥ 10 percentage points higher among participants receiving MPH than placebo at any time over the 10-week study period: nausea (70% vs. 57%), vomiting (38% vs. 28%) and depression (51% vs. 38%). In contrast, mild, moderate or severe weight loss was reported more commonly (≥ 10 percentage points higher) by participants receiving placebo than by those receiving MPH (57% vs. 46%). The only severe AE to differ substantially between treatment groups was the frequency of 'feeling drowsy' (11% in MPH group vs. 22% in placebo-treated participants).

Strengths and weaknesses in relation to other studies

It is noteworthy that although previous systematic reviews and meta-analyses^{14,15} have suggested that MPH may

TABLE 3 Summary of randomised controlled trial findings

Author	N	Cancer population	Dose ^a	Duration	Summary finding	Notes
Bruera 2006 ¹⁹	112	Mixed types, all stages	Mean 11.5 mg/day	1 week	No benefit MPH: FACIT-F 9.6-point improvement Placebo: FACIT-F 7.5-point improvement	'As required' dosing schedule
Butler 2007 ²³	68	Brain tumour, primary or secondary receiving radiotherapy	10–30 mg/day	> 8 weeks (depending on the duration of radiation therapy)	No benefit d-MPH (dexmethylphenidate): FACIT-F 1-point worsening Placebo: FACIT-F 2.3-point improvement	Note use of d-MPH Individually titrated dose
Mar Fan 2008 ²²	57	Breast cancer, early stage, receiving adjuvant chemotherapy	10–20 mg/day Actual dose not reported	Median 12 weeks (depending on the duration of chemotherapy)	No benefit d-MPH: FACIT-F 3-point improvement Placebo: FACIT-F 1-point improvement	Note use of d-MPH Placebo run-in for 3–4 weeks Then continued to end of chemotherapy Dose adjustments
Lower 2009 ¹⁶	154	Mixed types (predominantly breast and ovarian), 2 years post chemotherapy. Stage not reported	Mean 25.5 mg/day	8 weeks	Benefit d-MPH: FACIT-F 10.5-point improvement Placebo: 6.8-point improvement	Note use of d-MPH Higher rate of drug-related AEs in treatment group Weekly dose adjustment Difference between groups of FACIT-F 3.7 points
Moraska 2010 ²¹	148	Mixed types, all stages	Maximum 54 mg/day	4 weeks	No benefit MPH: BFI usual fatigue score AUC for weeks 1–4 mean 50.33 Placebo: BFI AUC mean 57.15	Long-acting MPH Dose adjustments Actual dose achieved not specified MPH group had 3.2% better fatigue score on average (a small effect size)
Roth 2010 ²⁵	32	Prostate cancer, advanced stage	5–30 mg/day	6 weeks	No benefit Two primary fatigue outcomes BFI and FSS No difference between MPH or placebo in change in total BFI scores, BFI interference or FSS scores	Dose adjustments More adverse effects in MPH group No difference in number of subjects with clinically meaningful change in total BFS scores Significant difference in change in BFI severity scale only
Bruera 2013 ²⁰	190	Mixed types, advanced stage	Mean 6.4 mg/day	2 weeks	No benefit MPH: FACIT-F 5.5-point improvement Placebo: 6.0-point improvement	Four-arm trial; 'as required' dosing ± nursing telephone intervention Nursing telephone intervention no more effective than control telephone intervention
Richard 2015 ¹⁷	24	Prostate cancer, all stages treated with LHRH agonist for > 6 months	10 mg/day	10 weeks	Benefit MPH: FACIT-F 7.7-point improvement Placebo: 1.4-point improvement	Fixed titration schedule starting at 5 mg/day up to 10 mg/day and then tapered
Pedersen 2020 ¹⁸	28	Mixed types, advanced stage	10 mg as required dosing	1-week trial Primary outcomes were change in VAS for tiredness 2 and 5 hours post dose	Benefit MPH: tiredness VAS improvements at 2 and 5 hours post dose were 20 mm and 17 mm Placebo: tiredness VAS improvements at 2 and 5 hours post dose were 8 mm and 5 mm	Within-patient comparison 10 mg doses vs. placebo

continued

TABLE 3 Summary of randomised controlled trial findings (continued)

Author	N	Cancer population	Dose ^a	Duration	Summary finding	Notes
Centeno 2022 ²⁴	77	Mixed types, advanced stage	10–25 mg/day	6 days	No benefit MPH: FACIT-F 4.9-point improvement Placebo: 6.4-point improvement	Dose adjustments Greater improvement in fatigue in placebo group

AUC, area under the curve; BFI, Brief Fatigue Inventory; FSS, Fatigue Severity Scale; LHRH, luteinising hormone-releasing hormone. a d-MPH is twice as potent as the racemic mixture [dextrorotatory, laevorotatory – methylphenidate (d,l-MPH)]. Thus, 10 mg d-MPH = 20 mg d,l-MPH.

be effective, the majority of individual studies included in such reviews have not reported benefit.^{19–25} Indeed, the positive findings from previous meta-analyses have largely been driven by the results of just one relatively large study. Lower and colleagues¹⁶ investigated d-MPH, the pharmacologically active portion of the drug, which is approximately twice as potent as MPH. In Lower's study, participants started at 10 mg/day of d-MPH (equivalent to 20 mg/day of MPH), and the dose and frequency were modified weekly over an 8-week period so that the mean final dose received was 25.5 mg/day. The study involved patients ($n = 154$) with different cancer diagnoses, the overwhelming majority of whom had either breast or ovarian cancer (90–91% of participants in each arm). Participants had previously had at least four cycles of cytotoxic chemotherapy (a mean of over 2 years previously) and were currently off treatment. The stage of disease was not reported, but 93% of participants had ECOG performance status 0 or 1. A key feature of Lower's study was that it involved a single-blind (placebo only) 7-day run-in phase. Participants who responded ($n = 8$) or had adverse effects ($n = 2$) or other problems ($n = 4$) with placebo were excluded from randomisation. After 8-week treatment, Lower and colleagues reported that FACIT-F scores had improved by 10.5 points in those receiving d-MPH and 6.8 points in those receiving placebo (a mean difference in change scores of 3.7 points). The discrepancy between Lower and colleagues' results and the majority of the other randomised controlled trials (RCTs), including our own, may be explained in various ways. It is likely that the population in Lower's trial was clinically different from the populations studied in other studies of cancer-related fatigue. All participants had a good performance status, and many of them may have even been disease-free at the time of study enrolment (on the basis that they had been off treatment for 2 years and many may have had potentially curative disease). The causes (and potential treatments) for fatigue in disease-free cancer survivors may be substantially different from those in patients with active disease, on treatment or in palliative care. It is also noteworthy that the doses of medication

used in the Lower study were higher than those attained in most other clinical trials (although more similar to the doses achieved in our own study). But perhaps the most important difference between Lower's study and other previous research was the decision to include a 1-week placebo-only run-in period, with placebo responders being subsequently excluded from randomisation. This is likely to have resulted in a smaller response in both treatment groups than would otherwise have been expected. This is particularly important because the reason that most previous studies have failed to demonstrate superiority of MPH over placebo has been, at least in part, due to significant responses³⁴ in the placebo arm. Finally, it should be noted that even though the study reported statistically significant superiority for d-MPH, the magnitude of the difference in change scores between treatment arms was only 3.7 points, which is less than the MCID our study was powered to detect.

Several other studies have tried to replicate Lower and coworkers' findings in patients with advanced cancer. Bruera and colleagues²⁰ undertook a four-armed (2×2 factorial) study comparing MPH versus placebo delivered in combination with either a nursing telephone or control intervention. The participants all had advanced cancer. They used an 'as required' dosing schedule of MPH 5 mg tablets, that permitted participants to receive up to a maximum of 20 mg/day for 14 days. The mean daily dose of MPH actually received was 6.4 mg/day. Although fatigue significantly improved from baseline in both groups (5.5-point improvement in MPH and 6.0-point improvement with placebo), there was no significant difference in the change scores between groups. Centeno and colleagues²⁴ also studied patients with advanced cancer, but in this trial, participants received an individually titrated regular dose of MPH over 6 days (starting at 15 mg/day and subsequently adjusted to between a minimum of 10 mg/day and a maximum of 25 mg/day). There was a significant improvement in fatigue in both groups (4.9-point improvement in MPH and 6.4-point improvement with placebo), but no significant difference in the change scores between groups.

Our study contributes to the existing literature by confirming the lack of effectiveness of MPH at reducing fatigue in patients with advanced cancer. One potential explanation for the inability of previous studies to demonstrate effectiveness of MPH may plausibly have been that many previous studies did not use regular dosing at a sufficiently high strength. Of the three previous studies¹⁶⁻¹⁸ which have observed MPH to be effective, one involved 'as required' dosing of 10 mg at a time¹⁸ and one involved regular dosing of 10 mg/day.¹⁷ Only Lower and colleagues' study (previously discussed) used a higher dose (final dose equivalent to MPH 51 mg). In our study, the mean daily dose of MPH was 30 mg/day, with many participants achieving the maximum permitted daily dose of 60 mg/day. Nonetheless, despite these relatively high doses, after 6 weeks of treatment, we did not detect any significant differences in fatigue in the intervention group.

The choice of a 5-point difference on the FACIT-F score as representing the MCID may be considered a potential limitation of our study. There is, after all, no consensus about the MCID for FACIT-F and so we had to make an informed decision about the appropriate cut-off on the basis of previous studies in this area. Two different approaches to determining the MCID have been used previously. Reddy and colleagues³¹ calculated the MCID by looking at changes in FACIT-F score and comparing it with changes in subjective GBSs, using pooled data from three clinical trials in palliative care patients with advanced cancer. They hypothesised that if participants in these trials had reported a change in their condition that was at least 'moderately important, consistently beneficial', then they should be considered to have had a clinically important improvement in fatigue. They found that a change in FACIT-F score of approximately ≥ 10 points corresponded to such an improvement. Rather than using a subjective improvement in perceived global benefit, Patrick and colleagues³⁵ calculated the MCID by using an 'anchor-based' approach. That is, they analysed data from a RCT³⁶ in which cancer patients were given either epoetin alfa or placebo and determined what change in FACIT-F score corresponded to at least a 10 g/l improvement in haemoglobin levels. They calculated the relationship between change in haemoglobin and change in FACIT-F score in two ways, either by comparing those with stable versus those with improved (> 10 g/l) haemoglobin levels (MCID 4.75 points) or by using regression (MCID 1.63 points). Similarly, Cella and coworkers used a combination of 'anchor-based' (in this case, a combination of haemoglobin levels, performance status and treatment response) and 'distribution-based' (1/2 SD or 1 standard

error of measurement) and estimated the MCID to be 3 points.

We believe that our choice of a MCID of 5 points is justified on several grounds. Firstly, in an evaluation of a symptomatic treatment to improve subjective fatigue in palliative care patients, it makes more sense to use a MCID based on a subjective measure of improvement (global benefit) as the benchmark, rather than a MCID derived from fatigue scores corresponding to a > 10 g/dl change in haemoglobin levels. Secondly, if we had used the most conservative estimates of a MCID suggested by Cella³⁷ and Patrick³⁵ (i.e. 3 and 2 points, respectively), this would have equated to a GBS corresponding to somewhere between 'Not beneficial' and 'Slightly beneficial'. Whereas a mean change of 5 points on FACIT-F score (the MCID used in our study and the higher estimate provided by Patrick and coworkers) corresponds to a GBS closer to 'Slightly beneficial' or 'Somewhat important, consistently beneficial'. Finally, post hoc support for our choice of at least a 5-point change as representing the MCID was the finding that, despite patients who received MPH having a nominally statistically significant mean improvement of 2 points on FACIT-F score at week 6 compared to placebo, more patients in the MPH than the placebo group considered that their overall condition had 'stayed the same' or 'got worse' [45/72 (63%) vs. 38/67 (57%)].

Limitations

Although we maintain that the choice of a MCID of 5 points on FACIT-F score was justifiable for the reasons described above, given the key importance of this figure for the design of the study, it may have been helpful to undertake further preparatory work to inform and support our chosen cut-off. This might have included, for instance, undertaking a wider consultation with patient and public involvement (PPI) groups and/or clinicians about the minimum levels of fatigue that are considered consequential, or even further empirical work to explore the relationship between fatigue levels and QoL or self-reported overall benefit.

The participants in our study were highly selected. This was driven by safety requirements and reflected the long list of cautions and contraindications that accompany the use of MPH in clinical practice. As a result, most fatigued patients at participating sites were not eligible for inclusion in the trial because they were gravely ill or else had clear contraindications to participation. Of the patients who were formally screened, only 162/297 (55%) were randomised. This suggests that, even if our study had demonstrated a statistical and clinical benefit for MPH, it

would have been unlikely to have become a widely used therapy in this population.

Our study failed to reach the originally planned sample size. Although, following modification of our protocol, permitting an adjustment in sample size and power (see section on protocol modifications), we did still manage to successfully recruit and retain sufficient participants to answer the primary objective.

Reflections on the project

Randomised controlled trials of IMPs [Clinical Trial of an Investigational Medicinal Product (CTIMP)] in palliative care are relatively uncommon, and much palliative care research focuses instead on the evaluation of services, policy-related issues and observational studies.³⁸⁻⁴⁰

Most CTIMPs in palliative care populations on the NIHR portfolio are trials of disease-modifying therapies (systemic anticancer therapy or radiotherapy trials) rather than evaluations of symptom-directed interventions. Palliative care studies are hard to plan, fund and deliver. There is consequently a paucity of robust data from clinical trials in palliative care to inform clinical practice about symptom management. The difficulties of undertaking trials in palliative care have been previously described. For example, Chen and colleagues³⁹ undertook interviews with 61 leading palliative care researchers and identified five major obstacles to the successful completion of research studies in this population: research funding; institutional capacity; researcher workforce issues; challenges related to the topic and/or the study population; and public and professional misunderstandings and misperceptions about undertaking research in this area. Despite such difficulties, and the added complication of an intervening global pandemic, methylphenidate versus placebo for fatigue in advanced cancer (MePFAC) became one of the few clinical trials of an IMP to have been successfully completed in this patient population in the UK. The investigators, therefore, consider it a great achievement to have completed this study and to have reached the required (albeit reduced) sample size, thus providing a definitive answer to the research question.

One of the key factors contributing to our success was the involvement of the Priment Clinical Trials Unit (CTU). Prior to leading the MePFAC study, the chief investigator (although previously a PI) had had no previous experience of leading a CTIMP and was reliant on the expertise and experience of the CTU to lead him through the processes required to set up and run a multicentre study. Correspondingly, however, the CTU had also had limited prior experience with undertaking RCTs in palliative care populations and needed to be mindful of ways in which

usual ways of operating may need to be modified to reduce the burdens on study participants (e.g. minimising number of data collected and limiting number of face-to-face visits). The chief investigator wishes to acknowledge the support of Professor Michael King as a co-applicant and mentor during the funding application process and the first few years of the study. Professor King was an experienced triallist and, although a psychiatrist by background, had also undertaken clinical research in palliative care populations. He was, therefore, able to advise on how the study design could be optimised for patients with advanced disease. Unfortunately, following a short illness, Professor King died in 2021, before the trial was completed. However, his contribution to the success of the project cannot be overstated.

Reflecting on the issue of the paucity of clinical trials in palliative care, there are relatively few research-active palliative care services in England. This meant that many of the MePFAC PIs and research sites were relatively inexperienced. For a significant proportion of the sites involved in the MePFAC study, this was their first involvement in a RCT of an IMP or even in a multicentre research project. Many palliative care studies are observational and/or use qualitative or survey methodologies. As a result, PIs and research delivery staff at each site required extensive and ongoing training and support, and this placed a large administrative burden on the central research project management team (chief investigator and trial manager).

Identifying, training and supporting PIs only partially addressed the workforce issues. Collaborating sites also needed to access research nurse time. Although, in theory, Clinical Research Network (CRN) nurses were available to support recruitment (at least at collaborating sites based in cancer centres), there were sometimes practical difficulties with accessing research nurse time. Cancer clinical trials are often disease-specific, and recruitment is usually supported by site-specific research nurses (e.g. lung cancer research nurses recruiting to lung cancer studies). However, MePFAC was open to all patients with advanced incurable cancer, rather than to patients with a specific tumour type. This ought to have made recruitment easier (more potentially eligible patients to be recruited), but in practice, it sometimes meant that recruitment to the MePFAC trial was considered a lower priority than recruitment to tumour-specific studies. At some centres, PIs benefited from dedicated palliative care research nurse time specifically to recruit to the MePFAC study; at other centres, responsibility for recruitment was 'distributed' across a number of different site-specific nurses. Our highest recruiting site (University Hospitals Sussex) had a

PI who was also a co-applicant, a dedicated NIHR-funded research nurse, and recruitment across tumour types was supported by all of the oncology consultants (with much of the recruitment occurring among patients with advanced cancer on the chemotherapy day unit). Some CRN nurses were also able to outreach to recruit participants at geographically remote hospice sites, but because the nurses were not based on site, this meant that (due to lack of availability) potential participants to the study may have been missed. The most effective hospice recruiting sites (John Eastwood Hospice, Sue Ryder Hospice and Pilgrims Hospices) had one or more research nurses on site (supported by a combination of charitable funding, with CRN and some industry-funded studies).

Recruitment sites based in cancer centres were generally supported by experienced research pharmacies and pharmacists who were very familiar with undertaking CTIMPs. In comparison to other members of the local site research team, these services seldom needed additional central support. However, some hospice sites initially expressed an interest in participating in the study but did not have adequate pharmacy support to undertake CTIMPs and were therefore deemed to be unsuitable for study participation. Other sites, who participated in the trial, needed to use research pharmacy services from their local hospital trusts.

After participants were recruited to the study, they needed to be reviewed on a weekly basis to be asked about perceived benefits and adverse effects, so that local PIs could make decisions about whether (and how) to adjust the dose of the study medication. Initially, the reviews at weeks 3, 6 and 10 were scheduled to be undertaken on site by PIs and locally employed research nurses, with the intervening assessments being undertaken remotely by centrally employed research nurses/clinical trial practitioners at University College London. However, following protocol amendments in response to the COVID pandemic, nearly all of these weekly reviews were undertaken remotely by the central team (some sites continued with face-to-face visits depending on local policies). The funding for these two centrally employed members of staff came from the NIHR project grant which funded the MePFAC trial. This additional, centrally funded workforce was essential to the success of the MePFAC trial. It meant that many more sites considered that they could participate in the study despite relative lack of access to research infrastructure support locally. The role of the two centrally employed research staff assumed even greater importance after the trial reopened following a pause for the COVID pandemic. Following a protocol amendment, it became possible for the centrally employed research nurses to undertake all

the weekly assessments (including assessments at weeks 3, 6 and 10, which had previously been undertaken face to face at local recruiting sites). This innovation was particularly important to the success of the trial at a time when other services were being stretched very thinly (because of, e.g. re-deployment of research staff to clinical front-line duties).

The COVID pandemic resulted in a significant increase in workload for MePFAC staff and collaborators [e.g. conducting risk assessments; closing and reopening sites; developing new standard operating procedures; submitting Research Ethics Committee (REC), Health Research Authority, and Medicines and Healthcare products Regulatory Agency amendments; retraining staff in new procedures; securing additional funding]. MePFAC was supported throughout by the funder. At the start of the pandemic, while the impact of the disruption was still uncertain, NIHR offered an immediate 6-month-no-cost extension. Later in the year, once the situation was somewhat clearer, NIHR agreed to a longer, funded extension, that allowed the study to reach its recruitment target.

Although the COVID pandemic entailed significant increase in workload, there were some positives to emerge. The changes that were made to the research protocol in response to the pandemic made the study much easier to conduct and less burdensome for participants (e.g. simplification of screening and consent process, fewer face-to-face visits, greater use of remote monitoring and home delivery of study medications). Future studies are much more likely to make greater use of remote monitoring and online data collection.

Major changes over the course of the trial

The MePFAC trial was originally planned to last for 3.5 years (42 months). In fact, the study took 6.5 years (78 months) to complete. This included two funded variations to contract (VTCs) and an approximate 1-year pause in recruitment as a result of the COVID pandemic. As previously described, one of our co-applicants, Professor Michael King, died on 10 September 2021. In order to contain costs, Professor King was not replaced, and the rest of the trial was completed by the original co-applicants. A list of the major changes that occurred to the protocol is provided in [Appendix 1, Table 4](#).

Impact of the COVID pandemic

The COVID pandemic caused major disruption to the study and increased costs. A summary of the actions that the study team took in response to the COVID

pandemic is provided in Supplementary Information (see [Report Supplementary Material 5](#)). Recruitment was significantly curtailed in early March 2020 as the impact of the pandemic began to affect NHS services. On 19 March 2020, the chief investigator took the decision to cease recruitment completely. At that point, the Trial Management Group (TMG) conducted a risk assessment and approached the funder for support to pause the trial with the aim of reopening when and if the pandemic allowed. NIHR allowed the study to continue with an initial 6-month-no-cost extension to account for the estimated length of time for which the COVID pandemic was (at that time) considered to be likely to affect recruitment. By chance, one of the centrally employed research nurses had resigned prior to the pandemic and had not yet been replaced. We, therefore, took the opportunity to save costs by delaying reappointment until the autumn. New recruitment was suspended between March and October; nonetheless, the remaining NIHR-funded staff were fully employed with the safe close-down of sites, data-checking, remote monitoring, preparation of protocol amendments and reapplications for research ethics and governance approvals for the revised protocol. Although we managed to reopen a few sites to recruitment by November 2020, recruitment did not immediately return to normal. That is because, by the autumn of 2020, COVID once again started to place the NHS under enormous stress, and most research sites did not have the capacity or capability to reopen. Even those sites that were able to remain open to recruitment were badly affected by social-distancing guidelines and then by another national lockdown. Between 19 March 2020 and 31 March 2021, only seven participants were recruited to the trial (from four sites). Recruitment only began to return to something approximating to pre-COVID levels after June 2021.

Protocol changes

The original protocol [v1.0 (5 May 2017)] was submitted to the London City and East REC for approval in June 2017 [Integrated Research Application System (IRAS) project ID 215297; REC reference number 17/LO/0871; protocol number 15/0592]. The final Study Protocol is available in Supplementary Information (see [Report Supplementary Material 1](#)), and the version history at the start of the document details all of the changes that occurred with each subsequent protocol amendment. A summary of the major changes to the protocol is provided in [Appendix 1, Table 4](#).

Funded variations to contract

Over the course of the study, there were two major variations to the original contract with NIHR. The first variation to contract (VTC1) was a request to extend

recruitment by 16 months (from 31 October 2020 to 28 February 2022). Principal changes included a reduction in minimum permissible eGFR from 60 ml/minute to 45 ml/minute and exclusion of patients only if they had uncontrolled (rather than pre-existing) heart failure, angina or drug dependency and if they had had MI or stroke within the previous year (rather than at any previous time). The amendment also included a reappraisal of the original assumptions underlying the randomisation target. Prior to starting the study, we had estimated that there would be 25% attrition. On that basis, we had estimated that we would need to recruit 230 participants to achieve 172 evaluable participants. However, study attrition (at the time of the VTC application) was running at 13%. We, therefore, modified our assumption to estimate that attrition over the course of the study would be no worse than 20%, and therefore the estimated sample size needed to accrue 172 evaluable patients could be reduced from 230 to 215 randomised participants without any change in the study power. VTC1 was submitted on 19 December 2019 and was awarded on 9 July 2020. However, it should be noted that between submission and the award of VTC1, the MePFAC trial (like most other UK research) was severely adversely affected by the COVID pandemic. Indeed, all recruitment to the trial was suspended in March 2020. At the time, it was estimated that it may be necessary to suspend recruitment for 6 months (in fact, the trial was effectively closed to recruitment for 12 months).

The second variation to contract (VTC2) was a request to extend the study by 20 months (from 28 February 2022 to 31 October 2023). Based on recruitment performance up until that point, it was no longer deemed feasible to recruit to the originally planned sample size (providing 90% power). However, recruitment targets were adjusted to ensure that a sufficient number of participants would be randomised ($n = 162$) to accrue a minimum of 130 evaluable participants (this would provide a minimum of 80%+ power, or higher if attrition was lower than estimated). In efforts to facilitate recruitment and retention to the study in the light of ongoing pandemic conditions, further modifications were made to the protocol, including greater use of remote (rather than face-to-face) follow-up assessments and merger of separate screening and enrolment visits.

Engagement with partners and stakeholders

The TMG consisting of the co-applicants, our PPI representative, the central research team (trial manager, research nurses and/or clinical trial practitioners), representatives from the CTU and other interested members of the extended research team, met on a monthly

basis throughout the trial (hybrid meeting to allow PIs to facilitate remote attendance).

Because many of the participating centres in the MePFAC study were relatively research-naive, the central research team made great efforts to engage with and support local PIs and site research teams. So, in addition to the TMG meetings, we held monthly virtual meetings for all participating sites, initially by telephone and later using an online virtual meeting platform [Microsoft Teams (Microsoft Corporation, Redmond, WA, USA)]. At these meetings, the chief investigator briefed sites about developments in the study, planned or approved protocol changes and AE reporting. In turn, sites shared information about the barriers and facilitators to conducting the study at their own sites and shared best practice to improve recruitment across the study. The chief investigator and the trial manager were also directly accessible to members of the wider research team by mobile phone and e-mail. The trial manager produced a newsletter for all participating sites, which was distributed three times per year and which shone a spotlight on areas of good practice and attempted to foster friendly rivalry between sites to boost recruitment. We promoted wider engagement of stakeholders by periodic updates about recruitment on Twitter [X Corp. (formerly Twitter) San Francisco, CA, USA] (tagging in NIHR Twitter account and the relevant local recruitment centres).

David Miodrag (PI at John Eastwood Hospice) reflected thus on his involvement in the study:

I had never been a PI, nor been directly involved in a CTIMP, before my involvement in MePFAC. When the trial started, I felt enthusiastic though daunted due to my lack of previous experience, although Prof. Stone, and Elli Enayat (Trial Manager), were very supportive and accessible throughout, and this put me at ease and gave me assurance and confidence. The regular MePFAC teleconferences and newsletters for updates and information sharing between sites were a great help and kept me motivated and well informed.

John Eastwood Hospice was one of the highest recruiting sites in the trial. There were several factors that contributed to our local success. We had two less than full time Research Nurses working on the study who undertook screening and attended multi-disciplinary team meetings at the hospice to identify potential participants (the nurses are partially funded by the NHS and partly by the John Eastwood Hospice charity). We gave several presentations about MePFAC to different clinical teams within the hospice at the outset to persuade clinicians to identify potential

participants. Our Day Hospice was a particularly fertile source of participants, and it reached a point where some Day Hospice patients requested to be screened for the trial having heard about it from their peers who were taking part.

Being a PI in MePFAC was invigorating and rewarding, and I am raring to be involved in future Palliative Care research, especially CTIMPS.

David Miodrag (PI)

Training and capacity strengthening activities

Prior to opening the study at any collaborating site, we held a site initiation visit to provide training to research staff on the protocol. Sites were also provided with access to an audio-recording and PowerPoint® (Microsoft Corporation, Redmond, WA, USA) slide set of the training materials for members of staff who could not be present at the site initiation visit. Training logs were kept to ensure that all staff had had the necessary training. Additional remote training was provided on the use of the study database and on the randomisation and pharmacy dispensing processes. Sites were given access to training videos about how to identify potentially eligible patients for the study and how to obtain informed consent. After the temporary pause in recruitment occasioned by the COVID pandemic, it was necessary to effectively relaunch the study at each site and to provide updated training on the new protocol. Ad hoc training was provided to new members of staff and PIs.

The MePFAC also provided an opportunity for more junior staff to gain experience with working on clinical trials. For example, as part of her NIHR Development and Skills Enhancement Award for Clinical Trials, Joanne Bayly (King's College London) observed some of the Trial Steering Committee (TSC) meetings (under the mentorship of Toby Provost). MePFAC was part of the NIHR Associate PI Scheme, which provides junior staff, who are interested in research, with 6 months' in-work training and an opportunity to gain practical experience with being involved in a clinical trial. Over the course of the study, we had two Associate PIs, one hosted at Royal Sussex County Hospital and another at University Hospital Southampton.

In June 2023, the chief investigator was invited to give a talk at a conference on research-active hospices which was attended by over 100 participants (academics, clinicians, patient and public representatives and research administrators). It is envisaged that this may lead to a community of practice to encourage and support future multicentre research studies. A report of the meeting has been produced and shared with NIHR and other

stakeholders and is available in Supplementary Information (see [Report Supplementary Material 6](#)).

Patient and public involvement

We involved patients and public at an early stage in our design and planning. A preliminary draft of our funding application was sent to the Marie Curie Expert Voices group to seek their views about the willingness of patients to participate in such a project, the appropriateness of using randomisation and of 'blinding'. We also asked patients and service users to comment on the proposed length of the study and the perceived burden of study participation. As a result of patient feedback, we strove to keep the patient burden to a minimum. We carefully selected outcome measures to be appropriate and well-used in this population. Working with our PPI collaborators, we were mindful of making sure that patient information leaflets provided a clear description of the potential side effects of study medications. PPI representatives were supportive of the plan to include weekly telephone contact during the study. Since the start of the study, one of our original PPI representatives (Kathy Seddon) has been on the TSC. Shortly after the study began, Peter Buckle, another member of Marie Curie Expert Voices PPI panel, joined the study TMG and has attended monthly meetings ever since.

Patient and public involvement in the MePFAC study has had several important benefits. There is sometimes a misconception among RECs that involving palliative care patients in research studies may be unduly onerous or burdensome. It was helpful for the research team to be able to reassure the REC that we had consulted PPI representatives during the course of the study to ensure that (as far as possible) the proposed trial design would likely be acceptable to patients with advanced cancer. We have been very grateful for the significant time commitment of our PPI members, particularly Peter Buckle who has attended monthly TMG meeting for the duration of the study. He has been able to provide a very useful perspective on issues that arose throughout the course of the study, for example, in deciding how the research team should respond to the challenges posed by the COVID pandemic. PPI has helped to ensure that the findings from our study have been communicated clearly so that their meaning and significance for patients and the public can be clearly understood. Moreover, Peter Buckle contributed to production of training videos, study management, trial oversight, interpretation of study data and the drafting of both this report and associated conference abstracts and other peer-reviewed publications.

Peter reflected on his contribution to the trial:

By way of background, my wife Wendy died from a glioblastoma at the age of 54 less than five months after diagnosis. She suffered from no fewer than 28 symptoms, side effects and disabilities, including severe fatigue. Obviously, this was for a shorter period than many other terminally ill cancer patients because of the speed of disease progression. This was my first experience of the death of a loved one, and after the event, it became quite clear to me that her end-of-life care was poor in many respects. The year after Wendy's death, I became a volunteer for the Marie Curie charity, and was an original member of their Research Voices group. As such, I had dealings with Professor Stone and the UCL Research group for palliative and end-of-life care and was pleased to be invited to join the TMG for this study.

It is always disappointing from a patient advocate viewpoint to find that an intervention does not show a significant benefit for patients who are suffering. However, there is value in the findings from this study despite this.

I would like to take this opportunity to make two observations. The first is to thank Professor Stone and all other TMG members for their appreciation of my experience and position, their patience when required to explain issues and their genuine and continual welcome of my input. Secondly, I must commend all involved for the innovative and professional way in which the trial was conducted during the Covid pandemic. This was most impressive.

To conclude, this study has exposed some of the difficulties that potentially arise in research into the neglected area of palliative and end-of-life care. I would like to see improvements to the support and infrastructure in this area going forward.

Peter Buckle, PPI representative, MePFAC trial

We have tried to highlight involvement of patients in the MePFAC study through various dissemination projects and outputs. The East Midlands NIHR produced a patient experience video about a patient who was involved in the MePFAC trial. *Sandra's Story* explained the importance of patient involvement in palliative care and the role of research within a hospice. The importance of undertaking research in hospices was also showcased in an article in the Pilgrims Hospices newsletter (Pilgrims Matters) which is distributed widely to hospice supporters and members of the public in Kent. Furthermore, a case study about the positive benefits for patients participating in palliative care research (using the MePFAC trial as an exemplar) was produced by the NIHR and is available on their website (<https://local.nihr.ac.uk/case-studies/grateful-mum-living-life-to-the-fullest-thanks-to-south-london-researchers/30658>).

Equity, diversity and inclusion

The MePFAC study enrolled 162 men and women, with advanced cancer from 17 palliative care services across England, including hospital support teams, palliative care outpatient clinics, community palliative care services and hospices. Our study sample was reasonably balanced with regard to the sexes, with 86/159 (54%) of the sample being women. According to Cancer Research UK statistics,⁴¹ adults aged 50–74 account for more than half (54%) of all new cancer cases, and the four most common cancers are breast, prostate, lung and bowel. The mean age of participants in the MePFAC trial was 63.7 years, and the four most common cancers in our study population mirrored the frequency of these diagnoses in the general population. In keeping with what one would expect of a palliative care population, 41% of our study sample were on strong opioids and 78% had either recently received, were currently receiving or were scheduled to start palliative disease-modifying therapies at the time of study enrolment.

In an effort to keep data collection to a minimum, we did not collect data about the ethnicity of participants in the trial. The rationale for this was that we wished to only collect the minimum number of data to reduce participant burden. Indeed, in the first version of the protocol, to minimise data collection procedures, we did not even collect detailed diagnostic data about patients' cancer diagnoses (we only recorded whether or not they fulfilled the study inclusion and exclusion criteria – advanced incurable cancer receiving palliative care). Moreover, we had no prior hypothesis (and there were no previous studies to suggest) that ethnicity would be a modifier of treatment response. However, in retrospect, the failure to collect ethnicity data was a limitation and has not allowed us to make any statements about the representativeness of included participants with regard to ethnic diversity.

The gender balance, age distribution, diagnostic spread, use of concomitant medication and wide geographical diversity of our recruitment strategy suggest that our findings are likely to be generalisable.

Impact and learning

The results of the MePFAC study are likely to lead to changes in clinical practice and to the treatment recommendations contained in existing professional guidelines.

In the UK, the Palliative Care Formulary (PCF)⁴² is used as the reference text for prescribers in palliative medicine.

The most recent edition of the formulary (PCF8) lists 'fatigue refractory to correction of underlying contributory factors' as one of the 'beyond licence' indications for MPH. However, the formulary notes that the use of psychostimulants for fatigue is controversial, and for this reason, use should be 'reserved for fatigue refractory to other measures'. The National Comprehensive Cancer Network guidelines recommend that MPH may be considered for use in patients on treatment, post treatment and at the end of life, although they state that the drug 'should be used cautiously and should not be used until treatment- and disease-specific morbidities have been characterised or excluded'.⁴³ The European Society of Medical Oncology guideline development committee on cancer-related fatigue was unable to reach consensus on the issue. Some panel members recommended that psychostimulants might be considered in selected patients but that their usefulness and safety should be re-evaluated after a short time, and others considered that these drugs could not be recommended.⁴⁴ The American Society of Clinical Oncology guidelines⁴⁵ concluded that 'evidence suggests that psychostimulants (e.g. MPH) and other wakefulness agents (e.g. modafinil) can be effectively used to manage fatigue in patients with advanced disease or those receiving active treatment. However, there is limited evidence of their effectiveness in reducing fatigue in patients after active treatment who are currently disease free'. On the basis of our research, MPH should no longer be recommended as a treatment for fatigue in patients with advanced cancer (even in selected cases or as a therapeutic trial for a short time period). The balance of the evidence now indicates that, even if MPH were to result in small improvements in fatigue (over and above those provided by placebo), the magnitude of such improvements is likely to be less than the MCID. There is stronger evidence for other management approaches (such as exercise), and further research in this area should focus on determining the optimum strategies for delivering such interventions and/or on the evaluation of other pharmacological and non-pharmacological approaches.

The results of our study have already been presented at the European Association of Palliative Care 13th World Research Congress (see [Report Supplementary Material 7](#)), and the main results have been published in a peer-reviewed journal.¹ Members of the research team plan to work with national and professional associations to ensure that the findings are incorporated into updated guidelines. One of the co-applicants is working on an updated systematic review and meta-analysis of RCTs which will include the data from the MePFAC trial.

Implication for decision-makers

Methylphenidate does not currently have a licence for the management of cancer-related fatigue, although individual practitioners may take responsibility for prescribing medication beyond the licenced indications. The PCF⁴² currently describes a limited role for prescribing MPH in palliative care populations beyond license, in situations where fatigue is refractory to other measures. However, in the light of the results of our study, clinicians should be discouraged from doing so. Local and professional guidelines should amend their recommendations accordingly. Palliative medicine higher specialist training programmes should discourage practitioners from using MPH for the relief of fatigue in palliative care patients with advanced cancer. Although there have been conflicting results from previous studies, the balance of evidence describes that MPH, although generally safe, is ineffective for this indication.

Research recommendations

Our research recommendations in priority order are, firstly, that a number of studies has now been undertaken to investigate the effectiveness or otherwise of MPH for the relief of fatigue in patients with advanced cancer, and the results of our study, combined with the balance of evidence from previous trials, suggests that further research to evaluate the effectiveness of this intervention, for this indication, in this population, is no longer warranted.

Secondly, although MPH was not effective at treating fatigue in advanced cancer, it was reasonably well-tolerated and safe to use. For that reason, it may still be reasonable to consider further trials to evaluate the effect of MPH on other symptoms of advanced cancer which are otherwise difficult to treat (e.g. opioid-induced drowsiness or low mood).

Finally, and notwithstanding the neutral results of our study (lack of effectiveness of MPH), cancer-related fatigue remains a significant problem for patients with advanced cancer, and improving the management of this symptom should remain a priority for research funders. There is a number of further plausible candidate pharmacological interventions that are in need of further evaluation in RCTs, including paroxetine,⁴⁶ anamorelin (a selective ghrelin agonist)⁴⁷ and ginseng.⁴⁸ Exercise is probably the intervention with the best evidence for effectiveness for relief of fatigue,^{8,49} although further research is needed into the best way to deliver exercise to patients with advanced cancer and to understand the extent to which

exercise should be used as part of a multimodal approach to fatigue management (combined with nutritional, psychological and pharmacological interventions).

Conclusions

There was no statistically or clinically significant difference in fatigue in patients with advanced cancer receiving MPH versus placebo after 6 (\pm 2) weeks. MPH should not be prescribed for this indication. Further trials of this MPH for fatigue in patients with advanced cancer receiving palliative care are not warranted. Although we found some nominal improvements in fatigue at other time points, the effects were small and below the level that would be meaningful to patients' well-being. Moreover, patients receiving MPH did not report improvements in overall QoL, nor did they feel that the MPH provided any greater benefit than placebo.

Additional information

CRedit contribution statement

Patrick Stone (<https://orcid.org/0000-0002-5765-9047>): Conceptualisation, Funding acquisition, Methodology, Project administration, Supervision, Visualisation, Writing – original draft, Writing – reviewing and editing.

Ollie Minton (<https://orcid.org/0000-0002-4258-8995>): Conceptualisation, Funding acquisition, Methodology, Project administration, Writing – reviewing and editing.

Alison Richardson (<https://orcid.org/0000-0003-3127-5755>): Conceptualisation, Funding acquisition, Methodology, Project administration, Writing – reviewing and editing.

Peter Buckle (<https://orcid.org/0000-0002-8139-2768>): Project administration, Writing – reviewing and editing.

Zinat E Enayat (<https://orcid.org/0000-0003-4384-9314>): Investigation, Project administration, Supervision, Validation, Writing – reviewing and editing.

Louise Marston (<https://orcid.org/0000-0002-9973-1131>): Data curation, Formal analysis, Project administration, Resources, Software, Validation, Visualisation, Writing – reviewing and editing.

Nick Freemantle (<https://orcid.org/0000-0001-5807-5740>): Conceptualisation, Formal analysis, Funding acquisition, Methodology, Project administration, Supervision, Validation, Writing – reviewing and editing.

Michael King (deceased): Conceptualisation, Funding acquisition, Methodology, Project administration.

Simon Noble: Supervision (TSC).

Toby Prevost: Supervision (TSC).

Kathy Seddon: Supervision (TSC).

Fliiss Murtagh: Supervision [Data Safety Monitoring Board (DSMB)].

Andrew Davies: Supervision (DSMB).

Paul Howard: Supervision (DSMB).

Deborah Stocken: Supervision (DSMB).

Laura Hennelly: Investigation.

Munirah Islam: Investigation.

Hinal Lukha: Investigation.

Anne Marie Downey: Data curation, Project administration, Supervision.

Lana Amyri: Project administration, Validation.

Zohra Khan: Project administration, Validation.

David Miodrag: Investigation, Project administration.

Lorna Brown: Investigation.

Melanie Hands: Investigation.

Andrew Tolliday: Investigation.

Paul Perkins: Investigation, Project administration.

Kate Tredgett: Provision.

Anne Parkinson: Investigation.

Angela Halley: Investigation, Project administration.

Sally-Anne Holman: Investigation.

Rookmeen Alighan: Investigation.

Sejal Jain: Investigation.

Mark Banting: Investigation, Project administration.

Soumen Saha: Investigation, Project administration.

Andrew Thorns: Investigation, Project administration.

Charlotte Brigden: Investigation.

Rose Ward: Investigation.

Sarah Stirrup: Investigation.

Bethany Jones: Investigation.

Becky Bright: Investigation.

Liam Gabb: Investigation.

Rachel Hogg: Investigation.

Sarah Parnacott: Investigation, Project administration.

Georgina Staine: Investigation.

Anne-marie Carey: Investigation, Project administration.

Sabrina Bajwah: Investigation, Project administration.

Stefania Stegner: Investigation.

Paramjote Kaler: Investigation.

Sarah Frearson: Investigation, Project administration.

Clementine Fitchett: Investigation.

Tamunoibim Anidima: Investigation.

David Brooks: Investigation, Project administration.

Catriona Mayland: Investigation, Project administration.

Angela Star: Investigation, Project administration.

Lisa Zeidan: Investigation.

Meredyth Harris: Investigation.

Maelie Swanick: Investigation, Project administration.

Katie Riches: Investigation, Project administration.

Ruth England: Investigation, Project administration.

Michael Bennett: Investigation, Project administration.

Carla Bruni: Investigation, Project administration.

Matthew Carey: Investigation, Project administration.

Faeqa Hami: Investigation, Project administration.

Alice Ngumo: Investigation.

Janice Carpenter: Investigation.

Data-sharing statement

This work uses data provided by patients and collected by the NHS as part of their care and support. Using patient data is vital to improve health and care for everyone. There is huge potential to make better use of information from people's patient records, to understand more about disease, develop new treatments, monitor safety and plan NHS services. Patient data should be kept safe and secure, to protect everyone's privacy, and it's important that there are safeguards to make sure that they are stored and used responsibly. Everyone should be able to find out about how patient data are used. #datasaveslives You can find out more about the background to this citation here: <https://understandingpatientdata.org.uk/data-citation.Requests> to share suitably anonymised data for scientific purposes should be made in writing and sent to priment@ucl.ac.uk for consideration. Data will only be shared upon completion of a data-sharing agreement.

Ethics statement

The London City and East REC gave approval for this study on 7 August 2017 (IRAS project ID 215297; REC reference number 17/LO/0871; protocol number 15/0592).

Information governance statement

University College London is committed to handling all personal information in line with the UK Data Protection Act (2018) and the General Data Protection Regulation (EU GDPR) 2016/679. Under the Data Protection legislation, University College London is the Data Controller, and you can find out more about how we handle personal data, including how to exercise your individual rights and the contact details for our Data Protection Officer here (www.ucl.ac.uk/data-protection/).

Disclosure of interests

Full disclosure of interests: Completed ICMJE forms for all authors, including all related interests, are available in the toolkit on the NIHR Journals Library report publication page at <https://doi.org/10.3310/GJPS6321>.

Primary conflicts of interest: Patrick Stone reports institutional funding from NIHR to undertake this work as Chief Investigator. He receives institutional core and programme funding from

Marie Curie. Ollie Minton received institutional funding from NIHR to undertake this work as Co-investigator. He reports payment for being national end of life advisor for Macmillan cancer support. Alison Richardson reports institutional funding from NIHR to undertake this work as Co-investigator. She also received institutional funding for her role as Chief Investigator NIHR ARC Wessex. She reports salaried employment as Head of Nursing Research, NHS England (secondment). Peter Buckle has no conflicts to declare. Zinat E Enayat has no conflicts to declare. Louise Marston reports institutional funding from NIHR. Nick Freemantle received institutional funding from NIHR to undertake this work as Co-investigator.

All authors have completed International Committee of Medical Journal Editors (ICMJE) Disclosure of Interest Statements.

Department of Health and Social Care disclaimer

This publication presents independent research commissioned by the National Institute for Health and Care Research (NIHR). The views and opinions expressed by authors in this publication are those of the authors and do not necessarily reflect those of the NHS, the NIHR, MRC, NIHR Coordinating Centre, the Health Technology Assessment programme or the Department of Health and Social Care.

This synopsis was published based on current knowledge at the time and date of publication. NIHR is committed to being inclusive and will continually monitor best practice and guidance in relation to terminology and language to ensure that we remain relevant to our stakeholders.

Trial registration

This trial is registered as EudraCT number 2017-001950-33 and ISRCTN 79478762.

Funding

This synopsis presents independent research funded by the National Institute for Health and Care Research (NIHR) Health Technology Assessment programme as award number 15/46/02.

Award publications

This synopsis provided an overview of the research award *Methylphenidate versus placebo for fatigue in advanced cancer (MePFAC)*. Other articles published as part of this thread are:

Stone PC, Minton O, Richardson A, Buckle P, Enayat ZE, Marston L, Freemantle N. Methylphenidate versus placebo for treating fatigue in people with advanced cancer: randomized, double-blind, multi-center, placebo-controlled trial. *J Clin Oncol* 2024;**42**:2382–93. <https://doi.org/10.1200/JCO.23.02639>

For more information about this research please view the award page (www.fundingawards.nihr.ac.uk/award/15/46/02).

Additional outputs

Stone PC, Minton O, Richardson A, Buckle P, Enayat ZE, Marston L, Freemantle N. Methylphenidate no more effective than placebo for treating cancer-related fatigue: randomised, double-blind, multi-centre, placebo-controlled trial. Oral abstract presented at the European Association of Palliative Care 13th World Research Congress, 16–18 May 2024, Barcelona, Spain.

About this synopsis

The contractual start date for this research was in May 2017. This synopsis began editorial review in February 2024 and was accepted for publication in March 2025. The authors have been wholly responsible for all data collection, analysis and interpretation, and for writing up their work. The Health Technology Assessment editors and publisher have tried to ensure the accuracy of the authors' synopsis and would like to thank the reviewers for their constructive comments on the draft document. However, they do not accept liability for damages or losses arising from material published in this synopsis.

Copyright

Copyright © 2025 Stone *et al.* This work was produced by Stone *et al.* under the terms of a commissioning contract issued by the Secretary of State for Health and Social Care. This is an Open Access publication distributed under the terms of the Creative Commons Attribution CC BY 4.0 licence, which permits unrestricted use, distribution, reproduction and adaptation in any medium and for any purpose provided that it is properly attributed. See: <https://creativecommons.org/licenses/by/4.0/>. For attribution the title, original author(s), the publication source – NIHR Journals Library, and the DOI of the publication must be cited.

Published by the NIHR Journals Library (www.journalslibrary.nihr.ac.uk), produced by Newgen Digitalworks Pvt Ltd, Chennai, India (www.newgen.co).

List of supplementary material

Report Supplementary Material 1

Methylphenidate versus placebo for fatigue in advanced cancer Protocol v14.0
17 January 2023

Report Supplementary Material 2

Statistical analysis plan v7 31 July 2023

Report Supplementary Material 3

Predictors of missingness

Report Supplementary Material 4

Kaplan–Meier survival curves

Report Supplementary Material 5

Changes in response to COVID

Report Supplementary Material 6

Research Active Hospices Report

Report Supplementary Material 7

EAPC Conference Abstract

Supplementary material can be found on the NIHR Journals Library report page (<https://doi.org/10.3310/GJPS6321>).

Supplementary material has been provided by the authors to support the report and any files provided at submission will have been seen by peer reviewers, but not extensively reviewed. Any supplementary material provided at a later stage in the process may not have been peer reviewed.

List of abbreviations

AE	adverse event
ALT	alanine aminotransferase
BP	blood pressure
CRN	Clinical Research Network
CTIMP	Clinical Trial of an Investigational Medicinal Product
CTU	Clinical Trials Unit
DBP	diastolic blood pressure
d-MPH	dexmethylphenidate
ECOG	Eastern Cooperative Oncology Group
eGFR	estimated glomerular filtration rate
EORTC QLQ-C15-PAL	European Organisation for Research and Treatment of Cancer Quality of Life Core 15 Palliative Care
EQ-5D-5L	EuroQol-5 Dimensions, five-level version

FACIT-F	Functional Assessment of Chronic Illness Therapy – Fatigue Scale (a 13-item fatigue scale)
GBS	Global Benefit Score
GI	gastrointestinal
HADS	Hospital Anxiety and Depression Scale
HADS-A	Hospital Anxiety and Depression Scale – Anxiety subscale
HADS-D	Hospital Anxiety and Depression Scale – Depression subscale
IMP	investigational medicinal product
IRAS	Integrated Research Application System
MCID	minimal clinically important difference
MePFAC	methylphenidate versus placebo for fatigue in advanced cancer
MI	myocardial infarction
MPH	methylphenidate
NRS	numerical rating scale
PCF	Palliative Care Formulary
PI	principal investigator
PPI	patient and public involvement
QoL	quality of life
RCT	randomised controlled trial
REC	Research Ethics Committee
SAE	serious adverse event
SBP	systolic blood pressure
SUSAR	suspected unexpected serious adverse reaction
TMG	Trial Management Group
TSC	Trial Steering Committee
VAS	visual analogue scale
VTC	variation to contract

References

1. Stone PC, Minton O, Richardson A, Buckle P, Enayat ZE, Marston L, Freemantle N. Methylphenidate versus placebo for treating fatigue in people with advanced cancer: randomized, double-blind, multi-center, placebo-controlled trial. *J Clin Oncol* 2024;**42**: 2382–93. <https://doi.org/10.1200/JCO.23.02639>
2. Al Maqbali M, Al Sinani M, Al Naamani Z, Al Badi K, Tanash MI. Prevalence of fatigue in patients with cancer: a systematic review and meta-analysis. *J Pain Symptom Manage* 2021;**61**:167–89.e14.
3. Stone P, Candemi DE, Kandola K, Montero L, Smetham D, Suleman S, et al. Management of fatigue in patients with advanced cancer. *Curr Treat Options Oncol* 2023;**24**:93–107.
4. Stone P, Richardson A, Ream E, Smith AG, Kerr DJ, Kearney N. et al. Cancer-related fatigue: inevitable, unimportant and untreatable? Results of a multi-centre patient survey. *Cancer Fatigue Forum. Ann Oncol* 2000;**11**:971–6.
5. O'Higgins CM, Brady B, O'Connor B, Walsh D, Reilly RB, et al. The pathophysiology of cancer-related fatigue: current controversies. *Support Care Cancer* 2018;**26**:3353–64.
6. Minton O, Richardson A, Sharpe M, Hotopf M, Stone P. Drug therapy for the management of cancer-related fatigue. *Cochrane Database Sys Rev* 2010;**2010**:CD006704.
7. Roila F, Fatigoni S. Fatigue. In Bosnjak S, Bozovic-Spasojevic I, Mountzios G, Wood J, editors. *ESMO Handbook of Supportive and Palliative Care*. Lugano, Switzerland: ESMO Press; 2022. pp. 175–81.
8. Toohey K, Chapman M, Rushby AM, Urban K, Ingham G, Singh B. The effects of physical exercise in the palliative care phase for people with advanced cancer: a systematic review with meta-analysis. *J Cancer Surviv* 2023;**17**:399–415.
9. Wang P, Wang D, Meng A, Zhi X, Zhu P, Lu L, et al. Effects of walking on fatigue in cancer patients: a systematic review and meta-analysis. *Cancer Nurs* 2022;**45**:E270–8.
10. Corbett TK, Groarke A, Devane D, Carr E, Walsh JC, McGuire BE, et al. The effectiveness of psychological interventions for fatigue in cancer survivors: systematic review of randomised controlled trials. *Syst Rev* 2019;**8**:324.
11. Poort H, Peters M, Bleijenberg G, Gielissen MF, Goedendorp MM, Jacobsen P, et al. Psychosocial interventions for fatigue during cancer treatment with palliative intent. *Cochrane Database Syst Rev* 2017;**7**:CD012030.

12. Kimko H, Cross T, Abernethy D. Pharmacokinetics and clinical effectiveness of methylphenidate. *Clin Pharmacokinet* 1999;**37**:457–70.
13. Dopheide J, Pliszka S. Attention-deficit-hyperactivity disorder: an update. *Pharmacotherapy: J Human Pharmacol Drug Therapy* 2009;**29**:656–79.
14. Belloni S, Arrigoni C, de Sanctis R, Arcidiacono MA, Dellafiore F, Caruso R. A systematic review of systematic reviews and pooled meta-analysis on pharmacological interventions to improve cancer-related fatigue. *Crit Rev Oncol Hematol* 2021;**166**:103373.
15. Mochamat MM, Cuhls H, Peuckmann-Post V, Minton O, Stone P, Radbruch L. Pharmacological treatments for fatigue associated with palliative care. *Cochrane Database Sys Rev* 2015. <https://doi.org/10.1002/14651858.CD006788.pub3>
16. Lower EE, Fleishman S, Cooper A, Zeldis J, Faleck H, Yu Z, Manning D. Efficacy of dexamethylphenidate for the treatment of fatigue after cancer chemotherapy: a randomized clinical trial. *J Pain Symptom Manage* 2009;**38**:650–62.
17. Richard PO, Fleshner NE, Bhatt JR, Hersey KM, Chahin R, Alibhai SMH, et al. Phase II, randomised, double-blind, placebo-controlled trial of methylphenidate for reduction of fatigue levels in patients with prostate cancer receiving LHRH-agonist therapy. *BJU Int* 2015;**116**:744–52.
18. Pedersen L, Lund L, Petersen MA, Sjogren P, Groenvold M. Methylphenidate as needed for fatigue in patients with advanced cancer. A prospective, double-blind, and placebo-controlled study. *J Pain Symptom Manage* 2020;**60**:992–1002.
19. Bruera E, Valero V, Driver L, Shen L, Willey J, Zhang T, et al. Patient-controlled methylphenidate for cancer fatigue: a double-blind, randomized, placebo-controlled trial. *J Clin Oncol* 2006;**24**:2073–8.
20. Bruera E, Yennurajalingam S, Palmer JL, Perez-Cruz PE, Frisbee-Hume S, Allo JA, et al. Methylphenidate and/or a nursing telephone intervention for fatigue in patients with advanced cancer: a randomized, placebo-controlled, phase II trial. *J Clin Oncol* 2013;**31**:2421–7.
21. Moraska AR, Sood A, Dakhil SR, Sloan JA, Barton D, Atherton PJ, et al. Phase III, randomized, double-blind, placebo-controlled study of long-acting methylphenidate for cancer-related fatigue: North Central Cancer Treatment Group NCCTG-N05C7 trial. *J Clin Oncol* 2010;**28**:3673–9.
22. Mar Fan HG, Clemons M, Xu W, Chemerynsky I, Breunis H, Braganza S, et al. A randomised, placebo-controlled, double-blind trial of the effects of d-methylphenidate on fatigue and cognitive dysfunction in women undergoing adjuvant chemotherapy for breast cancer. *Support Care Cancer* 2008;**16**:577–83.
23. Butler JM Jr, Case LD, Atkins J, Frizzell B, Sanders G, Griffin P, et al. A phase III, double-blind, placebo-controlled prospective randomized clinical trial of d-threo-methylphenidate HCl in brain tumor patients receiving radiation therapy. *Int J Radiat Oncol Biol Phys* 2007;**69**:1496–501.
24. Centeno C, Roji R, Portela MA, De Santiago A, Cuervo MA, Ramos D, et al. Improved cancer-related fatigue in a randomised clinical trial: methylphenidate no better than placebo. *BMJ Support Palliat Care* 2022;**12**:226–34.
25. Roth AJ, Nelson C, Rosenfeld B, Scher H, Slovin S, Morris M, et al. Methylphenidate for fatigue in ambulatory men with prostate cancer. *Cancer* 2010;**116**:5102–10.
26. Yellen S, Cella D, Webster K, Blendowski C, Kaplan E. Measuring fatigue and other anemia-related symptoms with the functional assessment of cancer therapy (FACT) measurement system. *J Pain Symptom Manage* 1997;**13**:63–74.
27. Groenvold M, Petersen MA, Aaronson NK, Arraras JI, Blazeby JM, Bottomley A, et al. EORTC QLQ-C15-PAL: the new standard in the assessment of health-related quality of life in advanced cancer? *Palliat Med* 2006;**20**:59–61.
28. EuroQol-Group. EuroQol-a new facility for the measurement of health-related quality of life. *Health Policy* 1990;**16**:199–208.
29. Zigmond AS, Snaith RP. The hospital anxiety and depression scale. *Acta Psychiatr Scand* 1983;**67**:361–70.
30. Jaeschke R, Guyatt GH, Keller J, Singer J. Interpreting changes in quality-of-life score in N of 1 randomized trials. *Control Clin Trials* 1991;**12**:226S–33S.
31. Reddy S, Bruera E, Pace E, Zhang K, Reyes-Gibby CC, Zhang K, et al. Clinically important improvement in the intensity of fatigue in patients with advanced cancer. *J Palliat Med* 2007;**10**:1068–75.
32. Gong S, Sheng P, Jin H, He H, Qi E, Chen W, et al. Effect of methylphenidate in patients with cancer-related fatigue: a systematic review and meta-analysis. *PLOS ONE* 2014;**9**:e84391.
33. Minton O, Richardson A, Sharpe M, Hotopf M, Stone PC. Psychostimulants for the management of cancer-related fatigue: a systematic review and meta-analysis. *J Pain Symptom Manage* 2011;**41**:761–7.
34. Roji R, Stone P, Ricciardi F, Candy B. Placebo response in trials of drug treatments for cancer-related fatigue: a systematic review, meta-analysis and meta-regression. *BMJ Support Palliat Care* 2020;**10**:385–94.

35. Patrick DL, Gagnon DD, Zagari MJ, Mathijs R, Sweetenham J, Sweetenham J, *et al.* Epoetin Alfa Study G. Assessing the clinical significance of health-related quality of life (HrQOL) improvements in anaemic cancer patients receiving epoetin alfa. *Eur J Cancer* 2003;**39**:335–45.
36. Littlewood TJ, Bajetta E, Nortier JW, Vercammen E, Rapoport B; for the Epoetin Alfa Study Group. Effects of epoetin alfa on hematologic parameters and quality of life in cancer patients receiving non-platinum chemotherapy: results of a randomized, double-blind, placebo-controlled trial. *J Clin Oncol* 2001;**19**:2865–74.
37. Cella D, Eton DT, Lai JS, Peterman AH, Merkel DE. Combining anchor and distribution-based methods to derive minimal clinically important differences on the Functional Assessment of Cancer Therapy (FACT) anemia and fatigue scales. *J Pain Symptom Manage* 2002;**24**:547–61.
38. Hui D, Arthur J, Dalal S, Bruera E. Quality of the supportive and palliative oncology literature: a focused analysis on randomized controlled trials. *Support Care Cancer* 2012;**20**:1779–85.
39. Chen EK, Riffin C, Reid MC, Adelman R, Warmington M, Mehta SS, *et al.* Why is high-quality research on palliative care so hard to do? Barriers to improved research from a survey of palliative care researchers. *J Palliat Med* 2014;**17**:782–7.
40. Clark J, Gardiner C, Barnes A. International palliative care research in the context of global development: a systematic mapping review. *BMJ Support Palliat Care* 2018;**8**:7–18.
41. Cancer Research UK. *Cancer Mortality Statistics*. 2023. URL: www.cancerresearchuk.org/cancer-info/cancer-stats/mortality/ (accessed 16 February 2024).
42. Wilcock A, Howard P, Charlesworth S, editors. *Palliative Care Formulary*. 8th edn. London, UK: Royal Pharmaceutical Press; 2022. p. 976.
43. NCCN. *NCCN Clinical Practice Guidelines in Oncology: Cancer Related Fatigue*. 2023. URL: www.nccn.org/guidelines/category_3 (accessed 16 February 2024).
44. Fabi A, Bhargava R, Fatigoni S, Guglielmo M, Horneber M, Roila F, *et al.*; ESMO Guidelines Committee. Electronic address: clinicalguidelines@esmo.org. Cancer-related fatigue: ESMO clinical practice guidelines for diagnosis and treatment. *Ann Oncol* 2020;**31**:713–23.
45. Bower JE, Bak K, Berger A, Breitbart W, Escalante CP, Ganz PA, *et al.*; American Society of Clinical Oncology. Screening, assessment, and management of fatigue in adult survivors of cancer: an American Society of Clinical oncology clinical practice guideline adaptation. *J Clin Oncol* 2014;**32**:1840–50.
46. Chow R, Bruera E, Sanatani M, Chiu L, Prsic E, Boldt G, Lock M. Cancer-related fatigue-pharmacological interventions: systematic review and network meta-analysis. *Support Palliat Care* 2021;**13**:274–80.
47. Yennurajalingam S, Basen-Engquist K, Reuben JM, Fellman BM, Shete S, Maddi R, *et al.* Anamorelin combined with physical activity, and nutritional counseling for cancer-related fatigue: a preliminary study. *Support Care Cancer* 2022;**30**:497–509.
48. Luo WT, Huang TW. Effects of ginseng on cancer-related fatigue: a systematic review and meta-analysis of randomized controlled trials. *Cancer Nurs* 2022;**46**:120–7.
49. Tomlinson D, Robinson PD, Oberoi S, Cataudella D, Culos-Reed N, Davis H, *et al.* Pharmacologic interventions for fatigue in cancer and transplantation: a meta-analysis. *Curr Oncol* 2018;**25**:e152–67.

Appendix 1 Summary of major changes to the protocol

This document summarises the changes to the protocol that occurred between the first participant being enrolled (29 June 2018) and the conclusion of the trial. When the trial opened to recruitment, the protocol was version 7.0 (19 March 2018).

TABLE 4 Major changes to the protocol

Change made	Rationale	Protocol version which introduced change
<i>Changes to inclusion criteria</i>		
Prognosis of 2–12 months removed as an inclusion criterion	Prognosis is difficult to predict, and this requirement was impeding identification of suitable patients	Version 8.0 (28 October 2018)
Requirement to be under care of specialist palliative care team changed to requirement to be receiving generalist or specialist palliative care	Not all suitable palliative care patients were under the care of specialist palliative care services at the time of identification	Version 8.0 (28 October 2018)

TABLE 4 Major changes to the protocol (continued)

Change made	Rationale	Protocol version which introduced change
Changes to exclusion criteria		
Cardiovascular exclusions modified so that it was only <i>uncontrolled</i> heart failure, <i>uncontrolled</i> angina or MI in the <i>last 1 year</i> that were regarded as exclusions	Original criteria relaxed following risk assessment and in light of slow recruitment	Version 8.0 (28 October 2018)
Cerebrovascular exclusions modified so that it was only stroke in the <i>last 1 year</i> that was regarded as an exclusion	Original criterion relaxed following risk assessment and in light of slow recruitment	Version 8.0 (28 October 2018)
Alcohol- or drug-dependency exclusion criterion was modified so that it was only dependency within <i>last 1 year</i> that was regarded as an exclusion	Original criterion relaxed following risk assessment and in light of slow recruitment	Version 8.0 (28 October 2018)
eGFR exclusion was reduced from < 60 ml/hour to < 45 ml/hour	Original criterion relaxed following risk assessment and in light of slow recruitment	Version 8.0 (28 October 2018)
Alkaline phosphatase (ALP) levels no longer regarded as an exclusion	Isolated raised ALP levels not indicative of hepatic dysfunction. Original criterion relaxed following risk assessment and in light of slow recruitment	Version 8.0 (28 October 2018)
Aspartate transferase (AST) levels no longer regarded as an exclusion	Many participating sites did not routinely analyse AST levels for liver function. ALT and bilirubin remained as exclusion criteria	Version 12.0 (6 July 2020)
Exclusion of inpatient hospital or hospice patients was removed	Some inpatients were otherwise suitable for the trial, and the exclusion criterion was affecting recruitment	Version 8.0 (28 October 2018)
Exclusion of patients who are currently in another CTIMP expanded to include patients who have been on a CTIMP <i>within last 4 weeks</i>	Exclusion criterion clarified in response to query from sites	Version 9.0 (20 May 2019)
Changes to trial procedures		
Window for dose titration increased from ± 3 days to ± 4 days	To allow more flexibility for dose titration particularly around weekends and public holidays	Version 9.0 (20 May 2019)
Collection of cancer diagnosis and ECOG performance status from participants at screening/baseline	Recognised to be an omission from the original protocol	Version 10.0 (22 August 2019)
Collection of baseline AE data	It was recognised that it was useful for PIs, when titrating the dose of MPH at subsequent weeks, to have information about baseline frequency and severity of common AEs	Version 10.0 (22 August 2019)
Changes to secondary outcomes		
References to carer satisfaction as an outcome were removed from the protocol	Inclusion of carer satisfaction in the protocol was an error; no data were collected on this outcome	Version 14.0 (9 January 2023)
Anxiety and depression were specified as secondary outcomes	Data on anxiety and depression had not previously been explicitly specified as secondary outcomes	Version 14.0 (9 January 2023)
Changes to sample size		
Sample size for randomised participants changed from 230 to 215–230	Sample size was based on the estimated number of evaluable participants. Due to below expected attrition, it was determined that as few as 215 randomised participants would still result in 172 evaluable participants with no loss of power	Version 12.0 (6 July 2020)

continued

TABLE 4 Major changes to the protocol (continued)

Change made	Rationale	Protocol version which introduced change
Sample size reduced from 215 to 230 randomised participants to 162–230 randomised participants. Estimated number of evaluable participants changed from 172 to 130–172	In light of below expected recruitment rates, funder agreed to extend trial to achieve at least 130 evaluable participants (estimated to require at least 162 randomised participants)	Version 14.0 (9 January 2023)
Changes made in response to COVID pandemic		
Emergency action to stop new recruitment, taper the dose of MPH for patients already on trial and then withdrawal of medication. Enrolled participants remained on follow-up but did not take IMP or placebo	To minimise any additional potential burden to the NHS that may have arisen as a result of avoidable visits to hospital occasioned by potential adverse effects from the IMP	Version 11.0 (17 March 2020)
Telephone assessments permitted to replace face-to-face visits at weeks 3, 6 and 10	During the COVID pandemic, face-to-face hospital assessments were severely restricted	Version 12.0 (6 July 2020)
Home delivery of IMP permitted	During the COVID pandemic, it was necessary to minimise unnecessary travel and hospital visits	Version 12.0 (6 July 2020)
Need for separate face-to-face screening visit (with written informed consent) was removed. Consent for screening tests (blood tests, BP and pulse) could now be verbal rather than written	During the COVID pandemic, it was necessary to minimise unnecessary travel and hospital visits	Version 12.0 (6 July 2020)
Screening and enrolment visits could be merged	During the COVID pandemic, it was necessary to minimise unnecessary travel and hospital visits	Version 12.0 (6 July 2020)

Appendix 2 Recruitment sites and principal investigators

TABLE 5 Recruitment sites and PIs

Site name	PI	Total number randomised
University Hospitals Sussex NHS Foundation Trust	Ollie Minton	36
University College London Hospitals	Paddy Stone	21
John Eastwood Hospice, Nottinghamshire	David Miodrag	18
Sue Ryder Hospice, Gloucestershire	Paul Perkins	13
Royal Marsden Hospital, London and Surrey	Angela Halley	13
University Hospital Southampton	Mark Banting	11
Pilgrims Hospices, Kent	Soumen Saha	10
Ashgate Hospice, Chesterfield	Sarah Parnacott	7
King's College London	Sabrina Bajwah	7
Imperial College Healthcare NHS Trust, London	Sarah Frearson	6
Chesterfield Royal Hospital	David Brooks	6
Weston Park Hospital, Sheffield	Catriona Mayland	4
Royal Derby Hospital	Maelie Swanick	3

TABLE 5 Recruitment sites and PIs (continued)

Site name	PI	Total number randomised
St Gemma's Hospice, Leeds	Michael Bennett	3
Sussex Community Palliative Care Team	Carla Bruni	2
Oxford University Hospitals	Matthew Carey	1
Buckinghamshire Healthcare NHS Trust	Faeqa Hami	1
The Christie NHS Foundation Trust, Manchester	Richard Berman	0
Royal Free	Philip Lodge	0

Appendix 3 Outcome data for each week of the trial

TABLE 6 Week 1 data by randomised group

Characteristic	Placebo		MPH	
	n/N or mean	% or (SD)	n/N or mean	% or (SD)
FACIT-F score	(n = 76) 28	(10)	(n = 80) 27	(10)
Stopped taking trial medication	2/76	3	2/81	2
Participant considers trial medication to be effective	10/76	13	13/81	16
GBS – stayed the same or got worse	56/76	74	53/81	65

TABLE 7 Week 2 data by randomised group

Characteristic	Placebo		MPH	
	n/N or mean	% or (SD)	n/N or mean	% or (SD)
FACIT-F score	(n = 74) 28	(12)	(n = 77) 30	(11)
Stopped taking trial medication	8/75	11	3/77	4
Participant considers trial medication to be effective	15/75	20	21/77	27
GBS – stayed the same or got worse	40/75	53	36/77	47

TABLE 8 Week 3 data by randomised group

Characteristic	Placebo		MPH	
	n/N or mean	% or (SD)	n/N or mean	% or (SD)
FACIT-F score	(n = 71) 28	(12)	(n = 76) 30	(11)
HADS depression score median (IQR)	(n = 71) 5	(4–8)	(n = 76) 5	(4–8)
HADS anxiety score median (IQR)	(n = 71) 4	(1–7)	(n = 76) 4	(2–6)
HADS total median (IQR)	(n = 71) 10	(5–16)	(n = 76) 9	(6–15)

continued

TABLE 8 Week 3 data by randomised group (continued)

Characteristic	Placebo		MPH	
	n/N or mean	% or (SD)	n/N or mean	% or (SD)
EORTC QLQ-C15-PAL				
Pain	(n = 71) 48	(17)	(n = 76) 47	(18)
Physical functioning	(n = 71) 44	(17)	(n = 76) 45	(17)
Emotional functioning	(n = 71) 38	(17)	(n = 76) 40	(16)
Fatigue	(n = 71) 62	(20)	(n = 76) 58	(19)
QoL	(n = 71) 28	(13)	(n = 76) 28	(12)
Nausea	(n = 71) 38	(20)	(n = 76) 43	(22)
Loss of appetite	(n = 71) 46	(25)	(n = 76) 45	(24)
Shortness of breath	(n = 71) 49	(24)	(n = 76) 50	(23)
Constipation	(n = 71) 37	(21)	(n = 76) 42	(22)
Sleep	(n = 71) 50	(26)	(n = 76) 45	(23)
EQ-5D-5L utility	(n = 71) 0.68	(0.20)	(n = 76) 0.69	(0.21)
SBP	(n = 71) 124	(17)	(n = 75) 129	(15)
DBP	(n = 71) 76	(12)	(n = 75) 78	(12)
Hypertension	2/71	3	0/75	0
Pulse rate	(n = 70) 83	(13)	(n = 75) 84	(13)
Pulse rhythm				
Regular	65/70	93	73/74	99
Irregular	2/70	3	1/74	1
Other	3/70	4	0/74	0
Stopped taking trial medication	10/71	14	8/76	11
Participant considers trial medication to be effective	21/71	30	24/76	32
GBS – stayed the same or got worse	43/71	61	42/76	55
IQR, interquartile range.				

TABLE 9 Week 4 data by randomised group

Characteristic	Placebo		MPH	
	n/N or mean	% or (SD)	n/N or mean	% or (SD)
FACIT-F score	(n = 72) 30	(12)	(n = 75) 32	(12)
Stopped taking trial medication	12/72	17	7/75	9
Participant considers trial medication to be effective – stayed the same or got worse	22/72	31	26/75	35
GBS – stayed the same or got worse	43/72	60	37/75	49

TABLE 10 Week 5 data by randomised group

Characteristic	Placebo		MPH	
	n/N or mean	% or (SD)	n/N or mean	% or (SD)
FACIT-F score	(n = 67) 31	(12)	(n = 73) 33	(10)
Stopped taking trial medication	14/67	21	6/73	8
Participant considers trial medication to be effective	21/67	31	25/73	34
GBS – stayed the same or got worse	33/67	49	43/73	59

TABLE 11 Week 6 data by randomised group

Characteristic	Placebo		MPH	
	n/N or mean	% or (SD)	n/N or mean	% or (SD)
FACIT-F score 6 weeks only	(n = 67) 31	(12)	(n = 72) 33	(11)
FACIT-F score primary outcome	(n = 72) 31	(12)	(n = 75) 32	(11)
HADS depression score median (IQR)	(n = 66) 5	(3–9)	(n = 72) 4	(2–8)
HADS anxiety score median (IQR)	(n = 66) 4	(2–6)	(n = 72) 4	(2–6)
HADS total median (IQR)	(n = 66) 10	(5–15)	(n = 72) 8	(4–15)
EORTC QLQ-C15-PAL				
Pain	(n = 66) 45	(18)	(n = 72) 46	(18)
Physical functioning	(n = 66) 44	(17)	(n = 72) 41	(16)
Emotional functioning	(n = 66) 35	(15)	(n = 72) 38	17
Fatigue	(n = 66) 55	(19)	(n = 72) 54	(17)
QoL	(n = 66) 28	(14)	(n = 72) 26	(11)
Nausea	(n = 66) 35	(19)	(n = 72) 41	(19)
Loss of appetite	(n = 66) 41	(23)	(n = 72) 47	(26)
Shortness of breath	(n = 66) 51	(26)	(n = 72) 45	(23)
Constipation	(n = 66) 36	(19)	(n = 72) 43	(22)
Sleep	(n = 66) 47	(25)	(n = 72) 44	(24)
EQ-5D-5L utility	(n = 66) 0.70	(0.22)	(n = 72) 0.71	(0.23)
SBP	(n = 63) 127	(16)	(n = 67) 128	(20)
DBP	(n = 63) 77	(9)	(n = 67) 78	(12)
Hypertension	2/63	3	2/67	3
Pulse rate	(n = 60) 85	(14)	(n = 67) 82	(12)
Pulse rhythm				
Regular	55/60	92	63/66	95
Irregular	1/60	2	2/66	3
Other	4/60	7	1/66	2

continued

TABLE 11 Week 6 data by randomised group (continued)

Characteristic	Placebo		MPH	
	n/N or mean	% or (SD)	n/N or mean	% or (SD)
Stopped taking trial medication	14/67	21	14/72	19
Participant considers trial medication to be effective	23/67	34	27/72	38
GBS – stayed the same or got worse	38/67	57	45/72	63
New medication				
Other analgesia	4/77	5	7/82	9
Strong opioids	9/76	12	3/82	4
Benzodiazepines	2/76	3	1/81	1
Antidepressants	2/77	3	4/81	5
Steroids	9/76	12	5/82	6
New medication or increased dose of existing medication				
Other analgesia	4/77	5	7/82	9
Strong opioids	12/76	16	7/82	9
Benzodiazepines	2/76	3	1/81	1
Antidepressants	2/77	3	4/81	5
Steroids	9/76	12	5/82	6

IQR, interquartile range.

TABLE 12 Week 7 data by randomised group

Characteristic	Placebo		MPH	
	n/N or mean	% or (SD)	n/N or mean	% or (SD)
FACIT-F score	(n = 64) 31	(13)	(n = 70) 33	(11)
Stopped taking trial medication	17/65	26	11/70	16
Participant considers trial medication to be effective	24/65	37	26/70	37
GBS – stayed the same or got worse	40/65	62	44/70	63

TABLE 13 Week 8 data by randomised group

Characteristic	Placebo		MPH	
	n/N or mean	% or (SD)	n/N or mean	% or (SD)
FACIT-F score	(n = 64) 31	(13)	(n = 69) 33	(11)
Stopped taking trial medication	15/64	23	14/70	20
Participant considers trial medication to be effective	28/64	44	29/70	41
GBS – stayed the same or got worse	41/64	64	49/70	70

TABLE 14 Week 9 data by randomised group

Characteristic	Placebo		MPH	
	n/N or mean	% or (SD)	n/N or mean	% or (SD)
FACIT-F score	(n = 62) 32	(12)	(n = 67) 33	(10)
Stopped taking trial medication	32/62	52	29/68	43
Participant considers trial medication to be effective	24/62	39	25/67	37
GBS – stayed the same or got worse	40/62	65	47/67	70

TABLE 15 Week 10 data by randomised group

Characteristic	Placebo		MPH	
	n/N or mean	% or (SD)	n/N or mean	% or (SD)
FACIT-F score	(n = 63) 31	(13)	(n = 69) 29	(12)
HADS depression score median (IQR)	(n = 61) 6	(2–8)	(n = 69) 6	(4–8)
HADS anxiety score median (IQR)	(n = 61) 3	(1–5)	(n = 69) 3	(1–7)
HADS total median (IQR)	(n = 61) 9	(4–13)	(n = 69) 9	(5–14)
EORTC QLQ-C15-PAL				
Pain	(n = 61) 46	(16)	(n = 69) 48	(19)
Physical functioning	(n = 61) 40	(13)	(n = 69) 41	(15)
Emotional functioning	(n = 61) 35	(17)	(n = 69) 40	(18)
Fatigue	(n = 61) 57	(21)	(n = 69) 61	(19)
QoL	(n = 61) 29	(12)	(n = 69) 29	(12)
Nausea	(n = 61) 35	(15)	(n = 69) 42	(23)
Loss of appetite	(n = 61) 42	(22)	(n = 69) 46	(22)
Shortness of breath	(n = 61) 51	(25)	(n = 69) 47	(24)
Constipation	(n = 61) 39	(23)	(n = 69) 41	(21)
Sleep	(n = 61) 46	(22)	(n = 69) 42	(22)
EQ-5D-5L utility	(n = 61) 0.71	(0.17)	(n = 69) 0.70	(0.21)
SBP	(n = 55) 124	(14)	(n = 63) 128	(17)
DBP	(n = 55) 75	(9)	(n = 62) 77	(11)
Hypertension	0/55	0	2/63	3
Pulse rate	(n = 53) 84	(13)	(n = 62) 82	(12)
Pulse rhythm				
Regular	52/54	96	57/61	93
Irregular	0/54	0	4/61	7
Other	2/54	4	0/61	0
Stopped taking trial medication	60/63	95	64/69	93
Participant considers trial medication to be effective	18/63	29	11/69	16
GBS – stayed the same or got worse	41/63	65	55/69	80

IQR, interquartile range.

This synopsis should be referenced as follows:

Stone P, Minton O, Richardson A, Buckle P, Enayat ZE, Marston L, Freemantle N. Methylphenidate versus placebo for fatigue in patients with advanced cancer: the MePFAC randomised controlled trial. *Health Technol Assess* 2025;29(36). <https://doi.org/10.3310/GJPS6321>

Appendix 4 Adverse events

TABLE 16 Number of participants experiencing any level of self-rated AE at any time over the 10 weeks by randomised group

AE	Placebo		MPH	
	n/N	%	n/N	%
Respiratory				
Cough	41/76	54	49/82	60
Sore throat	33/76	43	35/82	43
Other airways symptoms	37/76	49	44/82	54
GI				
Abdominal pain	45/76	59	47/82	57
Diarrhoea	41/76	54	40/82	49
Nausea	43/76	57	57/82	70
Vomiting	21/76	28	31/82	38
Dry mouth	53/76	70	60/82	73
Other GI	42/76	55	43/82	52
Mood or mental state				
Anxiety	42/76	55	50/82	61
Depression	29/76	38	42/82	51
Irritability	50/76	66	51/82	62
Aggression	16/76	21	11/82	13
Mood swings	30/76	39	34/82	41
Abnormal behaviour	5/76	7	6/82	7
Other mood or mental state	10/76	13	10/82	12
Skin or hair				
Hair loss	18/76	24	25/82	30
Itch	32/76	42	40/82	49
Skin rashes	22/76	29	27/82	33
Other skin or hair	16/76	21	11/82	13
Miscellaneous				
Loss of appetite	55/76	72	63/82	77
Lost weight	43/76	57	38/82	46
Heart racing	25/76	33	26/82	31
Abnormal heart rhythms	12/76	16	11/82	13
Headache	46/76	61	46/82	56
Felt dizzy	42/76	55	52/82	63
Felt drowsy	61/76	80	62/82	76
Difficulty sleeping	58/76	76	60/82	73

TABLE 16 Number of participants experiencing any level of self-rated AE at any time over the 10 weeks by randomised group (*continued*)

AE	Placebo		MPH	
	n/N	%	n/N	%
Abnormal muscle movements	37/76	49	36/82	44
Been abnormally active	10/76	13	8/82	10
Joint pain	52/76	68	53/82	65
Fever	14/76	18	19/82	23
Cold or flu-like symptoms	34/76	44	41/82	50

TABLE 17 Number of participants experiencing self-rated 'severe' AE any time over the 10 weeks by randomised group

AEs	Placebo		MPH	
	n/N	%	n/N	%
Respiratory				
Cough	8/76	11	5/82	6
Sore throat	7/76	9	1/82	1
Other respiratory	12/76	16	11/82	13
GI				
Abdominal pain	11/76	14	7/82	9
Diarrhoea	5/76	7	10/82	12
Nausea	5/76	7	7/82	9
Vomiting	2/76	3	1/82	1
Dry mouth	13/76	17	10/82	12
Other GI	12/76	16	8/82	10
Mood or mental state				
Anxiety	8/76	11	5/82	6
Depression	5/76	7	1/82	1
Irritability	6/76	8	3/82	4
Aggression	2/76	3	1/82	1
Mood swings	4/76	5	1/82	1
Abnormal behaviour	1/76	1	1/82	1
Other mood or mental state	2/76	3	1/82	1
Skin or hair				
Hair loss	2/76	3	2/82	2
Itch	2/76	3	2/82	2
Skin rashes	4/76	5	1/82	1
Other skin or hair	4/76	5	2/82	2

continued

TABLE 17 Number of participants experiencing self-rated 'severe' AE any time over the 10 weeks by randomised group (*continued*)

AEs	Placebo		MPH	
	n/N	%	n/N	%
Miscellaneous				
Loss of appetite	14/76	18	11/82	13
Lost weight	0/76	0	4/82	5
Heart racing	2/76	3	2/82	2
Abnormal heart rhythms	1/76	1	0/82	0
Headache	8/76	11	3/82	4
Felt dizzy	7/76	9	7/82	9
Felt drowsy	17/76	22	9/82	11
Difficulty sleeping	16/76	21	14/82	17
Abnormal muscle movements	3/76	4	2/82	2
Been abnormally active	1/76	1	1/82	1
Joint pain	12/76	16	7/82	9
Fever	2/76	3	3/82	4
Cold or flu-like symptoms	4/76	5	3/82	4

TABLE 18 Any level ('mild', 'moderate' or 'severe') of self-reported AEs by randomised group in weeks 1 and 2

AE	Week 1				Week 2			
	Placebo		MPH		Placebo		MPH	
	n/N	%	n/N	%	n/N	%	n/N	%
Respiratory								
Cough	14/76	18	20/81	25	16/75	21	19/78	24
Sore throat	10/76	13	4/81	5	9/75	12	13/78	17
Other respiratory	10/76	13	18/81	22	15/75	20	17/78	22
GI								
Abdominal pain	17/76	22	27/81	33	22/75	29	22/77	29
Diarrhoea	12/76	16	14/81	17	18/75	24	9/77	12
Nausea	18/76	24	31/81	38	20/75	27	26/77	34
Vomiting	6/76	8	7/81	9	9/75	12	9/77	12
Dry mouth	35/76	46	37/81	46	36/75	48	41/77	53
Other GI	11/76	14	19/81	23	14/75	19	10/77	13
Mood or mental state								
Anxiety	21/76	28	17/81	21	21/75	28	16/77	21
Depression	11/76	14	17/81	21	13/75	17	12/77	16

TABLE 18 Any level ('mild', 'moderate' or 'severe') of self-reported AEs by randomised group in weeks 1 and 2 (continued)

AE	Week 1				Week 2			
	Placebo		MPH		Placebo		MPH	
	n/N	%	n/N	%	n/N	%	n/N	%
Irritability	25/76	33	27/81	33	20/75	27	23/77	30
Aggression	6/76	8	3/81	4	5/75	7	2/77	3
Mood swings	13/76	17	13/81	16	7/75	9	9/77	12
Abnormal behaviour	0/76	0	1/81	1	0/75	0	0/77	0
Other mood or mental state	1/76	1	1/81	1	1/75	1	3/77	4
Skin or hair								
Any skin or hair symptoms	19/76	25	30/81	37	16/75	21	26/77	34
Hair loss	7/76	9	13/81	16	4/75	5	10/77	13
Itch	8/76	11	19/81	23	12/75	16	14/77	18
Skin rashes	5/76	7	7/81	9	2/75	3	5/77	6
Other skin or hair	2/76	3	3/81	4	1/75	1	5/77	6
Miscellaneous								
Loss of appetite	26/76	34	27/81	33	32/75	43	31/78	40
Lost weight	11/76	14	12/81	15	14/75	19	7/77	9
Heart racing	6/76	8	5/81	6	9/75	12	7/77	9
Abnormal heart rhythms	1/76	1	5/81	6	3/75	4	3/77	4
Headache	20/76	26	23/81	28	23/75	31	26/77	34
Felt dizzy	24/76	32	17/81	21	25/75	33	25/77	32
Felt drowsy	37/76	49	34/81	42	34/75	45	31/77	40
Difficulty sleeping	34/76	45	34/81	42	32/75	43	34/77	44
Abnormal muscle movements	13/76	17	16/81	20	14/75	19	13/77	17
Been abnormally active	0/76	0	2/81	2	1/75	1	2/77	3
Joint pain	23/76	30	28/81	35	22/75	29	26/77	34
Fever	1/76	1	5/81	6	1/75	1	4/77	5
Cold or flu-like symptoms	10/76	13	13/81	16	6/75	8	16/77	21
Summary data								
Number of AE median (IQR)	5/76	(3–8)	6/81	(4–9)	6/75	(3–9)	7/78	(3–9)
Number of mild AE median (IQR)	3/76	(2–5)	4/81	(2–5)	3/75	(1–6)	4/78	(2–6)
Number of moderate AE median (IQR)	1/76	(0–3)	2/81	(0–3)	1/75	(0–3)	1/78	(0–3)
Number of severe AE median (IQR)	0/76	(0–1)	0/81	(0–1)	0/75	(0–1)	0/78	(0–1)
IQR, interquartile range.								

TABLE 19 Any level ('mild', 'moderate' or 'severe') of self-reported AEs by randomised group in weeks 3 and 4

AE	Week 3				Week 4			
	Placebo		MPH		Placebo		MPH	
	n/N	%	n/N	%	n/N	%	n/N	%
Respiratory								
Cough	12/71	17	20/77	26	16/72	22	20/75	27
Sore throat	9/71	13	8/77	10	8/72	11	11/75	15
Other respiratory	10/71	14	14/77	18	12/72	17	13/75	17
GI								
Abdominal pain	19/71	27	14/76	18	17/72	24	17/75	23
Diarrhoea	18/71	25	11/76	14	22/72	31	18/75	24
Nausea	18/71	25	28/76	37	18/72	25	33/75	44
Vomiting	4/71	6	10/76	13	5/72	7	6/75	8
Dry mouth	24/71	34	35/76	46	35/72	49	41/75	55
Other GI	10/71	14	12/76	16	8/72	11	11/75	15
Mood or mental state								
Anxiety	16/71	23	15/76	20	21/72	29	18/75	24
Depression	13/71	18	12/76	16	15/72	21	15/75	20
Irritability	21/71	30	18/76	24	23/72	32	23/75	31
Aggression	4/71	6	3/76	4	2/72	3	4/75	5
Mood swings	12/71	17	12/76	16	12/72	17	8/75	11
Abnormal behaviour	2/71	3	0/76	0	1/72	1	1/75	1
Other mood or mental state	2/71	3	1/76	1	3/72	4	1/75	1
Skin or hair								
Hair loss	2/71	3	9/76	12	8/72	11	5/75	7
Itch	9/71	13	13/76	17	14/72	19	15/75	20
Skin rashes	4/71	6	8/76	11	6/72	8	6/75	8
Other skin or hair	6/71	8	4/76	5	2/72	3	1/75	1
Miscellaneous								
Loss of appetite	23/71	32	29/76	38	25/72	35	32/75	43
Lost weight	11/71	15	14/75	19	12/72	17	13/75	17
Heart racing	8/71	11	9/76	12	5/72	7	5/75	7
Abnormal heart rhythms	4/71	6	3/76	4	3/72	4	1/75	1
Headache	18/71	25	20/76	26	18/72	25	21/75	28
Felt dizzy	21/71	30	25/76	33	21/72	29	25/75	33
Felt drowsy	35/71	49	35/76	46	37/72	51	34/75	45
Difficulty sleeping	30/71	42	30/76	39	35/72	49	24/75	32
Abnormal muscle movements	12/71	17	12/76	16	15/72	21	14/75	19

TABLE 19 Any level ('mild', 'moderate' or 'severe') of self-reported AEs by randomised group in weeks 3 and 4 (continued)

AE	Week 3				Week 4			
	Placebo		MPH		Placebo		MPH	
	n/N	%	n/N	%	n/N	%	n/N	%
Been abnormally active	4/71	6	2/76	3	2/72	3	2/75	3
Joint pain	22/71	31	23/76	30	29/72	40	26/75	35
Fever	3/71	4	4/76	5	3/72	4	5/75	7
Cold or flu-like symptoms	6/71	8	17/76	22	5/72	7	15/75	20
Summary data								
Number of AE median (IQR)	5/71	(3–9)	6/77	(3–10)	6/72	(4–8)	6/75	(4–10)
Number of mild AE median (IQR)	4/71	(2–5)	3/77	(2–5)	3/72	(2–6)	4/75	(3–7)
Number of moderate AE median (IQR)	1/71	(0–3)	1/77	(0–3)	1/72	(0–3)	1/75	(0–2)
Number of severe AE median (IQR)	0/71	(0–1)	0/77	(0–0)	0/72	(0–0)	0/75	(0–1)
IQR, interquartile range.								

TABLE 20 Any level ('mild', 'moderate' or 'severe') of self-reported AEs by randomised group in weeks 5 and 6

AE	Week 5				Week 6			
	Placebo		MPH		Placebo		MPH	
	n/N	%	n/N	%	n/N	%	n/N	%
Respiratory								
Cough	13/67	19	23/73	32	17/67	25	19/72	26
Sore throat	10/67	15	10/73	14	7/67	10	5/72	7
Other respiratory	16/67	24	10/73	14	14/67	21	9/72	13
GI								
Abdominal pain	17/67	25	15/73	21	11/67	16	21/72	29
Diarrhoea	12/67	18	13/73	18	14/67	21	9/72	13
Nausea	15/67	22	30/73	41	15/67	22	28/72	39
Vomiting	4/67	6	3/73	4	6/67	9	10/72	14
Dry mouth	30/67	45	37/73	51	29/67	43	32/72	44
Other GI	8/67	12	11/73	15	10/67	15	11/72	15
Mood or mental state								
Anxiety	19/67	28	17/73	23	15/67	22	20/72	28
Depression	7/67	10	16/73	22	8/67	12	19/72	26
Irritability	21/67	31	17/73	23	15/67	22	20/72	28
Aggression	4/67	6	1/73	1	3/67	4	3/72	4
Mood swings	10/67	15	7/73	10	8/67	12	10/72	14
Abnormal behaviour	0/67	0	0/73	0	1/67	1	3/72	4
Other mood or mental state	2/67	3	0/73	0	1/67	1	0/72	0

continued

TABLE 20 Any level ('mild', 'moderate' or 'severe') of self-reported AEs by randomised group in weeks 5 and 6 (*continued*)

AE	Week 5				Week 6			
	Placebo		MPH		Placebo		MPH	
	n/N	%	n/N	%	n/N	%	n/N	%
Skin or hair								
Hair loss	9/67	13	6/73	8	6/67	9	8/72	11
Itch	12/67	18	16/73	22	11/67	16	12/72	17
Skin rashes	3/67	4	6/73	8	8/67	12	9/72	13
Other skin or hair	3/67	4	0/73	0	6/67	9	1/72	1
Miscellaneous								
Loss of appetite	26/67	39	32/73	44	18/67	27	29/72	40
Lost weight	7/67	10	14/73	19	14/67	21	16/72	22
Heart racing	4/67	6	7/73	10	7/67	10	8/72	11
Abnormal heart rhythms	5/67	7	0/73	0	5/67	7	2/72	3
Headache	15/67	22	19/73	26	22/67	33	20/72	28
Felt dizzy	20/67	30	20/73	27	17/67	25	28/72	39
Felt drowsy	33/67	49	29/73	40	29/67	43	30/72	42
Difficulty sleeping	31/67	46	31/73	42	27/67	40	26/72	36
Abnormal muscle movements	15/67	22	11/73	15	16/67	24	20/72	28
Been abnormally active	3/67	4	0/73	0	2/67	3	1/72	1
Joint pain	27/67	40	26/73	36	27/67	40	21/72	29
Fever	2/67	3	2/73	3	3/67	4	3/72	4
Cold or flu-like symptoms	7/67	10	12/73	16	8/67	12	14/72	19
Summary data								
Number of AE median (IQR)	6/67	(4–8)	6/73	(3–8)	5/67	(3–9)	6/72	(3–9)
Number of mild AE median (IQR)	3/67	(2–5)	4/73	(2–6)	3/67	(2–6)	4/72	(2–6)
Number of moderate AE median (IQR)	1/67	(0–4)	1/73	(0–3)	1/67	(0–3)	1/72	(0–4)
Number of severe AE median (IQR)	0/67	(0–0)	0/73	(0–0)	0/67	(0–1)	0/72	(0–1)

IQR, interquartile range.

TABLE 21 Any level ('mild', 'moderate' or 'severe') of self-reported AEs by randomised group in weeks 7 and 8

AE	Week 7				Week 8			
	Placebo		MPH		Placebo		MPH	
	n/N	%	n/N	%	n/N	%	n/N	%
Respiratory								
Cough	17/64	27	17/70	24	15/64	23	21/69	30
Sore throat	8/64	13	9/70	13	7/64	11	8/69	12
Other airways symptoms	11/64	17	8/70	11	9/64	14	10/69	14

TABLE 21 Any level ('mild', 'moderate' or 'severe') of self-reported AEs by randomised group in weeks 7 and 8 (continued)

AE	Week 7				Week 8			
	Placebo		MPH		Placebo		MPH	
	n/N	%	n/N	%	n/N	%	n/N	%
GI								
Abdominal pain	9/64	14	16/70	23	17/64	27	13/69	19
Diarrhoea	16/64	25	15/70	21	12/64	19	7/69	10
Nausea	15/64	23	26/70	37	17/64	27	24/69	35
Vomiting	2/64	3	11/70	16	6/64	9	9/69	13
Dry mouth	31/64	48	35/70	50	28/64	44	35/69	51
Other GI	4/64	6	5/70	7	8/64	13	5/69	7
Mood or mental state								
Anxiety	15/64	23	20/70	29	16/64	25	18/69	26
Depression	9/64	14	15/70	21	11/64	17	11/69	16
Irritability	16/64	25	24/70	34	17/64	27	21/69	30
Aggression	1/64	2	3/70	4	1/64	2	3/69	4
Mood swings	4/64	6	11/70	16	8/64	13	8/69	12
Abnormal behaviour	1/64	2	1/70	1	0/64	0	0/69	0
Other mood or mental state	0/64	0	0/70	0	2/64	3	1/69	1
Skin or hair								
Hair loss	10/64	16	5/70	7	7/64	11	4/69	6
Itch	13/64	20	10/70	14	11/64	17	9/69	13
Skin rashes	4/64	6	10/70	14	5/64	8	7/69	10
Other skin or hair	2/64	3	0/70	0	2/64	3	0/64	0
Miscellaneous								
Loss of appetite	19/64	30	31/70	44	22/64	34	24/69	35
Lost weight	8/64	13	13/70	19	9/64	14	12/69	17
Heart racing	8/64	13	5/70	7	6/64	9	2/69	3
Abnormal heart rhythms	2/64	3	1/70	1	3/64	5	0/69	0
Headache	18/64	28	22/70	31	13/64	20	20/69	29
Felt dizzy	19/64	30	15/70	21	16/64	25	22/69	32
Felt drowsy	29/64	45	28/70	40	27/64	42	23/69	33
Difficulty sleeping	26/64	41	24/70	34	25/64	39	23/69	33
Abnormal muscle movements	10/64	16	12/70	17	14/64	22	13/69	19
Been abnormally active	2/64	3	2/70	3	2/64	3	1/69	1
Joint pain	24/64	38	26/70	37	23/64	36	24/69	35
Fever	3/64	5	1/70	1	0/64	0	4/69	6
Cold or flu-like symptoms	10/64	16	12/70	17	5/64	8	10/69	14

continued

TABLE 21 Any level ('mild', 'moderate' or 'severe') of self-reported AEs by randomised group in weeks 7 and 8 (continued)

AE	Week 7				Week 8			
	Placebo		MPH		Placebo		MPH	
	n/N	%	n/N	%	n/N	%	n/N	%
Summary data								
Number of AE median (IQR)	6/64	(3–8)	6/70	(4–9)	5/64	(3–8)	5/69	(2–9)
Number of mild AE median (IQR)	4/64	(2–6)	4/70	(3–6)	3/64	(2–5)	4/69	(2–6)
Number of moderate AE median (IQR)	1/64	(0–3)	1/70	(0–3)	1/64	(0–3)	0/69	(0–2)
Number of severe AE median (IQR)	0/64	(0–0)	0/70	(0–0)	0/64	(0–0)	0/69	(0–0)

IQR, interquartile range.

TABLE 22 Any level ('mild', 'moderate' or 'severe') of self-reported AEs by randomised group in weeks 9 and 10

AE	Week 9				Week 10			
	Placebo		MPH		Placebo		MPH	
	n/N	%	n/N	%	n/N	%	n/N	%
Respiratory								
Cough	14/62	23	14/67	21	11/63	17	16/69	23
Sore throat	4/62	6	6/67	9	4/63	6	8/69	12
Other respiratory	12/62	19	11/67	16	12/63	19	7/69	10
GI								
Abdominal pain	11/62	18	13/67	19	16/63	25	16/69	23
Diarrhoea	11/62	18	7/67	10	13/63	21	10/69	14
Nausea	16/62	26	16/67	24	15/63	24	16/69	23
Vomiting	7/62	11	3/67	4	7/63	11	6/69	9
Dry mouth	27/62	44	36/67	54	25/63	40	30/69	43
Other GI	7/62	11	9/67	13	12/63	19	8/69	12
Mood or mental state								
Anxiety	15/62	24	17/67	25	16/63	25	20/69	29
Depression	9/62	15	13/67	19	6/63	10	19/69	28
Irritability	13/62	21	19/67	28	15/63	24	19/69	28
Aggression	3/62	5	2/67	3	3/63	5	4/69	6
Mood swings	6/62	10	4/67	6	7/63	11	11/69	16
Abnormal behaviour	0/62	0	0/67	0	0/63	0	0/69	0
Other mood or mental state	0/62	0	1/67	1	2/63	3	4/69	6
Skin or hair								
Hair loss	8/62	13	7/67	10	6/63	10	9/69	13
Itch	9/62	15	10/67	15	9/63	14	8/69	12
Skin rashes	4/62	6	8/67	12	5/63	8	5/69	7
Other skin or hair	1/62	2	1/67	1	4/63	6	1/69	1

TABLE 22 Any level ('mild', 'moderate' or 'severe') of self-reported AEs by randomised group in weeks 9 and 10 (continued)

AE	Week 9				Week 10			
	Placebo		MPH		Placebo		MPH	
	n/N	%	n/N	%	n/N	%	n/N	%
Miscellaneous								
Loss of appetite	21/62	34	17/67	25	19/63	30	27/69	39
Lost weight	6/62	10	9/67	13	7/62	11	15/69	22
Heart racing	5/62	8	3/67	4	7/63	11	6/69	9
Abnormal heart rhythms	2/62	3	0/67	0	3/63	5	0/69	0
Headache	11/62	18	15/67	22	13/63	21	17/69	25
Felt dizzy	20/62	32	21/67	31	20/63	32	21/69	30
Felt drowsy	29/62	46	26/67	39	31/63	49	37/69	54
Difficulty sleeping	26/62	42	19/67	28	27/63	43	24/69	35
Abnormal muscle movements	9/62	15	13/67	19	13/63	21	14/69	20
Been abnormally active	0/62	0	0/67	0	1/63	2	1/69	1
Joint pain	24/62	39	23/66	35	22/63	35	28/69	41
Fever	2/62	3	2/68	3	2/63	3	3/69	4
Cold or flu-like symptoms	6/62	10	8/67	12	7/63	11	9/69	13
Summary data								
Number of AE median (IQR)	5/62	(3-8)	4/68	(2-8)	6/63	(2-8)	6/69	(3-9)
Number of mild AE median (IQR)	3/62	(2-5)	4/68	(2-6)	3/63	(1-5)	3/69	(2-6)
Number of moderate AE median (IQR)	1/62	(0-2)	0/68	(0-1)	1/63	(0-3)	1/69	(0-3)
Number of severe AE median (IQR)	0/62	(0-0)	0/68	(0-0)	0/63	(0-0)	0/69	(0-1)
IQR, interquartile range.								