

## **METHYLPHENIDATE VERSUS PLACEBO FOR FATIGUE IN ADVANCED CANCER (MePFAC) PROTOCOL**

Long title of the trial	Methylphenidate versus placebo for fatigue in advanced cancer
Short title of trial	MePFAC
Version and date of protocol	Version 4.0 21-Sep-2017
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Sponsor protocol number	15/0592
Funder (s)	NIHR HTA
EudraCT number	2017-001950-33
IRAS ID	215297
Active IMP(s)	methylphenidate
Phase of trial	III
Sites	Multiple sites
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## SIGNATURES

The undersigned confirm that the following protocol has been agreed and accepted and that the Chief Investigator agrees to conduct the trial in compliance with the approved protocol and will adhere to the principles outlined in the Medicines for Human Use (Clinical Trials) Regulations 2004 (SI 2004/1031), amended regulations (SI 2006/1928) and any subsequent amendments of the clinical trial regulations, GCP guidelines, Priment's SOPs, and other regulatory requirements as amended.

I agree to ensure that the confidential information contained in this document will not be used for any other purpose other than the evaluation or conduct of the clinical investigation without the prior written consent of Priment.


I also confirm that I will make the findings of the study publically available through publication or other dissemination tools without any unnecessary delay and that an honest accurate and transparent account of the study will be given; and that any discrepancies from the study as planned in this protocol will be explained.

**Chief Investigator:** Patrick Stone

**Sign:** 

**Date:** 21<sup>st</sup> September 2017

**Sponsor Representative:** Charlene Griffith

**Sign:** 

**Date:** 21<sup>st</sup> September 2017

For the purposes of this document, Priment is representing the Sponsor.

## VERSION HISTORY

Version number	Version date	Reason for Change
1.0	05-May-2017	Original protocol submitted to REC for approval
2.0	30-Jun-2017	<ol style="list-style-type: none"> <li>1. Section 5 (Trial flow chart) has been amended to more accurately reflect the content of protocol. The pre-screening visit includes recording of NRS. The screening visit includes recording of pulse. The baseline visit includes recording of HADS. Visit 3 includes recording of EQ5D-5L</li> <li>2. Section 11.2 (Consent for screening) has been amended to harmonise with other sections of the protocol which explain that a fresh blood specimen is only required as part of screening if no relevant blood test has been performed in the previous 14 days.</li> <li>3. Section 18.2 (Recording adverse events) and Section 18.3 (Assessment of adverse events) have both been amended to clarify that non-serious adverse events will be recorded weekly and assessed for severity, but that serious adverse events will additionally be assessed for causality and expectedness and will be reported to the sponsor within 24 hours.</li> </ol>
3.0	19-Jul-2017	Section 5 (Trial Flow Chart) has been corrected to remove the recording of HADS from the screening assessment.
4.0	21-Sept-2017	<ol style="list-style-type: none"> <li>1. Section 3 (Trial Personnel); details of IMP manufacturer have been entered</li> <li>2. Summary; has been amended to refer to 5 (rather than 4) pilot sites</li> <li>3. Section 8.1.1; a <math>\pm 2</math> week window for collection of the primary outcome has been introduced</li> <li>4. Section 8.2.1.5 (Satisfaction of patients and carers); the statement that "patient preference for continued treatment will be recorded" has been deleted as participants will remain blinded as to their treatment allocation.</li> <li>5. Section 8.3.2 (planned recruitment rate); Table has been amended to include five sites in the pilot phase and for first site to open in January 2018.</li> <li>6. Section 9.1.4 (Dose Titration); this section has been modified to include collection of data about concomitant medication.</li> <li>7. Section 9.4 (Tapering); the tapering schedule has been altered to allow longer period on lower doses prior to stopping.</li> <li>8. Section 11.5.1 (Patient identifiers and contact details); now includes mention that data on ethnicity will be collected from study participants.</li> <li>9. Section 11.8 (Treatment procedures); the flexibility around the weekly assessments has been increased from <math>\pm 3</math> to <math>\pm 4</math> days.</li> </ol>

		<p>10. Section 11.9 (Table of study assessments); The NRS is only being recorded at screening and baseline visits and the summary table has been corrected accordingly. Concomitant medication will occur weekly and the summary table has been corrected accordingly.</p> <p>11. Section 11.12.4 (Distinction between stopping study medication and withdrawal from the study); this is a new section which details what happens if participants stop taking the trial medication.</p> <p>12. Section 11.12.5 (Withdrawal due to inability to tolerate the lowest dose of study medication); this section has been altered in order to be consistent with section 11.12.4</p> <p>13. Section 11.12.6 (Withdrawal of individual participants due to adverse events); this section has been altered in order to be consistent with section 11.12.4</p> <p>14. Section 12.1 (Treatment of participants); The table showing the standard titration schedule has been amended to be consistent with Section 11.8</p> <p>15. Section 13.9 (Source of IMPs including placebo); this section has been updated to include the name of the manufacturer</p> <p>16. Section 14.1 (Confidentiality); this section has been simplified to remove specific details about the systems and databases to be used for electronic storage. The original plan to use the Data Safe Haven at UCL has been changed to now use an alternative system. This change is necessary to simplify the management of the trial, as it will be essential that research nurses have access to participant's contact details in a timely manner to enable the weekly follow up visits to be conducted in accordance to the trial protocol.</p> <p>17. Sections 14.3 (Trial database) and Section 14.4 (Data collection and handling) have been added to the protocol.</p> <p>18. Section 16 (Statistical considerations); variables has been changed to outcomes</p> <p>19. Section 16.1.2 (Primary outcome analysis); this section has been altered to allow more flexibility in the timing of the analysis of the primary outcome for participants where data at six weeks is missing.</p> <p>20. Section 16.1.3 (Secondary outcome analysis); variables has been changed to outcomes</p> <p>21. Section 17.1 (Trial Management Group); junior statistician has been changed to trial statistician</p>

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## 2 LIST OF ABBREVIATIONS

Term	Definition
ADHD	Attention Deficit Hyperactivity Disorder
AE	Adverse Event
ALP	Alkaline Phosphatase
ALT	Alanine aminotransferase
AST	Aspartate aminotransferase
AR	Adverse Reaction
CA	Competent Authority
CI	Chief Investigator
CRF	Case Report Form
CRO	Contract Research Organisation
CTA	Clinical Trial Authorisation
CTIMP	Clinical Trial of Investigational Medicinal Product
DSH	Data Safe Haven
DSMB	Data Safety and Monitoring Board
DSUR	Development Safety Update Report
EC	European Commission
eCRF	Electronic case report form
eGFR	Estimated glomerular filtration rate
EMA	European Medicines Agency
EORTC QLQ-C15-PAL	European Organisation for Research and Treatment of Cancer core Quality of Life Palliative Care questionnaire
EQ-5D-5L	EuroQol EQ-5D 5 level
EU	European Union
EUCTD	European Clinical Trials Directive
EudraCT	European Clinical Trials Database
EudraVIGILANCE	European database for Pharmacovigilance
FACIT-F	Functional Assessment of Chronic Illness Therapy
GAfREC	Governance Arrangements for NHS Research Ethics
GBS	Global Benefit Score
GCP	Good Clinical Practice
GGT	Gamma-glutamyltransferase
GMP	Good Manufacturing Practice
HRA	Health Research Authority
HTA	Health Technology Assessment

IB	Investigator Brochure
ICF	Informed Consent Form
IMP	Investigational Medicinal Product
IMPD	Investigational Medicinal Product Dossier
ISF	Investigator Site File
ISRCTN	International Standard Randomised Controlled Trials Number
JRO	Joint Research Office
MA	Marketing Authorisation
MePFAC	Methylphenidate versus Placebo for Fatigue in Advanced Cancer
MHRA	Medicines and Healthcare products Regulatory Agency
MPH	Methylphenidate
MS	Member State
Main REC	Main Research Ethics Committee
NHS IC	National Health Service Information Centre
NHS R&D	National Health Service Research & Development
NIHR	National Institute for Health Research
NIMP	Non Investigational Medicinal Product
pCRF	Paper case report form
PI	Principal Investigator
PIS	Participant Information Sheet
QA	Quality Assurance
QC	Quality Control
QP	Qualified Person for release of trial drug
RCT	Randomised Control Trial
REC	Research Ethics Committee
SAE	Serious Adverse Event
SAR	Serious Adverse Reaction
SDV	Source Document Verification
SOP	Standard Operating Procedure
SmPC	Summary of Product Characteristics
SSA	Site Specific Assessment
SUSAR	Suspected Unexpected Serious Adverse Reaction
TMG	Trial Management Group
TRG	Trial Review Group
TSC	Trial Steering Committee
UK	United Kingdom of Great Britain and Northern Ireland

### 3 TRIAL PERSONNEL

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## 4 SUMMARY

<b>Title:</b>	Methylphenidate versus placebo for fatigue in advanced cancer
<b>Short title:</b>	MePFAC
<b>Trial medication:</b>	Methylphenidate 5mgs tablets Matching Placebo tablets
<b>Phase of trial:</b>	III
<b>Objectives:</b>	To estimate clinical effectiveness of methylphenidate versus placebo for cancer-related fatigue in patients receiving specialist palliative care
<b>Type of trial:</b>	Prospective, randomised, double-blind, placebo-controlled trial with internal pilot in palliative care patients with advanced cancer
<b>Trial design and methods:</b>	<p>Primary outcome is fatigue at 6 weeks measured by the fatigue sub-scale of Functional Assessment of Chronic Illness Therapy (FACIT-F). Secondary outcomes (measured at 3 and 9 weeks) are other measures of quality of life (using European Organisation for Research and Treatment of Cancer core Quality of Life Palliative Care questionnaire [EORTC QLQ-C15-PAL] and the EuroQol EQ-5D 5 level [EQ-5D-5L]), adverse events, activities of daily living; appetite; satisfaction of patients and carers; survival and need for other medication.</p>

Potentially eligible patients will be identified and provided with study information and asked for consent for formal screening. At screening, if no recent blood results are available, a fresh specimen will be obtained (full blood count, liver and renal function) and blood pressure will be assessed. Patients who are confirmed as eligible will be invited for a baseline assessment, asked for consent to enrol in the study, and will be randomised. After randomisation, face-to-face assessments will occur at weeks 3, 6 and 9 and will include; completion of outcome measures and blood pressure. Patients will be contacted by telephone at least weekly so that study medication can be titrated according to response and adverse effects. The comparator group will receive individually titrated placebo tablets. Both groups will receive usual care.

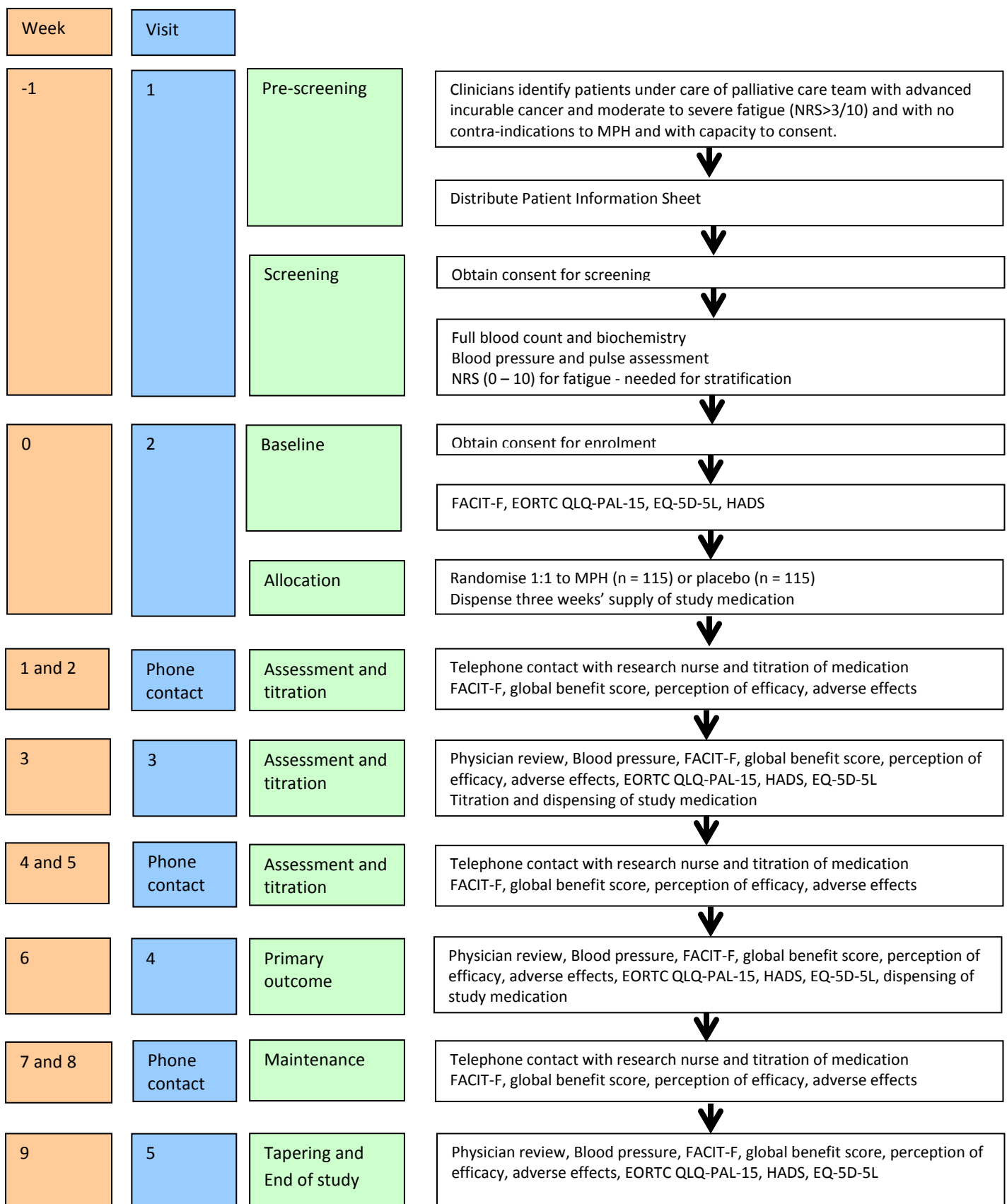
During the last week of the study, the dose of medication or placebo will be tapered, and will stop at the end of the ninth week. At the end of the study participants will be managed according to local clinical practice and circumstances.

**Pilot:**

Feasibility of recruitment strategy, randomisation and follow-up will be evaluated during a pilot phase at five centres during the first nine months of recruitment. During the pilot phase (months 10-18) recruitment should exceed 70% of rate expected once trial is fully established. If recruitment is less than 50% the study will be terminated. If recruitment is between 50 – 70% the HTA will be consulted about continuation.

<b>Trial duration per participant:</b>	9 weeks
<b>Estimated total trial duration:</b>	28 months
<b>Planned trial sites:</b>	10
<b>Total number of participants planned:</b>	230
<b>Main inclusion/exclusion criteria:</b>	<p>Patients with advanced cancer with cancer-related fatigue and receiving palliative care</p> <p><b><u>Inclusions:</u></b> 18+ years; advanced incurable cancer of all tumour types; moderate or severe fatigue on numerical rating scale (&gt;3/10); informed consent; prognosis 2-12 months; under the care of a specialist palliative care team</p> <p><b><u>Exclusions:</u></b> Known sensitivity or contraindication to methylphenidate; severe anaemia; decompensated liver failure; current or previous psycho-stimulant use in last month; currently an inpatient in a hospital or a hospice.</p>
<b>Statistical methodology and analysis:</b>	<p>With 230 randomised and 172 evaluable patients (25% attrition), this study has 90% power to detect a difference of 5-points on FACIT-F (effect size 0.5) between groups at 5% significance (two sided). Randomization will be computer generated and stratified by centre, by receipt of palliative cancer treatment, by baseline HADS depression score and by initial fatigue score &gt;7.</p>

## 5 TRIAL FLOW CHART



## 6 INTRODUCTION

### 6.1 BACKGROUND

Cancer-related fatigue is characterised by an overwhelming sense of tiredness or exhaustion which is unrelieved by rest and is associated with cancer or its treatment [1, 2]. It is a widespread problem in people with cancer at all stages of their illness, whether on or off treatment [3-6] and is particularly common in patients receiving palliative care with reports of up to 78% of such patients being affected [4, 7]. Cancer-related fatigue is considered by patients to affect their daily lives more than pain or nausea/vomiting [8]. In patients with advanced cancer, fatigue can be debilitating and have adverse consequences for quality of life [9].

It is estimated there are currently two million people in the UK who are living with cancer or who are cancer survivors [10]. There were 161,823 deaths from cancer in the UK in 2012 [11]. The vast majority of cancer patients experience fatigue during the course of their illness [3-5] and particularly in the palliative phase [7]. Fatigue remains under-recognised and under-treated [8, 12]. People with advanced cancer want to maintain their quality of life for as long as possible and fatigue is known to detract significantly from this [4, 7, 9, 13-15]. Persistent fatigue may also affect patients' ability to maintain independence and may increase the costs of care and the burden on informal carers. This research has been designed in response to an NIHR HTA commissioning brief; to determine the clinical effectiveness of Methylphenidate in the treatment of cancer-related fatigue in patients receiving palliative care.

### 6.2 PRECLINICAL DATA

Section 5.3 of the Summary of Product Characteristics [16] lists the pre-clinical safety data relating to methylphenidate.

In life-time rat and mouse carcinogenicity studies, increased numbers of malignant liver tumours were noted in male mice only. The significance of this finding to humans is unknown. Methylphenidate did not affect reproductive performance or fertility at low multiples of the clinical dose. Methylphenidate is not considered to be teratogenic in rats and rabbits. Foetal toxicity (i.e. total litter loss) and maternal toxicity was noted in rats at maternally toxic doses.

### 6.3 CLINICAL DATA

There have been several Cochrane reviews of treatments for cancer-related fatigue including reviews of exercise interventions [17], psycho-educational approaches [18] and pharmacological therapies [19]. The latter review found evidence in support of erythropoietin for fatigue in anaemic cancer patients and for psycho-stimulants (methylphenidate and dexamethylphenidate) in varied cancer populations.

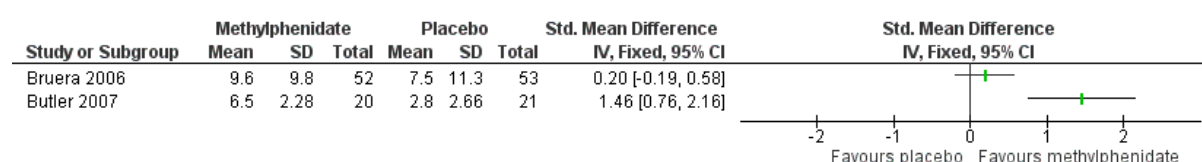
Methylphenidate is a central nervous system stimulant (psycho-stimulant). It is an inhibitor of catecholamine re-uptake and increases central dopamine and noradrenaline levels [20]. It is a short-acting drug with a half-life of one to four hours. It has been widely used for decades

as a treatment for Attention Deficit Hyperactivity Disorder (ADHD) in children. In this population (and for this indication) it has been shown to be both safe and effective [21]. It has also been used in patients with cancer as a treatment for both depression and fatigue [22-24], but the evidence for its effectiveness for these indications in cancer patients is equivocal.

In preparation for this research project we have updated our previously published [19, 25, 26] systematic reviews on the pharmacological treatments for cancer related fatigue. We identified six clinical trials of methylphenidate undertaken in patients with cancer (n = 666). Our meta-analysis indicated an overall statistically significant effect [SMD = -0.20; 95% CI -0.38 to -0.01;  $z = 2.06$ ;  $p = 0.04$ ] providing some evidence in support of this intervention in heterogeneous cancer populations (mixed stages and treatment statuses). Most recently, members of our research group contributed to a Cochrane review of pharmacological treatments for fatigue in palliative care patients (including both cancer and non-cancer patients) [27]. Meta-analysis suggested an estimated significant effect for methylphenidate in cancer-related fatigue in palliative care patients [SMD = 0.49, 95% CI 0.15 to 0.83].

In our systematic review of psychostimulants for cancer-related fatigue we reported that, these drugs do not appear to cause major problems (adverse effects) in this group of patients [26]. This finding is supported by the results of a systematic review of safety concerns regarding the longer term use of methylphenidate [28]. The author of this review identified 26 trials and concluded that expected non serious adverse effects were minimal in short term use (up to 6-8 weeks of treatment). In the short term, methylphenidate was well tolerated and no serious side effects were observed. There was little information on long term safety. Methylphenidate was associated with a modest rise in blood pressure and heart rate. No studies were found that addressed the question of whether therapeutic use of methylphenidate ever leads to dependence. The danger for abuse is highest when taken for non-therapeutic reasons such as use as a performance enhancer [29]. It is therefore unlikely that addiction will be a significant risk in palliative care patients with advanced progressive cancer.

Figure 1 Forest plot of comparison: Methylphenidate in palliative cancer, outcome: Methylphenidate



## 6.4 RATIONALE AND RISKS/BENEFITS

This research has been commissioned for the NHS by the NIHR prioritisation group. Overall, the evidence for methylphenidate as a treatment for cancer-related fatigue, although suggestive of effectiveness, is inconclusive. Moreover, in the context of an intervention that



is unlikely to have any survival benefits, the balance between efficacy and adverse effects is crucial. There is therefore a strong justification for undertaking a suitably powered, double blind, randomised controlled trial. The problem being addressed by our research proposal is to address the research question posed in the NIHR HTA commissioning brief, "What is the clinical effectiveness of methylphenidate (MPH) in the treatment of cancer-related fatigue in patients receiving palliative care?"

There is no "standard" care pathway for the management of cancer-related fatigue. Fatigue is not routinely assessed or monitored by healthcare staff in the UK. When fatigue is identified by clinicians, it is frequently regarded as being inevitable and untreatable [8]. The US National Comprehensive Cancer Network publishes clinical practice guidelines for the management of fatigue [3] but these are not routinely followed in the UK. For palliative care patients the guidance recommends provision of information, general strategies for the management of fatigue (e.g. energy conservation or distraction), physical activity, psychosocial interventions, psychostimulants or corticosteroids. All of the recommendations are graded at level 2A (i.e. based upon lower-level evidence, and NCCN consensus). The authors comment that pharmacological interventions remain investigational.

The Department of Health's End of Life Care Strategy and NICE have both stated that research to inform the provision of better care in the last year of life is crucially important [30-32]. Research to determine the best way to manage cancer-related fatigue in patients receiving palliative care is an important aspect of this mission. Overall, the evidence for the effectiveness of methylphenidate as a treatment for cancer-related fatigue, although suggestive of effectiveness, remains inconclusive. There remains a need to undertake an adequately powered confirmatory trial to inform the clinical management of this debilitating symptom. This study will answer the question about effectiveness, and will determine if there is benefit to quality of life and other important outcomes. This will clarify the role that methylphenidate should play in the management of fatigue in the context of advanced cancer.

## **6.5 ASSESSMENT AND MANAGEMENT OF RISK**

The active ingredient in the IMP is methylphenidate (the international non-proprietary name for  $\alpha$ -Phenyl-2-piperidineacetic acid methyl ester hydrochloride). Methylphenidate is licensed for use as a part of a comprehensive treatment programme for attention-deficit hyperactivity disorder (ADHD) in children aged 6 years of age and over when remedial measures alone prove insufficient [16]. Safety and efficacy of MPH have not yet been established in adults or the elderly.

Methylphenidate is a widely used medication in children and young adults. Following some concerns about possible adverse effects, the European Medicines Agency (EMA) completed a review of the safety of medicines containing methylphenidate in 2009. The Agency's Committee for Medicinal Products for Human Use (CHMP) concluded that the benefits of

these medicines outweigh their risks when used to treat children aged six years and above and adolescents with attention deficit/hyperactivity disorder [33].

The SPC [16] lists the following adverse effects [Note: Very common ( $\geq 1/10$ ); common ( $\geq 1/100$  to  $< 1/10$ ); uncommon ( $\geq 1/1000$  to  $< 1/100$ ); rare ( $\geq 1/10,000$  to  $< 1/1000$ ); very rare ( $< 1/10,000$ ); not known (cannot be estimated from available data)].

### **6.5.1 MAIN SOURCES OF RISK ASSOCIATED WITH IMP**

#### **6.5.1.1 Infections and infestations**

*Common:* Nasopharyngitis

#### **6.5.1.2 Blood and lymphatic disorders**

*Very rare:* Anaemia, leucopenia, thrombocytopenia, thrombocytopenic purpura

*Unknown:* Pancytopenia

#### **6.5.1.3 Immune system disorders**

*Uncommon:* hypersensitivity reactions such as angioneurotic oedema, anaphylactic reactions, auricular swelling, bullous conditions, exfoliative conditions, urticaria, pruritis, rashes and eruptions

#### **6.5.1.4 Metabolism and nutritional disorders**

*Common:* anorexia, decreased appetite, moderately reduced weight and height gain during prolonged use in children

#### **6.5.1.5 Psychiatric disorders**

*Very common:* insomnia, nervousness

*Common:* anorexia, affect lability, aggression, agitation, anxiety, depression, irritability, abnormal behaviour

*Uncommon:* psychotic disorders, auditory, visual, and tactile hallucinations, anger, suicidal ideation, mood altered, mood swings, restlessness, tearfulness, tics, worsening of pre-existing tics or Tourette's syndrome, hypervigilance, sleep disorder

*Rare:* mania, disorientation, libido disorder

*Very rare:* suicidal attempt (including completed suicide), transient depressed mood, abnormal thinking, apathy, repetitive behaviours, over-focusing,

*Not known:* delusions, thought disturbances, confessional state, dependence, logorrhea.

Cases of abuse and dependence have been described, more often with immediate release formulations (frequency not known)

#### **6.5.1.6 Nervous system disorders:**

*Very common:* Headache

*Common:* Dizziness, dyskinesia, psychomotor hyperactivity, somnolence

*Uncommon:* Sedation, tremor

*Very rare:* Convulsions, choreo-athetoid movements, reversible ischaemic neurological deficit, neuroleptic malignant syndrome (NMS: Reports were poorly documented and in most cases, patients were also receiving other drugs, so the role of methylphenidate is unclear).

*Not known:* Cerebrovascular disorders (including vasculitis, cerebral haemorrhages, cerebrovascular accidents, cerebral arteritis, cerebral occlusion), grand mal convulsions, migraine

#### **6.5.1.7 Eye disorders**

*Uncommon:* Diplopia, blurred vision

*Rare:* Difficulties in visual accommodation, mydriasis, visual disturbance

#### **6.5.1.8 Cardiac disorders**

*Common:* Arrhythmia, tachycardia palpitations

*Uncommon:* Chest pain

*Rare:* Angina pectoris

*Very rare:* Cardiac arrest, myocardial infarction

*Not known:* Supraventricular tachycardia, bradycardia, ventricular extrasystoles, extrasystoles

#### **6.5.1.9 Vascular disorders**

*Common:* Hypertension

*Very rare:* Cerebral arteritis and/or occlusion, peripheral coldness, Raynaud's phenomenon

#### **6.5.1.10 Respiratory, thoracic and mediastinal disorders**

*Common:* Cough, pharyngolaryngeal pain

*Uncommon:* dyspnoea

#### **6.5.1.11 Gastro-intestinal disorders:**

*Common:* Abdominal pain, diarrhoea, nausea, stomach discomfort and vomiting. These usually occur at the beginning of treatment and may be alleviated by concomitant food intake. Dry mouth.

*Uncommon:* Constipation

#### **6.5.1.12 Hepatobiliary disorders**

*Uncommon:* Hepatic enzyme elevations

*Very rare:* Abnormal liver functions, including hepatic coma

#### **6.5.1.13 Skin and subcutaneous tissue disorders**

*Common:* Alopecia, pruritis, rash, urticaria

*Uncommon:* Angioneurotic oedema, bullous conditions, exfoliate conditions

*Rare:* Hyperhidrosis, macular rash, erythema

*Very rare:* erythema multiforme, exfoliate dermatitis, fixed drug eruption

#### **6.5.1.14 Musculoskeletal, connective tissue and bone disorders**

*Common:* Arthralgia

*Uncommon:* Myalgia, muscle twitching

*Very rare:* Muscle cramps

#### **6.5.1.15 Renal and urinary disorders**

*Uncommon:* Haematuria

#### **6.5.1.16 Reproductive system and breast disorders**

*Rare:* Gynaecomastia

*Unknown:* Erectile dysfunction

#### **6.5.1.17 General disorders and administration site conditions**

*Common:* Pyrexia, growth retardation during prolonged use in children

*Uncommon:* Chest pain, fatigue

*Very rare:* Sudden cardiac death

*Not known:* Chest discomfort, hyperpyrexia

#### **6.5.1.18 Investigations**

*Common:* Changes in blood pressure and heart rate (usually an increase), weight decreased

*Uncommon:* Cardiac murmur, hepatic enzyme increased

*Very rare:* Blood alkaline phosphatase increased, blood bilirubin increased, platelet count decreased, white blood count abnormal

#### **6.5.1.19 Pharmacokinetic interactions**

The SPC advises that there are reports indicating that methylphenidate may inhibit the metabolism of coumarin anticoagulants, anticonvulsants (e.g. phenobarbital, phenytoin, primidone) and some antidepressants (tricyclics and selective serotonin reuptake inhibitors).

#### **6.5.1.20 Pharmacodynamic interactions**

##### **6.5.1.20.1 Anti-hypertensives**

The SPC advises that Methylphenidate may decrease the effectiveness of drugs used to treat hypertension.

##### **6.5.1.20.2 Use with drugs that elevate blood pressure**

Caution is advised in patients being treated with methylphenidate with any other drug that can also elevate blood pressure. Because of possible hypertensive crisis, methylphenidate is contraindicated in patients being treated (currently or within the preceding 2 weeks) with non-selective, irreversible MAO-inhibitors.

##### **6.5.1.20.3 Use with alcohol**

Alcohol may exacerbate the adverse CNS effects of psychoactive drugs, including methylphenidate.

#### 6.5.1.20.4 Use with halogenated anaesthetics

There is a risk of sudden blood pressure increase during surgery. If surgery is planned, methylphenidate treatment should not be used on the day of surgery.

#### 6.5.1.20.5 Use with centrally acting alpha-2 agonists

Serious, adverse events, including sudden death, have been reported in concomitant use with clonidine. The safety of using methylphenidate in combination with clonidine or other centrally acting alpha-2 agonists has not been systematically evaluated.

#### 6.5.1.20.6 Use with dopaminergic drugs

Caution is recommended when administering methylphenidate with dopaminergic drugs, including antipsychotics. Because a predominant action of methylphenidate is to increase extracellular dopamine levels, methylphenidate may be associated with pharmacodynamic interactions when co-administered with direct and indirect dopamine agonists (including DOPA and tricyclic antidepressants) or with dopamine antagonists including antipsychotics.

#### 6.5.1.21 Pregnancy

There is a limited amount of data from the use of methylphenidate in pregnant women. Cases of neonatal cardiorespiratory toxicity, specifically foetal tachycardia and respiratory distress have been reported in spontaneous case reports. Studies in animals have only shown evidence of reproductive toxicity at maternally toxic doses.

#### 6.5.1.22 Lactation

Methylphenidate has been found in the breast-milk of a woman treated with methylphenidate. There is one case report of an infant who experienced an unspecified decrease in weight during the period of exposure but recovered and gained weight after the mother discontinued treatment with methylphenidate. A risk to the suckling child cannot be excluded.

#### 6.5.1.23 Elderly

The SPC advises that safety and efficacy of methylphenidate have not established in the elderly.

### 6.5.2 HOW MAIN SOURCES OF RISK WILL BE MINIMISED IN THIS STUDY

#### 6.5.2.1 Cardiovascular status

The SPC for methylphenidate states that patients who are being considered for treatment should have a careful history (including assessment for a family history of sudden cardiac or unexplained death or malignant arrhythmia) and physical exam undertaken to assess for the presence of cardiac disease. Patients who develop symptoms such as palpitations, exertional chest pain, unexplained syncope, dyspnoea or other symptoms suggestive of cardiac disease during methylphenidate treatment should undergo a prompt specialist cardiac evaluation. Stimulant products are not recommended in children or adolescents with known cardiac structural abnormalities, cardiomyopathy, serious heart rhythm abnormalities, or other

serious cardiac problems that may place them at increased vulnerability to the sympathomimetic effects of a stimulant medicine.

*In this study cardiovascular risk will be minimised by* excluding patients with known pre-existing cardiovascular disorders including severe hypertension, heart failure, arterial occlusive disease, angina, haemodynamically significant congenital heart disease, cardiomyopathies, myocardial infarction, potentially life-threatening arrhythmias and channelopathies (all conditions for which the use of MPH is contraindicated). After initial consent potential participants will also be further screened by measurement of blood pressure – to exclude patients with severe untreated hypertension (BP >160/100mmHg). All study participants will be reviewed by a study nurse or doctor on a weekly basis for the duration of the trial (either by telephone or face-to-face) and cardiovascular side-effects will be monitored. Participants will also have BP and pulse rate measured at baseline, three, six and nine weeks. If hypertension is detected at one of the face-to-face assessments then the PI will make a clinical decision to either; adopt a policy of watchful waiting; modify existing anti-hypertensive medication; reduce the dose of study IMP; or withdraw the patient from the study depending upon clinical circumstances and the severity of the hypertension.

#### **6.5.2.2 Cerebrovascular disorders**

MPH is contra-indicated in patients with pre-existing cerebrovascular disorders cerebral aneurysm, vascular abnormalities including vasculitis or stroke or known risk factors for cerebrovascular disorders. Cerebral vasculitis appears to be a very rare idiosyncratic reaction to methylphenidate exposure. There is little evidence to suggest that patients at higher risk can be identified and the initial onset of symptoms may be the first indication of an underlying clinical problem. Early diagnosis, based on a high index of suspicion, may allow the prompt withdrawal of methylphenidate and early treatment. The diagnosis should therefore be considered in any patient who develops new neurological symptoms that are consistent with cerebral ischemia during methylphenidate therapy. These symptoms could include severe headache, numbness, weakness, paralysis, and impairment of coordination, vision, speech, language or memory.

*In this study cerebrovascular risk will be minimised by* excluding patients with known pre-existing cerebrovascular disorders, cerebral aneurysm, or vascular abnormalities including vasculitis or stroke. After initial consent, potential participants will also be further screened by measurement of blood pressure – to exclude patients with severe untreated hypertension (BP >160/100mmHg). All study participants will be reviewed by a study nurse or doctor on a weekly basis for the duration of the trial (either by telephone or face-to-face) and cerebrovascular side-effects will be monitored. Participants will also have BP and pulse rate measured at baseline, three, six and nine weeks.

#### **6.5.2.3 Psychiatric disorders**

The SPC notes that, treatment-emergent psychotic symptoms (visual/tactile/auditory hallucinations and delusions) or mania in children and adolescents without prior history of

psychotic illness or mania can be caused by methylphenidate at usual doses as can the emergence or worsening of aggression or hostility. If such symptoms occur, consideration should be given to a possible causal role for methylphenidate and discontinuation of treatment may be appropriate. Patients with emergent suicidal ideation or behaviour during treatment for ADHD should be evaluated immediately by their physician. Consideration should be given to the exacerbation of an underlying psychiatric condition and to a possible causal role of methylphenidate treatment.

Methylphenidate is associated with the worsening of pre-existing anxiety, agitation or tension. Particular care should be taken in using methylphenidate to treat ADHD in patients with co morbid bipolar disorder (including untreated type 1 bipolar disorder or other forms of bipolar disorder) because of concern for possible precipitation of a mixed/manic episode in such patients. Prior to initiating treatment with methylphenidate, patients with co morbid depressive symptoms should be adequately screened to determine if they are at risk for bipolar disorder; such screening should include a detailed psychiatric history, including a family history of suicide, bipolar disorder, and depression.

*In this study psychiatric risk will be minimised* by excluding patients with a known diagnosis or history of; severe depression; anorexia nervosa/anorexic disorders; suicidal tendencies; psychotic symptoms; severe mood disorders; mania; schizophrenia; psychopathic/borderline personality disorder; or a diagnosis or history of severe and episodic (Type 1) Bipolar (affective) disorder (that is not well controlled). At baseline participants will also complete the Hospital Anxiety and Depression Scale to document the extent of any affective symptoms and to screen for any undiagnosed symptomatology. All study participants will be reviewed by a study nurse or doctor on a weekly basis for the duration of the trial (either by telephone or face-to-face) and psychiatric side-effects will be monitored.

#### 6.5.2.4 Seizures

The SPC states that methylphenidate should be used with caution in patients with epilepsy. If seizure frequency increases or new-onset seizures occur, methylphenidate should be discontinued.

Nonetheless MPH has been safely used in adult patients with brain tumours who were undergoing radiotherapy [34] none of whom experienced seizures.

*In this study seizure risk will be minimised* by allowing investigators discretion to exclude patient suffering from any other significant disease or disorder which, in their opinion, may put the participant at risk or affect the participant's ability to take part in the study. Patients with brain tumours will not be excluded unless they have a history of seizures.

All study participants will be reviewed by a study nurse or doctor on a weekly basis for the duration of the trial (either by telephone or face-to-face) and side-effects will be monitored.

#### 6.5.2.5 Abuse, misuse and diversion

MPH is a controlled drug and patients should be carefully monitored for the risk of diversion, misuse and abuse of methylphenidate. The SPC recommends that methylphenidate should be used with caution in patients with known drug or alcohol dependency because of a potential for abuse, misuse or diversion.

*In this study the risk of abuse, misuse and diversion will be minimised* by excluding patients with known drug or alcohol dependency. In addition we will only dispense three weeks' supply of IMP at each visit. All study participants will be reviewed by a study nurse or doctor on a weekly basis for the duration of the trial and we will conduct pill counts at each face-to-face meeting.

#### 6.5.2.6 Excipients: galactose/sucrose intolerance

The IMP contains lactose and therefore patients with rare hereditary problems of galactose intolerance, the Lapp lactase deficiency or glucose-galactose malabsorption should not take this medicine.

*In this study the risk of adverse reactions to the excipients will be minimised* by excluding patients with known intolerance syndromes.

#### 6.5.2.7 Renal or hepatic insufficiency

The SPC notes that, there is no experience with the use of methylphenidate in patients with renal or hepatic insufficiency.

*In this study the risk associated with using MPH in patients with renal or hepatic insufficiency will be minimised* by excluding patients with severe renal or liver failure (as judged by the results of clinical biochemistry test obtained after initial consent).

#### 6.5.2.8 Potential for gastrointestinal obstruction

MPH tablets should not ordinarily be administered to patients pre-existing severe GI narrowing (pathologic or iatrogenic) or in patients with dysphagia or significant difficulty in swallowing tablets.

*In this study the risk associated with potential gastrointestinal obstruction will be minimised* by excluding patients with severe dysphagia from the study.

#### 6.5.2.9 Drug interactions

*In this study the risk associated with drug interactions will be minimised* by excluding; patients who are planned to have general anaesthesia in the next nine weeks; patients receiving treatment with non-selective, irreversible monoamine oxidase (MAO) inhibitors, or within a minimum of 14 days of discontinuing those drugs; patients currently receiving psychostimulants, or previous psycho-stimulant use in last month; currently receiving treatment with clonidine, warfarin or modafinil.



We will not exclude patients from the study who drink moderate amounts of alcohol, but they will be cautioned that alcohol may exacerbate the adverse CNS effects of methylphenidate. This is the same approach that is adopted in palliative care patients with the use of opioid medication where patients are cautioned about the possible adverse effects but are not prohibited from drinking.

Similarly we will not exclude patients who are taking tricyclic anti-depressants or dopamine antagonists since these medications are widely used in palliative care patients. Patients will be advised that interactions may occur and that the dose of study medication or concomitant medication may need to be adjusted in those circumstances.

#### **6.5.2.10 Pregnancy and lactation**

*In this study the risk associated with administration during pregnancy or lactation will be minimised by excluding females of childbearing potential and by requesting males to use an effective method of contraception (hormonal or barrier method of birth control; abstinence) from the time consent is signed until 6 weeks after treatment discontinuation. Females of childbearing potential must have a negative pregnancy test within 7 days prior to being registered for trial treatment. Females must not be breastfeeding.*

#### **6.5.2.11 Elderly**

The SPC advises that safety and efficacy of methylphenidate have not established in the elderly. However, since palliative care patients are typically elderly, we will not be excluding patients from the study solely on the basis of age. Participants will be cautioned that safety and efficacy in this group has not been established.

### **6.5.3 RISK CATEGORISATION**

On the basis that this trial involves a medicinal product that is already licensed in many EU Member States; relates to the evaluation of an off-label use that is already part of established practice in some units; and is supported by published evidence and guidelines; the trial should be categorised as:

- Type A = no higher than the risk of standard medical care

## **7 OBJECTIVES**

### **7.1 PRIMARY:**

To compare FACIT-F fatigue score in patients with advanced cancer receiving individually titrated doses of methylphenidate with patients receiving placebo after six weeks' treatment.

## 7.2 SECONDARY:

To compare secondary outcomes (other measures of quality of life, adverse events, activities of daily living; appetite; satisfaction of patients and carers; survival and need for other medication) between patients receiving methylphenidate and placebo.

To compare adverse effects in patients receiving methylphenidate and placebo.

## 8 OUTCOMES

### 8.1 PRIMARY OUTCOME

#### 8.1.1 THE FATIGUE SUB-SCALE OF FUNCTIONAL ASSESSMENT OF CHRONIC ILLNESS THERAPY (FACIT-F)

The primary outcome for this study is fatigue at 6 weeks ( $\pm 2$  weeks) measured by the fatigue sub-scale of the Functional Assessment of Chronic Illness Therapy (FACIT-F) questionnaire [42]. The FACIT Measurement System is a collection of QOL questionnaires targeted to the management of chronic illness [41]. The Fatigue Sub-scale consists of 13-items specifically related to fatigue [42]. It is probably the best validated and most widely used cancer-related fatigue specific outcome measure [43] and has been used as the primary outcome in numerous previous studies [27]. Each item can be answered on a 5-point scale with responses varying from “not at all” to “very much”. Scores can range between 0 and 52 with higher scores representing more fatigue. The scale was initially developed and validated in a heterogeneous group of cancer patients receiving treatment. It has subsequently been used in large numbers of clinical studies and in intervention trials. It has demonstrated convergent validity with other measures [44], known-groups validity and sensitivity to change [3].

### 8.2 SECONDARY OUTCOMES

Secondary outcomes (measured at 3, 6 and 9 weeks) are other measures of quality of life, adverse events, activities of daily living; appetite; satisfaction of patients and carers; survival and need for other medication (assessed at 6 week assessment only).

#### 8.2.1 OTHER MEASURES OF QUALITY OF LIFE

##### 8.2.1.1 *European Organisation for Research and Treatment of Cancer Palliative care Quality of Life Questionnaire (EORTC QLQ-C15-PAL)*

This is a well-validated modification of the larger 30-item EORTC QLQc30 questionnaire [47] which has been abbreviated to make it both more relevant and easier to complete for palliative care patients. The QLQ-C15-PAL [46] is recommended for use in patients with advanced, incurable, and symptomatic cancer with a median life expectancy of a few months. It consists of 15 items covering the following domains; overall quality of life, physical functioning, emotional functioning, pain,

fatigue, nausea, anorexia, dyspnoea, constipation and insomnia. Participants are asked to rate each item on a four-point scale (except quality of life which is rated on a 7-point scale). Scores are then transformed onto a 0–100 scale: a higher score represents a higher (i.e. ‘better’) level of functioning, or a higher (i.e. ‘worse’) level of symptoms. Minimal important clinical differences for the various symptom sub-scales of the EORTC QLQ-C15-PAL have recently been proposed [48].

#### **8.2.1.2 EQ-5D-5L**

This is a standardised instrument for use as a measure of health outcomes. It provides a simple descriptive profile and a single preference based index value for health status that can be used in cost-effectiveness analyses. It consists of questions relating to five dimensions of quality of life; mobility, self-care, usual activities, pain/discomfort and anxiety/depression. Each dimension has 5 levels: no problems, slight problems, moderate problems, severe problems, and extreme problems. There is also a vertical, visual analogue scale to record the respondent’s self-rated health with the anchors being; ‘Best imaginable health state’ and ‘Worst imaginable health state’ [49, 50].

#### **8.2.1.3 Activities of daily living**

Activities of daily living will be measured using the mobility, self-care and usual activity domains of the EQ-5D-5L (see above).

#### **8.2.1.4 Appetite**

Appetite will be measured using the anorexia item on the EORTC QLQ-C15-PAL (see above).

#### **8.2.1.5 Satisfaction of patients and carers**

Satisfaction of patients will be measured on a weekly basis using the Global benefit score (GBS) – This is a measure of global perception of drug benefit [35, 36]. The GBS is scored on a 7-point scale depending upon how the following statement is completed; “Overall with regard to fatigue I found the medication is...” with responses ranging from “not beneficial” to “greatly important”.

Once participants have completed the nine week follow up they will be given the option to continue (or start) methylphenidate according to local clinical practice and circumstances.

#### **8.2.1.6 Need for other medication**

The need for other medication (specifically steroids, antidepressants, anxiolytics and analgaesics) will be measured by asking participants about concomitant medication use at the start of the study and at the 6 week assessment.

#### **8.2.1.7 Survival**

Survival of patients after recruitment to the study will be measured by asking patients for permission to flag their records with the NHS Information Centre (NHS IC).

### 8.2.1.8 Adverse events

Adverse events or reactions will be documented on the case report form and graded as mild, moderate or severe (see Section 18).

## 8.3 SAMPLE SIZE AND RECRUITMENT

### 8.3.1 SAMPLE SIZE CALCULATION

There is no consensus about the magnitude of the change on the FACIT-F that should be considered to be clinically meaningful.

At one extreme Patrick et al. [37] and Cella et al [38] reported an MCID of 2 to 5 points and 3-points respectively. These authors determined MCID by relating changes in FACIT-F with changes in “objective” measures such as haematocrit or performance status. At the other extreme Reddy et al [36] determined the MCID by relating changes in FACIT-F with changes in a subjective “Global Benefit Score (GBS)” and reported that a reduction of 10-points or more was associated with a GBS of  $\geq 4$ , representing a subjective change that was, “moderately important, consistently beneficial”. They also reported [36] that a median change of 7.5 points or a mean change of 9.3 points on the FACIT-F corresponded to at least a 3-point score on the GBS scale (somewhat important, consistently beneficial).

We have elected to power the study adequately to look for a difference of 5 points on FACIT-F (effect size of 0.5). There is sufficient justification for this to be considered a clinically significant improvement, and the resulting sample size is achievable. Moreover, this effect size corresponds closely with the findings of a recent Cochrane review of pharmacological treatments for fatigue in palliative care patients [27] which estimated a significant benefit for methylphenidate over placebo with a standardised mean difference of 0.49 (95% CI 0.15 to 0.830).

With 230 randomised and 172 evaluable patients (25% attrition), this study will have 90% power to detect a difference of 5-points on FACIT-F (effect size 0.5) between groups at 5% significance (two sided).

### 8.3.2 PLANNED RECRUITMENT RATE

Initially we have estimated that each site will recruit one patient per month during the pilot and the initial set-up phase of the full trial. Once the trial is fully established and recruiting at all 10 sites we have estimated that the recruitment rate will increase to approximately 1.3 patients per site per month. The full details about the estimated number of sites opened and cumulative study accrual are shown in the Table below.

### Planned recruitment rate

Study month	Date	Cumulative number of recruiting sites	Cumulative number of participants	Notes
1	May 2017	0	0	Study set up
2	Jun 2017	0	0	Study set up
3	Jul 2017	0	0	Study set up
4	Aug 2017	0	0	Study set up
5	Sept 2017	0	0	Study set up
6	Oct 2017	0	0	Study set up
7	Nov 2017	0	0	Study set up
8	Dec 2017	0	0	Study set up
9	Jan 2018	1	1	Pilot phase
10	Feb 2018	2	2	Pilot phase
11	Mar 2018	3	4	Pilot phase
12	Apr 2018	4	8	Pilot phase
13	May 2018	5	12	Pilot phase
14	Jun 2018	5	16	Pilot phase
15	Jul 2018	5	20	Pilot phase
16	Aug 2018	5	24	Pilot phase
17	Sept 2018	5	28	Pilot phase
18	Oct 2018	5	32	Pilot phase
19	Nov 2018	6	38	Full study
20	Dec 2018	8	46	Full study
21	Jan 2019	10	56	Full study
22	Feb 2019	10	66	Full study
23	Mar 2019	10	76	Full study
24	Apr 2019	10	89	Full study
25	May 2019	10	102	Full study
26	Jun 2019	10	115	Full study
27	Jul 2019	10	128	Full study
28	Aug 2019	10	141	Full study
29	Sept 2019	10	154	Full study
30	Oct 2019	10	167	Full study
31	Nov 2019	10	180	Full study
32	Dec 2019	10	193	Full study
33	Jan 2020	10	206	Full study
34	Feb 2020	10	219	Full study
35	Mar 2020	10	230	Full study

## 9 TRIAL DESIGN

### 9.1 OVERALL DESIGN

#### 9.1.1 PURPOSE OF RESEARCH

This research has been designed to answer a commissioning brief from the NIHR HTA on the clinical effectiveness of methylphenidate in the treatment of cancer-related fatigue in patients receiving palliative care.

### **9.1.2 DESCRIPTION OF DESIGN**

This is a prospective, randomised, double-blind, parallel group, placebo-controlled study.

### **9.1.3 DURATION OF TREATMENT**

Study participants will remain on treatment for nine weeks. They will have the dose of their medication titrated on a weekly basis following either telephone consultation with a study nurse (weeks 1, 2, 4, 5, 7 and 8) or following face-to-face assessment with a member of the study team (weeks 3 and 6). During the last week of the study (week 9) the dose of the medication or placebo will be tapered and the medication will stop at the end of week nine. At the end of week 9 the study will end. At that point participants will be managed according to local clinical practice and circumstances. This may include the prescription of methylphenidate if that is deemed to be clinically indicated. Patient preferences for continued treatment will be recorded.

### **9.1.4 DOSE TITRATION**

At weekly intervals after study medication has been dispensed, participants will be contacted by telephone (weeks 1, 2, 4, 5, 7 and 8) or face-to-face (weeks 3, 6 and 9). The telephone calls will be made by one of two centrally employed research nurses at UCL. The research nurses will be senior nurses with experience of oncology / palliative care or an associated speciality. They will have (or will receive) training in communication skills. The research nurses will ask study participants the following information over the telephone (each participant will be provided with a written copy of the questionnaires to facilitate scoring);

- FACIT-F score – This will be read out to the participant and the responses recorded by one of the study nurses on the CRF.
- Global benefit score (GBS) – This is a measure of global perception of drug benefit [35, 36]. The GBS is scored on a 7-point scale depending upon how the following statement is completed; “Overall with regard to fatigue I found the medication is...” with responses ranging from “not beneficial” to “greatly important”. The questions will be read to respondents over the phone and responses recorded on the CRF.
- Patient perception of efficacy; the nurse will ask “Is fatigue now adequately controlled?”, and will record the answer on the CRF.
- Presence and severity of side effects. Adverse events or reactions will be documented on the case report form and graded as mild moderate or severe (see Section 18).
- List of concomitant medications

At the face-to-face assessments (weeks 3, 6 and 9) these same questions will be posed by the research nurses or by the PI (or delegate). Once again responses will be recorded on the CRF.

#### 9.1.4.1 *Responsibility for dose titration*

At the first assessment study participants will be instructed by the PI to start at dose level 1 (one capsule twice daily of either methylphenidate 5mgs or matching placebo). They will be instructed to continue at this dose level until they have been reviewed by the research team (either by telephone contact from the centrally employed research nurse at UCL or by the local PI). At the weekly review, patients will be advised to either remain on the current dose of the medication, increase, decrease, or stop the medication altogether (see Section 9.2).

The decision about how to adjust the dose of medication will be made by the local PI on the basis of the patients' responses to the questions described in 9.1.4 (above). The patient's responses will be communicated to the local PI via the "Sealed Envelope" database, or by secure email (either using NHS mail if the PI has an account or using encrypted email [AES-256 standard]). "Sealed Envelope" is an independent data management company ("Sealed Envelope") who have been commissioned by the Priment Clinical Trials Unit to support randomisation and data management for the MePFAC study.

It is anticipated that in most circumstances the PI will not need to contact the study participant directly and that they can be advised to alter the dose of study medication on the basis of the information relayed to them by the centrally employed research nurse. If necessary, the PI will contact the patient directly (either by telephone or by arranging a face-to-face visit) before sanctioning a change in the dose of the study medication. A record will be made of any such additional contacts. The frequency with which it is necessary for PIs to directly supervise the titration of the study medication will be monitored during the pilot phase of the study and may influence the procedures adopted in the roll-out of the full study.

## 9.2 CRITERIA FOR DOSE ESCALATION

On the basis of the answers obtained at each assessment visit (see section 9.1.4) or telephone call, study participants will be advised either;

- To increase to the next dose level if
  - Fatigue is not adequately controlled
  - There are no dose-limiting adverse effects
- To remain at the current dose level if
  - Fatigue is adequately controlled
  - There are no dose-limiting adverse effects
- To reduce to the previous dose level (or stop study medication if only on level 1) if
  - There are dose limiting side-effects

The National Cancer Institute describes a dose limiting adverse effect as one which is "serious enough to prevent an increase in dose or level of that treatment" [39]. This is likely to include

any adverse effect graded as “severe”, and may include adverse effects graded as “moderate” (see Section 18).

***Standard titration schedule***

<b>Dose level</b>	<b>Days</b>	<b>Total daily dose of methylphenidate 5mg</b>	<b>Dose schedule</b>
1	0 -7 ( $\pm 3$ )	2 tablets	In two divided doses
2	8 – 14 ( $\pm 3$ )	4 tablets	In two divided doses
3	15 – 21 ( $\pm 3$ )	6 tablets	In two divided doses
4	22 – 28 ( $\pm 3$ )	8 tablets	In two divided doses
5	29 – 35 ( $\pm 3$ )	10 tablets	In three divided doses
6	36 – 42 ( $\pm 3$ )	12 tablets	In three divided doses

### **9.3 MAINTENANCE (OR REDUCTION)**

During weeks 7 and 8 the dose of study medication will remain unaltered at whatever dose level was reached during week 6 of the study (Days 36 – 42), unless participants report does-limiting adverse events at their weekly telephone call with the study nurse.

***Standard maintenance schedule***

<b>Days</b>	<b>methylphenidate 5mg tablets</b>
43 - 49 ( $\pm 3$ )	Continue at level reached during dose titration or reduce due to adverse events
50 - 56 ( $\pm 3$ )	Continue at level reached during dose titration or reduce due to adverse events

### **9.4 TAPERING**

Since it is not advisable to stop treatment with methylphenidate abruptly (due to the risk of discontinuation phenomena), medication will be tapered during the last week of the study (regardless of whether participants are receiving placebo or active medication). Participants will follow the following tapering schedule.

***Standard tapering schedule***

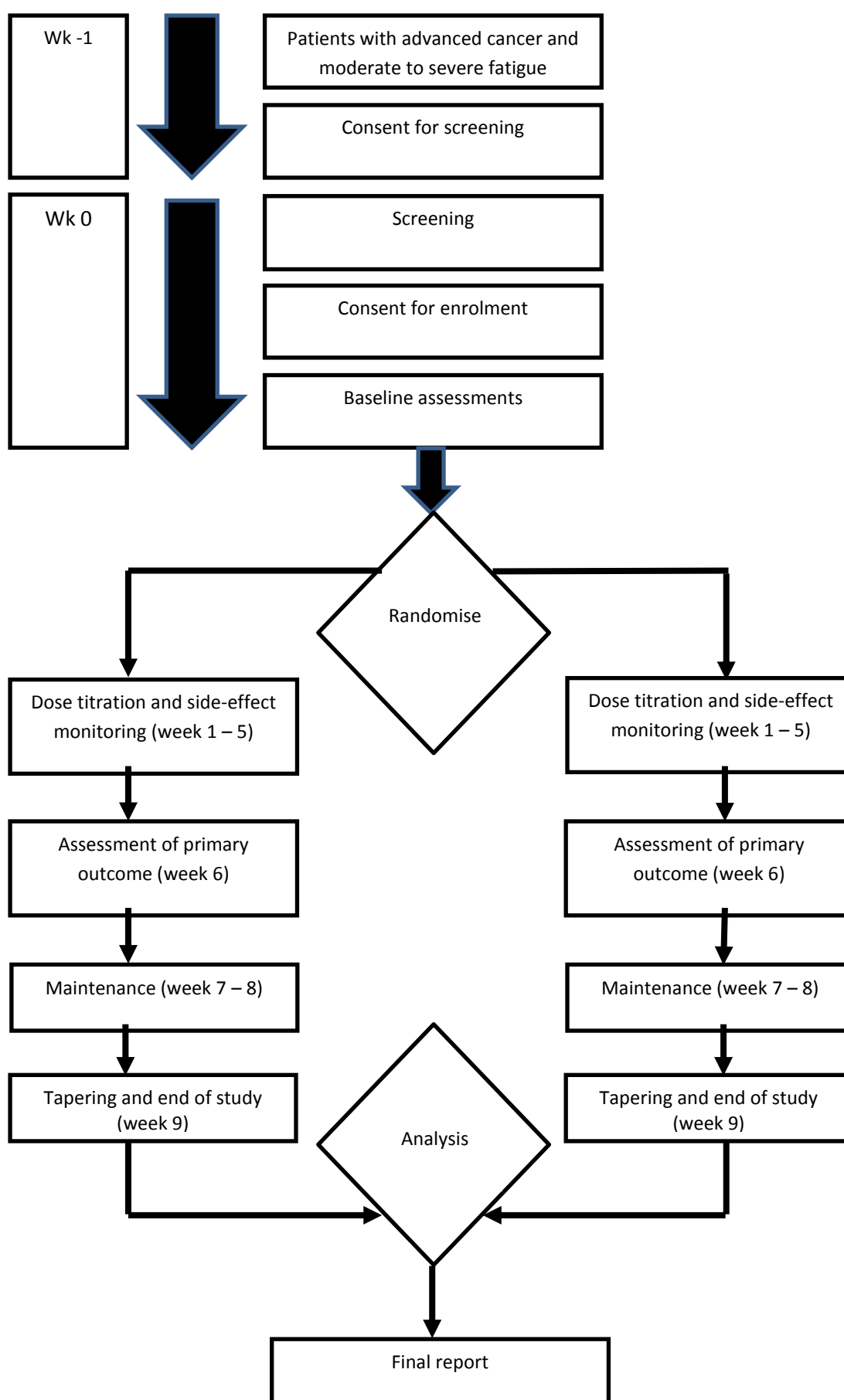
<b>Days</b>	<b>methylphenidate 5mg tablets</b>
57 - 58	4 tablets twice daily or maintenance dose (whichever is lower)
59 – 60	2 tablets twice daily or maintenance dose (whichever is lower)
61 - 63	1 tablet twice daily

Thus, for example;



- A participant who was taking 6 tablets of study medication during the maintenance phase would reduce to 4 tablets twice daily for days 57-58; 2 tablets twice daily for days 59-60; and 1 tablet twice daily for day 61-63; and then stop.
- A participant who had been taking 3 tablets twice daily during the maintenance phase would remain on that dose until Day 59 at which point they would reduce the dose to 2 tablets twice daily for two days; then 1 tablet twice daily for three days and then stop.

## 9.5 TRIAL SCHEMATIC



## 9.6 RECRUITMENT

The target population for this study is community patients with advanced incurable cancer under the care of a specialist palliative care team.

It is planned that this study will take place at 10 different palliative care services. It is planned that at least four sites will be involved during the internal pilot phase. The palliative care services themselves span community, hospital support teams and hospice services (including day care and outpatients). However in line with the commissioning brief inpatients in either the hospital or the hospice will be excluded.

### 9.6.1 SCREENING

A comprehensive screening log will be maintained at each participating site. The screening log will include the following information on all potentially eligible referrals to the participating service: age, gender, extent of disease, estimated prognosis, whether patient was approached by a member of the clinical team about formal screening for the study (if not, why not), whether patient agreed to speak to a member of the research team (no reason for not speaking to a member of the research team need be given, but if a reason is volunteered this will be recorded), whether patient agreed to participate in formal screening, whether or not they were eligible and whether or not they agreed to participate in study enrolment (no reason for non-participation need be given, but if a reason is volunteered this will be recorded).

#### 9.6.1.1 *Pre-screening by clinical staff*

Initial screening will be undertaken by clinical staff and will identify patients who broadly fulfil the inclusion and exclusion criteria (i.e. advanced incurable cancer with fatigue without contra-indications to methylphenidate). In line with good clinical practice [40] clinicians will ask patients to rate their fatigue on an 11 point (0 – 10) Numerical Rating Scale (NRS) – “How would you rate your fatigue on a scale of 0 – 10 over the past 7 days?” [40]. Only patients who score >3/10 (indicating moderate – severe fatigue) will be potentially eligible for the study. The screening log will contain information about the number of patients who were potentially eligible along with their NRS fatigue score.

Potential study participants will be informed about the study, will be provided with a Patient Information Sheet (PIS) and will be invited to meet a member of the research team to discuss the study in detail.

#### 9.6.1.2 *Screening after consent*

After a potentially eligible patient has been identified by a member of the clinical team, and after they have provided written informed consent, they will be formally screened in order to see whether they fulfil the inclusion and exclusion criteria.

## 10 SELECTION OF PARTICIPANTS

### 10.1 INCLUSION CRITERIA

1. Aged 18 years or over
2. Participant is willing and able to give informed consent for participation
3. Advanced incurable cancer of all tumour types
4. Moderate or severe fatigue (>3/10 on a numerical rating scale)
5. Prognosis 2-12 months (as estimated by clinician)
6. Able and willing to comply with all study requirements, including ability to participate in study for nine weeks
7. Under the care of a specialist palliative care team
8. Willing to allow his or her General Practitioner to be notified of participation in the study

### 10.2 EXCLUSION CRITERIA

1. Females of childbearing potential and males must be willing to use an effective method of contraception (hormonal or barrier method of birth control; true abstinence) from the time consent is signed until 6 weeks after treatment discontinuation and inform the trial if pregnancy occurs. For the purpose of clarity, true abstinence is when this is in line with the preferred and usual lifestyle of the subject. Periodic abstinence (e.g., calendar, ovulation, symptothermal, post-ovulation methods), declaration of abstinence, withdrawal, spermicides only or lactational amenorrhoea method for the duration of a trial, are not acceptable methods of contraception)
2. Females of childbearing potential must have a negative pregnancy test within 7 days prior to being registered for trial treatment.
3. Females must not be breastfeeding.
4. Known sensitivity to methylphenidate or to any of the excipients.
5. History of glaucoma
6. Known pheochromocytoma
7. Planned general anaesthesia in the next nine weeks
8. During treatment with non-selective, irreversible monoamine oxidase (MAO) inhibitors, or within a minimum of 14 days of discontinuing those drugs
9. Hyperthyroidism or thyrotoxicosis
10. Known diagnosis or history of severe depression, anorexia nervosa/anorexic disorders, suicidal tendencies, psychotic symptoms, severe mood disorders, mania, schizophrenia, psychopathic/borderline personality disorder
11. Known diagnosis or history of severe and episodic (Type 1) Bipolar (affective) disorder (that is not well controlled)
12. Known pre-existing cardiovascular disorders including severe hypertension (BP >160/100mmHg), heart failure, arterial occlusive disease, angina, haemodynamically

- significant congenital heart disease, cardiomyopathies, myocardial infarction, potentially life-threatening arrhythmias and channelopathies
13. Pre-existing cerebrovascular disorders, cerebral aneurysm, vascular abnormalities including vasculitis or stroke or known risk factors for cerebrovascular disorders
  14. Current or previous psycho-stimulant use in last month
  15. Severe anaemia (Haemoglobin < 80g/L)
  16. Platelets <50 × 10<sup>3</sup>/μL
  17. White blood count >30 × 10<sup>9</sup>/L
  18. Estimated glomerular filtration rate [eGFR] <60 ml/minute per 1.73 m<sup>2</sup>
  19. Liver function tests elevated >3 x upper limit of normal (either ALT >165 U/L; or AST > 144 U/L; or ALP > 345 U/L; or GGT > 144 U/L; or Bilirubin > 3.6mg/dL)
  20. Currently an inpatient in a hospital or a hospice
  21. Currently participating in another research study involving an investigational product
  22. English not first language or unable to read English
  23. Current treatment with clonidine, warfarin, monoamine oxidase inhibitors or modafinil
  24. History of previous or current substance or alcohol abuse
  25. Unable to swallow tablets/capsules
  26. History of poorly controlled epilepsy, or seizures related to underlying brain tumour
  27. Any other significant disease or disorder which, in the opinion of the Investigator, may put the participant at risk or affect the participant's ability to take part in the study

Patients who are still receiving tumour-directed therapies (e.g. chemotherapy or radiotherapy) will not be excluded from the study provided that the treatment is with palliative intent and that the expected prognosis is 2 – 12 months. Patients will be stratified by whether or not they are in receipt of disease-modifying treatment as this may be expected to affect their fatigue levels one way or another (see Section 11.6).

## 11 STUDY PROCEDURES AND SCHEDULE OF ASSESSMENTS

### 11.1 PARTICIPANT IDENTIFICATION

Referrals to participating services will be pre-screened for potential eligibility. Participants will be identified by members of the participating clinical palliative care services (depending on local arrangements, this may include research nurses who are considered part of the clinical team in many services). Potential participants may be identified from; community palliative care; day care; or outpatient services. Usually identification will occur as part of a routine clinical interaction (outpatient appointment; attendance at day centre or home visit). Occasionally identification of potential participants will occur as a result of a telephone consultation (as frequently happens in community palliative care settings). If a patient is felt to be potentially eligible, but no member of the clinical team is easily able to make contact with the patient by phone or face-to-face, then they may be sent a letter of introduction about the study by a research nurse and this letter of invitation will be

subsequently followed up. Posters highlighting the existence of the study may also be placed in public spaces (such as outpatient waiting areas or in hospice day centres, allowing patients the opportunity to self-refer for consideration of study inclusion.

Potential study participants will be informed about the study, will be provided with a Patient Information Sheet (PIS) and will be invited to meet a member of the research team to discuss the study in detail and to obtain informed consent to be screened.

## **11.2 CONSENT FOR SCREENING**

A two stage consent process will be adopted; consent for screening (described here) and consent for study enrolment (described in Section 11.4).

Before formal screening for eligibility can be undertaken consent must be obtained. At this point consent will only be for the purpose of allowing for formal assessment of eligibility. If no recent blood result is available (within 14 days of screening) then a fresh blood specimen will be obtained. Blood pressure will be recorded. The Investigator, or a person delegated by the Investigator (often a research nurse) will obtain written informed consent from each participant prior to formal screening, following adequate explanation of the aims, methods, anticipated benefits and potential hazards of the study. Consent will normally be taken by a research nurse who has been GCP trained, is suitably qualified and experienced, and has been delegated this duty by the CI/PI on the delegation log.

The PI will record when the patient information sheet (PIS) has been given to the participant. Although it is important that potential participants are given adequate time to consider whether or not to participate in the study, it is also important to minimise participant burden and to reduce the need for unnecessary hospital/hospice visits.

Formal screening may, if the patient agrees, be undertaken at the same visit at which the patient was identified as being potentially eligible for participation. However, if the patient prefers, then they may return to see a member of the research team at a later date.

A copy of the signed “Informed Consent for Screening” form will be given to the participant. The original signed form will be retained at the study site and a copy placed in the medical notes.

## **11.3 SCREENING PERIOD**

After a potentially eligible patient has been identified by a member of the clinical team, and after they have provided written informed consent, they will be formally screened in order to see whether they fulfil the inclusion and exclusion criteria.

This will involve:

- Review and documentation of eligibility criteria

- Full blood count and routine biochemistry - when relevant blood tests are available from within the previous two weeks no further blood tests will be necessary.
- For females of childbearing potential a negative pregnancy test must be obtained within 7 days prior to being registered for trial treatment
- Measurement and documentation of blood pressure – to exclude patients with severe untreated hypertension (BP >160/100mmHg)

Patients who (after formal screening) are not eligible to participate in the study (as judged by the PI or delegate) will be informed of this outcome and the reasons for ineligibility will be explained. In some cases it may be possible to formally rescreen for eligibility again if circumstances have changed (e.g. a temporarily high blood pressure may have been corrected, or an abnormal blood result may have resolved).

Patients who (after formal screening) are found to be eligible for the study will be contacted (usually by phone) and invited back for a baseline assessment and to enrol in the study. The baseline assessment will occur between 1 -14 days after screening.

#### **11.4 CONSENT FOR STUDY ENROLMENT**

At the baseline visit (see Section 11.5), eligibility will be confirmed by the PI (or delegate) and documented in the case report form. No clinical trial procedures will be conducted prior to taking consent from the participant.

Participants will be invited to provide informed consent to enrol in the study. The Investigator or designee will explain that participants are under no obligation to enter the trial and that they can withdraw at any time during the trial, without having to give a reason. A copy of the signed “Informed Consent for study Enrolment” form will be given to the participant. The original signed form will be filed in the medical notes and a copy filed in the Investigator site file.

If new safety information results in significant changes in the risk/benefit assessment, the consent form will be reviewed and updated if necessary and enrolled participants will be re-consented as appropriate.

#### **11.5 BASELINE ASSESSMENT**

The baseline visit will occur between 1-14 days from the screening visit. Before any baseline data are collected patients will be asked to provide written informed consent to study enrolment. The following data will then be collected;

##### **11.5.1 PATIENT IDENTIFIERS AND CONTACT DETAILS**

It will be necessary to collect information about the participant’s name, date of birth, ethnicity, NHS number, address and contact telephone number. This is necessary to allow the study team to characterise the study population and to contact the participants on a weekly basis during the dose titration, maintenance and tapering

phase and to “flag” the participants with the NHS Information Centre (NHS IC) for survival analysis.

### 11.5.2 QUESTIONNAIRES

- Functional Assessment of Chronic Illness Therapy Fatigue scale (FACIT-F) – The FACIT Measurement System is a collection of QOL questionnaires targeted to the management of chronic illness [41]. The Fatigue Sub-scale consists of 13-items specifically related to fatigue [42]. It is probably the best validated and most widely used cancer-related fatigue specific outcome measure [43] and has been used as the primary outcome in numerous previous studies [25]. Each item can be answered on a 5-point scale with responses varying from “not at all” to “very much”. Scores can range between 0 and 52 with higher scores representing more fatigue. The scale was initially developed and validated in a heterogeneous group of cancer patients receiving treatment. It has subsequently been used in large numbers of clinical studies and in intervention trials. It has demonstrated convergent validity with other measures [44], known-groups validity and sensitivity to change [38].
- The Hospital Anxiety and Depression Scale (HADS) [45] - this is a 14-item screening tool. It consists of separate scales for anxiety (HADS-A) and depression (HADS-D). The scale was developed for use amongst hospital inpatients and is designed to minimize the biological features of these conditions. It has been previously validated in patients with advanced cancer [46]. Scores on each subscale can range between 0 (no symptoms of depression/anxiety) to 21 (numerous and severe symptoms). The HADS scores will be used to describe the baseline characteristics of study participants and the HADS-D score will be used to stratify study participants according to their degree of depressive symptomatology.
- European Organisation for Research and Treatment of Cancer Palliative care Quality of Life Questionnaire (EORTC QLQ-C15-PAL) [47]. This is a well-validated modification of the larger 30-item EORTC QLQ-C30 questionnaire [48] which has been abbreviated to make it both more relevant and easier to complete for palliative care patients. The QLQ-C15-PAL is recommended for use in patients with advanced, incurable, and symptomatic cancer with a median life expectancy of a few months. It consists of 15 items covering the following domains; overall quality of life, physical functioning, emotional functioning, pain, fatigue, nausea, anorexia, dyspnoea, constipation and insomnia. Participants are asked to rate each item on a four-point scale (except quality of life which is rated on a 7-point scale). Scores are then transformed onto a 0–100 scale: a higher score represents a higher (i.e. ‘better’) level of functioning, or a higher (i.e. ‘worse’) level of symptoms. Minimal important clinical differences for the various symptom sub-scales of the EORTC QLQ-C15-PAL have recently been proposed [49].
- EQ-5D-5L – This is a standardised instrument for use as a measure of health outcomes. It provides a simple descriptive profile and a single preference based index value for



health status that can be used in cost-effectiveness analyses. It consists of questions relating to five dimensions of quality of life; mobility, self-care, usual activities, pain/discomfort and anxiety/depression. Each dimension has 5 levels: no problems, slight problems, moderate problems, severe problems, and extreme problems. There is also a vertical, visual analogue scale to record the respondent's self-rated health with the anchors being; 'Best imaginable health state' and 'Worst imaginable health state' [50, 51].

### **11.5.3 CLINICAL EXAMINATION**

- BP and pulse measurement

### **11.5.4 END OF BASELINE VISIT**

At the end of this visit the patient will be randomised (using the online randomisation service provided by Sealed Envelope) and will then be dispensed the study medication or placebo.

## **11.6 RANDOMISATION PROCEDURES**

Randomisation will be performed by the PI or delegate and undertaken using an independent data management company ("Sealed Envelope") who have been commissioned by the Priment Clinical Trials Unit to support randomisation and data management for the MePFAC study. Treatment allocation (1:1) will be done using a permuted-block randomisation stratified to four factors; the centre, receipt of palliative cancer treatment, baseline HADS depression score, and whether or not patients are considered to be "severely" fatigued (initial fatigue score >7/10 on a numerical rating scale).

## **11.7 UNBLINDING**

### **11.7.1 EMERGENCY UNBLINDING**

The study code will only be broken for valid medical or safety reasons e.g. in the case of a severe adverse event where it is necessary for the investigator or treating health care professional to know which treatment the patient is receiving before the participant can be treated. Where possible, members of the research team will remain blinded.

The code breaks for the trial will be held by the on-call palliative care consultant at UCLH. In this way a senior clinician will be available to unblind the study 24 hours per day. The on-call consultants will be briefed on how to access the on-line system for code-breaking and will be provided with a SOP for doing so.

In the event a code is required to be unblinded a formal request for unblinding will be made by the Investigator/treating health care professional. If the person requiring the unblinding is a member of the investigating team then a request to the holder of the code break envelope/list, or their delegate will be made and the unblinded information

obtained. If the person requiring the unblinding is not the CI/PI then that health care professional will notify the investigating team that an unblinding is required for a trial participant and a decision to unblind will be made in consultation with the clinical and research teams. The treating physician will have the ultimate decision and right to unblind the patient.

On receipt of the treatment allocation details the CI/PI or treating health care professional will deal with the participant's medical emergency as appropriate.

The CI/PI will document the breaking of the code and the reasons for doing so on the CRF/data collection tool, in the site file and medical notes. It will also be documented at the end of the study in any final study report and/or statistical report. The CI/investigating team will notify Priment (acting on behalf of the Sponsor) by email as soon as possible following the code break detailing the necessity for the code break. The written information will be disseminated to the Data Safety and Monitoring Board for review in accordance with the DSMB Charter.

#### **11.7.2 UNBLINDING FOR THE SUBMISSION OF SUSAR REPORTS:**

The following procedure will be used to unblind for the submission of a SUSAR report to the regulatory agencies.

- A member of Priment will contact the pharmacy via telephone in the first instance, requesting unblinding information from the randomization list.
- The pharmacist will provide their email address and name for the request to be formalised in an email.
- Priment or delegate will provide in the email the protocol number, trial name, name of the requester, reason for unblinding, and deadline by which they wish to receive the unblinded information.
- Priment will report the SUSAR to the MHRA if the patient is on active treatment. SUSARs that occur in patients receiving a placebo are not required to be reported to the MHRA.
- This information will not be forwarded to the trial team and will be kept in Priment files.

#### **11.8 TREATMENT PROCEDURES**

Methylphenidate 5mgs tablets and placebo will be prepared by the IMP manufacturer. At weekly intervals ( $\pm 4$  days) after study medication has been dispensed, participants will be contacted by telephone (weeks 1, 2, 4, 5, 7 and 8) or face-to-face (weeks 3, 6 and 9) and the study medication (or placebo) will be titrated by the PI in response to information provided by the research staff (see Sections 9.1.4.1 and 9.2). Study medication will be dispensed at the baseline assessment, week 3 ( $\pm 4$  days) and week 6 ( $\pm 4$  days). The four days' flexibility on either side of the scheduled assessment days is to allow for contingencies. On visit days, pill

counts will be performed to assess compliance to IMP (see Section 13.11). At the face-to face assessment at the end of week 9 ( $\pm 4$  days) the study will end. At that point participants will be assessed by the local clinical service and a decision will be made about whether or not methylphenidate should be prescribed depending upon local clinical assessment and patient and physician preference.

### 11.9 TABLE OF STUDY ASSESSMENTS

Table of assessments	Pre-screening	Screening visit <sup>b</sup>	Treatment period									
			Baseline visit <sup>d</sup>									Final visit
Week (±4days)	-2	-2	0	1	2	3	4	5	6	7	8	9
Contact #	1	1 <sup>b</sup>	2	3	4	5	6	7	8	9	10	11
F2F Visit	X <sup>a</sup>	X	X	-	-	X	-	-	X	-	-	X
Tel contact	X <sup>a</sup>	-	-	X	X	-	X	X	-	X	X	-
NRS Fatigue	X	X	X	-	-	-	-	-	-	-	-	-
Medical history	X	X	-	-	-	-	-	-	-	-	-	-
Informed consent for screening	-	X	-	-	-	-	-	-	-	-	-	-
Formal eligibility determination	-	X	-	-	-	-	-	-	-	-	-	-
BP	-	X	X	-	-	X	-	-	X	-	-	X
Pulse	-	X	X	-	-	X	-	-	X	-	-	X
Full blood count	-	X <sup>c</sup>	-	-	-	-	-	-	-	-	-	-
Biochemistry	-	X <sup>c</sup>	-	-	-	-	-	-	-	-	-	-
Informed consent for enrolment	-	-	X	-	-	-	-	-	-	-	-	-
Randomisation	-	-	X	-	-	-	-	-	-	-	-	-
IMP administration	-	-	X	-	-	X	-	-	X	-	-	-
FACIT-F	-	-	X	X	X	X	X	X	X	X	X	X
HADS	-	-	X	-	-	X	-	-	X	-	-	X
EORTC QLQ-C15-PAL	-	-	X	-	-	X	-	-	X	-	-	X
EQ-5D-5L	-	-	X	-	-	X	-	-	X	-	-	X
GBS	-	-	-	X	X	X	X	X	X	X	X	X
Perception of efficacy	-	-	-	X	X	X	X	X	X	X	X	X
Adverse event review	-	-	-	X	X	X	X	X	X	X	X	X
Pill counts to assess compliance	-	-	-	-	-	X	-	-	X	-	-	X
Concomitant medication review	-	-	X	X	X	X	X	X	X	X	X	X
Physician's withdrawal checklist	-	-	-	-	-	-	-	-	-	-	-	X

a Pre-screening contact may either be face-to-face or by telephone

b The formal screening visit may occur at the same time as identification or may occur at a later date

c If blood results are available from within the previous two weeks then no fresh blood test is required

d The baseline visit may occur between 1 – 14 days after the formal screening visit

## **11.10 METHODS**

### **11.10.1 LABORATORY PROCEDURES**

Blood specimens will be processed in local laboratories following local policies and procedures. When relevant blood results are available from within the previous two weeks (and when there is no clinical indication for a fresh specimen to be collected) then no further blood specimen will be required.

### **11.11 DEFINITION OF END OF TRIAL**

The end of the trial will be the date of the last visit, telephone follow up or home visit by the last trial participant.

## **11.12 DISCONTINUATION/WITHDRAWAL OF PARTICIPANTS AND ‘STOPPING RULES’**

### **11.12.1 INTERNAL PILOT**

After initial start-up (i.e. during months 13-18), the rate of recruitment at the pilot sites should be at least 70% of the rate expected once the trial is fully established. If recruitment rates reach this figure then this will indicate that recruitment to the full study will be achievable given realistic strategies such as opening one or two new sites to compensate. If recruitment rates are less than 50% then we would conclude that recruitment to the full study would be unachievable. If the recruitment rate is between 50%-70% then we would consult with HTA.

The recruitment rate once the trial is fully established is projected to be 1.3 participants per centre per month. Therefore the stopping rules for the study at the end of the pilot phase are shown below.

<b>Recruitment rate during months 13-18 of pilot phase</b>	<b>Action</b>
>0.91 patients/centre/month	Proceed
0.65 to 0.91 patients/centre/month	Consult with HTA
<0.65 patients/centre/month	Stop

### **11.12.2 MAIN STUDY**

The main study may be terminated early on the advice of the Data Safety and Monitoring Board or the Trial Steering Committee. This may occur, for example, as a result of information to suggest that patient safety is at risk (either as a result of adverse events or in response to information about the IMP arising from other sources).

#### **11.12.3 WITHDRAWAL OF INDIVIDUAL PARTICIPANTS AT THEIR OWN REQUEST**

If a patient chooses to withdraw from the study voluntarily then they are not obliged to give a reason for doing so. However, they will be asked to attend a withdrawal meeting with a PI (or delegate) and any reasons for withdrawal that are volunteered will be documented.

#### **11.12.4 DISTINCTION BETWEEN STOPPING STUDY IMP AND WITHDRAWAL FROM THE STUDY**

Participants may choose to stop (or may not be able to tolerate) the study medication. These patients will remain on study follow-up for the full nine week period, unless they ask to be withdrawn (see 11.12.3 above). To minimise study burden, participants who are no longer taking the study medication may undergo a simplified follow up procedure involving only telephone assessments of fatigue and adverse events as a minimum.

#### **11.12.5 WITHDRAWAL DUE TO INABILITY TO TOLERATE THE LOWEST DOSE OF STUDY MEDICATION**

The dose of IMP will be individually titrated on a weekly basis. However, if there are dose-limiting adverse effects at the lowest dose level, then the trial participant will be instructed to stop study medication and will either be withdrawn from the study (see Section 11.12.3) or will continue to be followed-up without taking further study medication (see 11.12.4). The National Cancer Institute describes a dose limiting adverse effect as one which is “serious enough to prevent an increase in dose or level of that treatment”[39]. This is likely to include any “severe” adverse event, and may include “moderate” adverse effects (see Section 18). The PI will assess the patient to decide whether they should remain in the study or be withdrawn depending on clinical judgment of the PI (or delegate) and patient preference.

#### **11.12.6 WITHDRAWAL OF INDIVIDUAL PARTICIPANTS DUE TO ADVERSE EVENTS**

Participants who have progressed beyond the baseline dose level, if they subsequently develop mild or moderate side-effects, will usually be advised to return to the previous dose level of the study medication and to remain in the trial. However participants may need to stop taking the study medication, regardless of dose level, if they develop serious adverse events. As described above this would include any “severe” adverse event, and may include “moderate” adverse effects, if they do not resolve after the participant returns to a lower dose level, depending on clinical judgment of the PI (or delegate). Participants who stop taking the study medication will either be withdrawn from the study (see Section 11.12.3), or else will remain on study follow up without taking the trial medication (see Section 11.12.4 above).

Participants will also have BP and pulse rate measured at baseline, three, six and nine weeks. If hypertension is detected at one of the face-to-face assessments then the PI will make a clinical decision to either; adopt a policy of watchful waiting; modify existing anti-hypertensive medication; reduce the dose of study IMP; withdraw the patient from the

study; or stop the study medication and keep the patient on follow-up depending upon clinical circumstances and the severity of the hypertension.

#### **11.12.7 DOCUMENTATION TO BE COMPLETED ON PARTICIPANT WITHDRAWAL**

In the event that a participant is withdrawn from the study a “Participant withdrawal” form will be completed.

## **12 NAME AND DESCRIPTION OF ALL DRUGS USED IN THE TRIAL**

Methylphenidate 5 (five) mg tablets and placebo will be prepared by the IMP manufacturer.

### **12.1 TREATMENT OF PARTICIPANTS**

Study participants will be prescribed individually titrated doses of IMP or placebo (see Section 9.2). All participants will start at dose level 1 and will only proceed to higher doses if they are tolerating the medication without dose-limiting adverse effects and if their fatigue remains inadequately controlled.

#### ***Standard titration schedule***

<b>Dose level</b>	<b>Days</b>	<b>Total daily dose of methylphenidate 5mg</b>	<b>Dose schedule</b>
1	0 -7 ( $\pm$ 4)	2 tablets	In two divided doses
2	8 – 14 ( $\pm$ 4)	4 tablets	In two divided doses
3	15 – 21 ( $\pm$ 4)	6 tablets	In two divided doses
4	22 – 28 ( $\pm$ 4)	8 tablets	In two divided doses
5	29 – 35 ( $\pm$ 4)	10 tablets	In three divided doses
6	36 – 42 ( $\pm$ 4)	12 tablets	In three divided doses

### **12.2 CONCOMITANT MEDICATION**

Current treatment with the following medications make patients ineligible for the study; clonidine, warfarin, monoamine oxidase inhibitors or modafinil (see Section 10.2 above). None of these medications may be commenced during the study.

## **13 INVESTIGATIONAL MEDICINAL PRODUCT**

### **13.1 NAME AND DESCRIPTION OF INVESTIGATIONAL MEDICINAL PRODUCT(S)**

The active ingredient in the IMP is Methylphenidate (the international non-proprietary name for  $\alpha$ -Phenyl-2-piperidineacetic acid methyl ester hydrochloride). Methylphenidate is licensed for use as a part of a comprehensive treatment programme for attention-deficit hyperactivity disorder (ADHD) in children aged 6 years of age and over when remedial

measures alone prove insufficient. Safety and efficacy of MPH have not yet been established in adults or the elderly.

Methylphenidate is licenced within the UK for ADHD in children and is a widely used medication. Following some concerns about possible adverse effects, the European Medicines Agency (EMA) completed a review of the safety of medicines containing methylphenidate in 2009. The Agency's Committee for Medicinal Products for Human Use (CHMP) concluded that the benefits of these medicines outweigh their risks when used to treat children aged six years and above and adolescents with attention deficit/hyperactivity disorder [33].

Methylphenidate is a Schedule 2 Controlled drug and the summary of drug arrangements will reflect regulations of controlled drug management to ensure correct storage, accountability and destruction requirements.

### **13.2 SUMMARY OF FINDINGS FROM NON-CLINICAL STUDIES**

Section 5.3 of the Summary of Product Characteristics [16] lists the pre-clinical safety data relating to methylphenidate.

In life-time rat and mouse carcinogenicity studies, increased numbers of malignant liver tumours were noted in male mice only. The significance of this finding to humans is unknown. Methylphenidate did not affect reproductive performance or fertility at low multiples of the clinical dose. Methylphenidate is not considered to be teratogenic in rats and rabbits. Foetal toxicity (i.e. total litter loss) and maternal toxicity was noted in rats at maternally toxic doses.

### **13.3 SUMMARY OF FINDINGS FROM CLINICAL STUDIES**

Methylphenidate is a central nervous system stimulant (psycho-stimulant). It is an inhibitor of catecholamine re-uptake and increases central dopamine and noradrenaline levels [20]. It is a short-acting drug with a half-life of two to three hours. It has been widely used for decades as a treatment for Attention Deficit Hyperactivity Disorder (ADHD) in children. In this population (and for this indication) it has been shown to be both safe and effective [21]. It has also been used in patients with cancer as a treatment for both depression and fatigue [22-24], but the evidence for its effectiveness for these indications in cancer patients is equivocal.

### **13.4 SUMMARY OF KNOWN AND POTENTIAL RISKS AND BENEFITS**

The full list of adverse effects of methylphenidate is detailed in the SPC and in Section 6.5 of the protocol (above).

A systematic review of psychostimulants for cancer-related fatigue reported that these drugs do not appear to cause major problems (adverse effects) in this group of patients [26]. This finding is supported by the results of a systematic review of safety concerns regarding the longer term use of methylphenidate [28]. The author of this review identified



26 trials and concluded that expected non serious adverse effects were minimal in short term use (up to 6-8 weeks of treatment). In the short term, methylphenidate was well tolerated and no serious side effects were observed. There was little information on long term safety. Methylphenidate was associated with a modest rise in blood pressure and heart rate. No studies were found that addressed the question of whether therapeutic use of methylphenidate ever leads to dependence. The danger for abuse is highest when taken for non-therapeutic reasons such as use as a performance enhancer [29]. It is therefore unlikely that addiction will be a significant risk in palliative care patients with advanced progressive cancer.

The potential benefits of methylphenidate relate to its potential to relieve cancer related fatigue. It is estimated there are currently two million people in the UK who are living with cancer or who are cancer survivors [10]. There were 161,823 deaths from cancer in the UK in 2012 [11]. The vast majority of cancer patients experience fatigue during the course of their illness [3-5] and particularly in the palliative phase [7]. Fatigue remains under-recognised and under-treated [8, 12]. People with advanced cancer want to maintain their quality of life for as long as possible and fatigue is known to detract significantly from this [4, 7, 9, 13-15]. Persistent fatigue may also affect patients' ability to maintain independence and may increase the costs of care and the burden on informal carers.

### **13.5 DESCRIPTION AND JUSTIFICATION OF ROUTE OF ADMINISTRATION AND DOSAGE**

The IMP is a tablet and will be taken orally. Since the IMP is not licensed for use as a treatment for cancer related fatigue, the dose schedule has been developed based on the published literature and expert opinion. The dose range in previous studies varied between 10mgs/day [52] and 54mgs/day [53]. The maximum daily dosage permitted for the licensed indication of methylphenidate for attention-deficit / hyperactivity disorder (ADHD) in children aged 6 years of age and over is 60mgs/day.

We have decided to individually titrate the dose of medication over a period of six weeks from a minimum of 5mgs twice a day up to a maximum of 20mgs three times a day.

### **13.6 DOSAGES, DOSAGE MODIFICATIONS AND METHOD OF ADMINISTRATION**

The dosage and dose modifications have been described in Sections 9.1.4; 9.2; 9.3 and 9.4

### **13.7 PREPARATION AND LABELLING OF INVESTIGATIONAL MEDICINAL PRODUCT**

Labelling of the investigational medicinal products will be in a blinded fashion and completed in accordance with the relevant EU GMP Annex 13. In order to maintain blinding, the packaging will be coded and both shelf life and storage conditions will be adjusted to maintain blinding. The investigational medicinal products will be packaged in Polyethylene bottles containing 42 tablets each.

### **13.8 DRUG ACCOUNTABILITY**

The IMP will be managed by Priment according to their SOPs. Patient packs will be stored in a local pharmacy, under the conditions stipulated by Priment, on behalf of the sponsor, and Schedule 2 Controlled drug regulations. IMP will be ordered from Priment on behalf of the Sponsor in accordance with an agreed schedule and a documented trial specific working procedure. The dispensing pharmacy (with the agreement of Priment, on behalf of the Sponsor) will be responsible for the destruction of unused and/or returned investigational medicinal products.

Full IMP accountability will be conducted during the trial, all IMPs that have been received from the manufacturer, to dispensing and drug returns will be logged in the accountability log held within the local pharmacy site file. A controlled drug register will be maintained with sufficient accountability as per regulations.

The IMP manufacturer will be responsible for QP release of all IMPs and it's shipment to trial sites. Secure courier services will be used as required. IMP shipment will have a temperature monitoring strip and will be accompanied by the relevant documentation that gives clear instructions on how to read the temperature and will allow the use only if no deviation occurred. These documents will be faxed or emailed back to the manufacturer to confirm receipt and quality of the IMP shipment (the original copy will be retained within the pharmacy file). In cases where the IMP shipping form indicates that the IMP was not stored correctly the product must not be used and the manufacturer is notified to organise a replacement.

All used/unused IMP will be collected from the patients by delegated site staff, who will then forward onto the corresponding research site Pharmacy for updating the drug accountability log in the pharmacy file. Drug destruction will occur once authorised by Priment that destruction can take place and the destruction of the IMP will be done in accordance with local pharmacy practice, and this will be documented accordingly.

#### **13.8.1 STORAGE AND HANDLING OF IMP**

Detailed instructions will be contained in the IMP management plan. IMP will be handled according to Schedule 2 Controlled drug regulations.

### **13.9 SOURCE OF IMPS INCLUDING PLACEBO**

The IMPs and placebo will be specifically prepared for this trial by WGK Consultancy Ltd, a UK third party manufacturer.

### **13.10 DOSE MODIFICATIONS**

Dose titration has been described in Section 9.1.4 and 9.2 (above).

Each week the dose of study medication may be titrated upwards or downwards depending upon efficacy and/or unwanted effects. If fatigue is not adequately controlled and there are no dose-limiting adverse effects, then the trial participant will be instructed

to increase by one dose level. If fatigue is adequately controlled and there are no dose-limiting adverse effects, then the trial participant will be instructed to remain at the same dose level. If there are dose-limiting adverse effects, then the trial participant will be instructed to reduce to the previous dose level (or stop study medication if only on level 1).

### **13.11 ASSESSMENT OF COMPLIANCE**

Compliance includes both adherences to IMP and Protocol study procedures.

Non-compliance to the Protocol study procedures will be documented on the deviation log by the investigator and reported to the Sponsor as agreed. Persistent noncompliance may lead the participant to be withdrawn from the study.

Compliance with taking the IMP will be assessed by performing pill counts at study visits in weeks 3, 6 and 9, and will be recorded on the CRF.

The study will be conducted in accordance with the current approved protocol, EU Good Clinical Practice (EU GCP), EU GCP and UK Regulations for CTIMPs (SI 2004/1031; as amended), Trust Information Governance Policy (or other local equivalent), the current Research Governance Framework, and Priment standard operating procedures.

Regular monitoring will be performed according to EU GCP. Data will be evaluated for compliance with the protocol and accuracy in relation to source documents. Following written standard operating procedures, the monitors will verify that the clinical trial is conducted and data are generated, documented and reported in compliance with the protocol, GCP and the applicable regulatory requirements. Priment will employ a contractor to perform monitoring, which will follow a plan drawn up by Priment, on behalf of the sponsor. The trial co-ordinator will be responsible for the monitoring of all sites.

Please see section 18.11 for information about procedures in the event of an overdose.

### **13.12 POST-TRIAL IMP ARRANGEMENTS**

No specific arrangements are in place for continuation of study medication. If patients would like to be prescribed methylphenidate then they will be assessed by the responsible clinician (usually a palliative care clinician) and a decision will be taken on the basis of individual clinical circumstances.

## **14 DATA MANAGEMENT**

All data will be collected and handled in accordance with the UK Data Protection Act 1998, Priment SOPs, UCL Information Security Policy, site Information Governance Policy and GCP. The CRF and trial specific documents held by the researcher will be stored securely with access restricted and limited to nominated research staff recorded on the delegation log.

### **14.1 CONFIDENTIALITY**

The Case Report Forms (CRFs) will not bear the participant's name. The participant's initials, date of birth and trial identification number, will be used for identification. All personal data collected will be managed according to Priment SOP Managing Personal Data.

### **14.2 DATA COLLECTION TOOLS AND SOURCE DOCUMENT IDENTIFICATION**

A data management plan will be created which will include details of the database, the data collection tools to be used in the trial and source document identification.

It will be the responsibility of the PI to ensure the accuracy of all data entered in the CRFs. Every effort will be made to maximise completeness of data. The delegation log will identify all those personnel with responsibilities for data collection and handling, including those who have access to the trial database.

### **14.3 TRIAL DATABASE**

The CRFs will be entered into a web-based clinical data management system, Red Pill, provided by Sealed Envelope through Priment.

Priment SOPs Validating Sealed Envelope Systems and Change Control for Sealed Envelope Systems will be followed to set up and manage changes to the trial database.

At the end of the trial, prior to analysis, Priment SOP Database Lock, Unlock and Closure will be followed.

### **14.4 DATA COLLECTION AND HANDLING**

All data will be collected and handled in accordance with Priment SOP Data Handling.

It will be the responsibility of the PI to ensure the accuracy of all data entered in the CRFs. Every effort will be made to maximise completeness of data. The delegation log will identify all those personnel with responsibilities for data collection and handling, including those who have access to the trial database.

### **14.5 DATA OWNERSHIP**

At the end of the trial, the data belong to UCL.

## **15 RECORD KEEPING AND ARCHIVING**

Archiving will be authorised by Priment following submission of the end of study report. Archiving will be conducted according to the relevant Priment SOP.

The Chief Investigator is responsible for the secure archiving of essential trial documents (for each site, if multi-site trial) and the trial database as per their trust policy. The sponsor and the investigator shall archive the content of the clinical trial master file for at least 25 years

after the end of the clinical trial. However, the medical files of subjects shall be archived in accordance with national law and site policy

Destruction of essential documents will require authorisation from Priment.

## **16 STATISTICAL CONSIDERATIONS**

Prof Nick Freemantle is the trial statistician who will be responsible for all statistical aspects of the trial from design through to analysis and dissemination.

Please note that a more detailed statistical analysis plan will be produced as a separate document at some point prior to the final analysis (as recommended by the ICHE9 guidelines). In this document, a more technical and detailed elaboration of the principal features stated in the protocol will be included. The plan will include detailed procedures for executing the statistical analysis of the primary and secondary outcomes and other data. The plan may be reviewed and possibly updated as a result of blind review of the data and will be finalized before breaking the blind. Formal records will be kept of when the statistical analysis plan was finalized as well as when the blind was subsequently broken.

### **16.1 STATISTICAL ANALYSES**

#### **16.1.1 SUMMARY OF BASELINE DATA AND FLOW OF PARTICIPANTS**

We will describe the characteristics of the screened population and those subsequently randomised. We will produce a consort flow diagram describing the flow of participants through the trial processes.

#### **16.1.2 PRIMARY OUTCOME ANALYSIS**

The primary analysis will be based on the intention to treat principle, using all available data. We will describe the difference in mean fatigue score, with 95% confidence intervals, derived from a generalised mixed model (with Gaussian error and an identity link function), including phase, treatment condition. Each participant will provide two values, one for baseline and one for follow up, grouped with a random intercept term. The denominator degrees of freedom for the test for treatment effect will be derived from the number of subjects.

In this trial it is expected that up to 25% of participants will be lost to attrition (death or withdrawal due to progressive disease) prior to the assessment of the primary outcome. In cases of missing data for the primary outcome, assessments at  $\pm 2$  weeks either side of the 6 week time point will be permitted. We will minimize loss to follow up, and have achieved very low rates in previous research studies.

### **16.1.3 SECONDARY OUTCOME ANALYSIS**

Secondary outcomes will be analysed using similar approaches. All principal analyses will be pre-specified in a statistical analysis plan and undertaken according to the standard operating procedures adopted by Priment Clinical Trials Unit, and in line with GCP.

### **16.1.4 SENSITIVITY AND OTHER PLANNED ANALYSES**

As we can reasonably assume that there is no relationship between mortality and the experimental condition, the principal analysis will be unbiased. However, in trials in oncology with a somewhat heterogeneous population, there is a considerable expectation of some degree of chance imbalance in the number of deaths per group. As we may also anticipate that the degree of fatigue will generally be higher in participants immediately before death, there is a clear risk of finding an apparent difference in fatigue due to differential and informative censorship. In order to address this risk in a supportive analysis, if drop out is greater among subjects in either arm we will undertake a joint model which incorporates the continuous outcome and the binomial alive / dead outcome, supporting the primary analysis.

As we will have several observations of fatigue score for most participants, we will additionally undertake an analysis incorporating all available data (extending the approach used for the primary analysis to one with multiple post randomisation observations per subject grouped as before using a random intercept term and appropriate denominator degrees of freedom). The results of these and other supportive analyses will be used to supplement our interpretation of the primary analysis.

### **16.2 INTERIM ANALYSIS**

There will be no interim analyses conducted with the exception of those required by the Data Safety and Monitoring Board (which will be addressed in a separate charter).

## **17 NAME OF COMMITTEES INVOLVED IN TRIAL**

### **17.1 TRIAL MANAGEMENT GROUP**

The MePFAC trial management group (TMG) will consist of the five co-applicants and the study manager. The TMG will meet (face-to-face or via teleconference) monthly, to direct the running of the study and prepare reports for the Health Technology Assessment (HTA). The TMG will meet regularly at minuted meetings to review adverse event logs, recruitment rates and all other aspects of the trial.

Prof Stone will have ultimate responsibility to deliver the research to high ethical and academic standards, on time, and within budget. The Study Manager will manage the study and will work with the research team at UCL. Prof Freemantle will direct the work of the trial statistician and will be responsible for statistical aspects of the trial. Prof King will provide overall trials advice and liaise closely with the Priment operations team. Prof Stone will be

responsible for the overall running of the study and will work closely with Natalia Lago (senior trial manager) at PRIMENT to oversee the work of the IT/database manager and QA manager. The PIs at each site will manage the local research nurses.

## **17.2 TRIAL STEERING COMMITTEE**

A Trial Steering Committee (TSC) will be established consisting of three members (a senior clinician who will be the independent chair, a statistician and a user representative). The TSC will meet six monthly during the study.

The role of the TSC will be to provide overall supervision for the study on behalf of the study sponsor and study funder and to ensure that the study is conducted to the rigorous standards set out in the Department of Health's Research Governance Framework for Health and Social Care and the Guidelines for Good Clinical Practice.

The main features of the TSC will be as follows:

- To provide advice, through its Chair, to the Chief Investigator(s), the Study Sponsor, the Study Funder, the Host Institution and the Contractor on all appropriate aspects of the trial
- To concentrate on progress of the study, adherence to the protocol, patient safety and the consideration of new information of relevance to the research question
- To consider the rights, safety and well-being of the study participants, which are the most important considerations and should prevail over the interests of science and society
- To ensure appropriate ethical and other approvals are obtained in line with the project plan
- To agree proposals for substantial protocol amendments and provide advice to the sponsor and funder regarding approvals of such amendments
- To provide advice to the investigators on all aspects of the study

## **17.3 DATA SAFETY AND MONITORING BOARD**

The TSC will advise on the composition of a Data Safety and Monitoring Board (DSMB). Terms of reference will be in place for each committee.

## 18 RECORDING AND REPORTING OF ADVERSE EVENTS AND REACTIONS

### 18.1 ADVERSE EVENT DEFINITIONS

Term	Definition
Adverse Event (AE)	Any untoward medical occurrence in a patient or clinical trial participant administered a medicinal product and which does not necessarily have a causal relationship with this treatment.
Adverse Reaction (AR)	Any untoward and unintended response in a patient or clinical trial participant to an investigational medicinal product which <b>is related</b> to any dose administered to that participant.  <i>This includes medication errors, uses outside of protocol (including misuse and abuse of product)</i>
Serious adverse event (SAE), serious adverse reaction (SAR) or unexpected serious adverse reaction	Any adverse event, adverse reaction or unexpected adverse reaction, respectively, that: <ul style="list-style-type: none"> <li>• results in death,</li> <li>• is life-threatening,</li> <li>• requires hospitalisation or prolongation of existing hospitalisation,</li> <li>• results in persistent or significant disability or incapacity, or</li> <li>• consists of a congenital anomaly or birth defect</li> </ul>
Important Medical Event	These events may jeopardize the participant or may require an intervention to prevent one of the above characteristics/consequences. Such events should also be considered 'serious'.
Unexpected adverse reaction	An adverse reaction the nature and severity of which is not consistent with the information about the medicinal product: <ul style="list-style-type: none"> <li>(a) in the case of a product with a marketing authorisation, in the summary of product characteristics for that product.</li> <li>(b) in the case of any other investigational medicinal product, in the investigator's brochure relating to the trial in question.</li> </ul>
SUSAR (Suspected Unexpected Serious Adverse Reaction)	Any SAR where the nature or severity of the event is not consistent with the applicable product information (e.g. IB for an unauthorised investigational product or SMPC for an authorised product).

### 18.2 RECORDING ADVERSE EVENTS

Adverse events will be recorded in the case report form following consent.



Clinically significant abnormalities in the results of objective tests will also be recorded as adverse events. If the results are not expected as part of disease or IMP, these will also be recorded as unexpected.

Adverse events (and their severity) will be recorded weekly on the case report form until each participant has stopped taking the trial medication.

All adverse events will be reportable to the Sponsor up to the last IMP administration.

### **18.3 ASSESSMENTS OF ADVERSE EVENTS**

Each adverse event will be assessed for severity. All Serious Adverse Events (SAE) will also be assessed for Causality and Expectedness (also see Section 18.4)

#### **A. SERIOUSNESS**

An event will be considered serious if it meets the definition for an SAE as defined in Section 18.1 “adverse event definition”.

#### **B. CAUSALITY**

The assessment of relationship of adverse events to the administration of IMP is a clinical decision based on all available information at the time of the completion of the case report form. The following categories will be used to define the causality of the adverse event:

Category	Definition
Definitely:	There is clear evidence to suggest a causal relationship, and other possible contributing factors can be ruled out.
Probably:	There is evidence to suggest a causal relationship, and the influence of other factors is unlikely
Possibly	There is some evidence to suggest a causal relationship (e.g. the event occurred within a reasonable time after administration of the trial medication). However, the influence of other factors may have contributed to the event (e.g. the patient’s clinical condition, other concomitant events).

Category	Definition
Unlikely	There is little evidence to suggest there is a causal relationship (e.g. the event did not occur within a reasonable time after administration of the trial medication). There is another reasonable explanation for the event (e.g. the patient's clinical condition, other concomitant treatments).
Not related	There is no evidence of any causal relationship.
Not Assessable	Unable to assess on information available.

### C. EXPECTEDNESS

Category	Definition
<i>Expected</i>	An adverse event that is which is consistent with the information about the IMP listed in SmPC.
<i>Unexpected</i>	An adverse event which is not consistent with the information about the IMP listed in the SmPC if licensed IMP.

The reference document to be used to assess expectedness against the IMP is Section 4.8 "undesirable effects" of the SmPC for methylphenidate (16/01/2015). The most up-to-date version of the SmPC will be used during the trial.

### D. SEVERITY

Category	Definition
Mild	The adverse event does not interfere with the volunteer's daily routine, and does not require intervention; it causes slight discomfort
Moderate	The adverse event interferes with some aspects of the volunteer's routine, or requires intervention, but is not damaging to health; it causes moderate discomfort
Severe	The adverse event results in alteration, discomfort or disability which is clearly damaging to health

#### **18.4 PROCEDURES FOR RECORDING AND REPORTING SERIOUS ADVERSE EVENTS**

All serious adverse events will be recorded in patient medical notes, CRFs, and the Priment SAE log. The SAE log will be reported to Priment regularly. All serious adverse events will be reported to the sponsor on an SAE form. The Chief or Principal Investigator will complete the sponsor's serious adverse event form and the form will be emailed to [primentsafetyreport@ucl.ac.uk](mailto:primentsafetyreport@ucl.ac.uk) within 24 hours of becoming aware of the event. The Chief or Principal Investigator will respond to any SAE queries raised by the sponsor as soon as possible.

#### **18.5 FOLLOW-UP OF PARTICIPANTS AFTER ADVERSE EVENTS**

After an adverse event participants will be followed up by the local clinical team / PI. Adverse events will be recorded up to the last dose of IMP has been administered.

Any SUSAR related to the IMP will need to be reported to Priment irrespective of how long after IMP administration the reaction has occurred.

#### **18.6 NOTIFICATION OF DEATHS**

All deaths will be reported to Priment irrespective of whether the death is related to disease progression, the IMP, or an unrelated event. Deaths will be reported on the SAE form.

#### **18.7 REPORTING SUSARS**

Priment will notify the REC and MHRA of all SUSARs. SUSARs that are fatal or life-threatening will be notified to the MHRA and REC within 7 days after Priment has learned of them. Other SUSARs will be reported to the REC and MHRA within 15 days after Priment has learned of them.

For details about the procedure for emergency unblinding see Section 11.7.

#### **18.8 DEVELOPMENT SAFETY UPDATE REPORTS**

Priment will provide the REC and the MHRA with Development Safety Update Reports (DSUR) which will be written in conjunction with the trial team and Priment. The report will be submitted within 60 days of the Developmental International Birth Date (DIBD) of the trial each year until the trial is declared ended.

#### **18.9 ANNUAL PROGRESS REPORTS**

An annual progress report (APR) will be submitted to the REC within 30 days of the anniversary date on which the favourable opinion was given, and annually until the trial is declared ended.

The chief investigator will prepare the APR.

### **18.10 PREGNANCY**

All pregnancies within the trial (either the trial participant or the participant's partner) will be reported to the Chief Investigator and Priment using the relevant Pregnancy Reporting Form within 24 hours of notification.

Pregnancy will not be considered an AE unless a negative or consequential outcome is recorded for the mother or child/foetus. If the outcome meets the serious criteria, this would be considered an SAE.

If a trial participant reports that they are pregnant then they will be withdrawn from the study and the trial medication will be stopped. The GP (and/or obstetrician) will be informed that the pregnancy was conceived while the participant (or their partner) was a participant in a CTIMP. No specific additional monitoring or management of the pregnancy will be required, but the outcome of the pregnancy will be recorded. No further follow up will be required.

### **18.11 OVERDOSE**

An overdose may be revealed by communication volunteered or elicited from the trial participant, or may be detected when pills are counted at the 3, 6 and 9 week assessments. If an overdose occurs this should be recorded on the deviation log as an adverse reaction. If the event is serious then it will be reported as a Serious Adverse Reaction following the above guidance for SAE reporting.

Detection of an overdose does not necessarily result in participant withdrawal from the study, unless associated with an event which necessitates withdrawal. In other cases patients who have overdosed will be directed to take the correct amount of study medication and will remain in the study and analysed on an "intention to treat" basis.

### **18.12 REPORTING URGENT SAFETY MEASURES**

If any urgent safety measures are taken, the PI/Priment will immediately and in any event no later than 3 days from the date the measures are taken, give written notice to the MHRA and the relevant REC of the measures taken and the circumstances giving rise to those measures. Priment SOPs will be followed.

### **18.13 NOTIFICATION OF SERIOUS BREACHES TO GCP AND/OR THE PROTOCOL**

A "serious breach" is a breach which is likely to affect to a significant degree –

- (a) the safety or physical or mental integrity of the participants of the trial; or
- (b) the scientific value of the trial.

Priment will notify the licensing authority in writing of any serious breach of –

(a) the conditions and principles of GCP in connection with that trial; or (b) the protocol relating to that trial, as amended from time to time, within 7 days of becoming aware of that breach.

The sponsor will be notified by Priment immediately of any case where the above definition applies during the trial conduct phase. Priment's SOP on 'serious breaches' will be followed with regards to reporting to REC and MHRA.

## **19 MONITORING AND INSPECTION**

A monitoring plan will be established for the trial based on the risk assessment. The trial will be monitored with the agreed plan.

The investigator(s)/ institution(s) will permit trial-related monitoring, audits, REC review, and regulatory inspection(s), providing direct access to source data/documents. Trial participants are informed of this during the informed consent discussion. Participants will consent to provide access to their medical notes.

## **20 ETHICS AND REGULATORY REQUIREMENTS**

Priment will work with the Chief Investigator to ensure that the trial protocol, patient information sheet, consent form, GP letter and submitted supporting documents have been approved by the appropriate regulatory body (MHRA in UK) and a main research ethics committee, prior to any participant recruitment. The protocol and all agreed substantial protocol amendments, will be documented and submitted for ethical and regulatory approval prior to implementation.

Before any site can enrol participants into the trial, the Chief Investigator/ Principal Investigator or designee will apply for local confirmation of capacity and capability. It is the responsibility of the Chief Investigator/ Principal Investigator or designee at each site to ensure that all subsequent amendments gain the necessary approval. This does not affect the individual clinician's responsibility to take immediate action if thought necessary to protect the health and interest of individual patients (see section for reporting urgent safety measures).

Within 90 days after the end of the trial, the CI/Priment will ensure that the main REC and the MHRA are notified that the trial has finished. If the trial is terminated prematurely, those reports will be made within 15 days after the end of the trial.

The CI will supply Priment with a summary report of the clinical trial, which will then be submitted to the MHRA and main REC within 1 year after the end of the trial.

## **20.1 PUBLIC AND PATIENT INVOLVEMENT**

Patients and public were involved at an early stage in our design and planning. A preliminary draft of the 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 kept the patient burden to a minimum. We carefully selected outcome measures to be suited and well-used in this population. We are mindful of making sure that the patient information leaflets provide a clear description of the potential side-effects of study medications. Service users were supportive of the plan to include weekly telephone contact during the study.

Two service user representatives (from Marie Curie Expert Voices) have been recruited and will be fully involved with the trial processes, including the development of patient information sheets. One representative will be a research team member and will attend regular Trial Management Group meetings to discuss issues arising and ensure smooth running of the study. The representative will be asked to help disseminate the study results via patient groups, conferences and co-authorships.

Members of Marie Curie Expert Voices are offered the same induction and support as all other volunteers for the charity and can access additional specific training dependent upon their individual needs.

## **21 FINANCE**

This study is funded by the NIHR Health Technology Assessment. Some staff working on the project are supported by Marie Curie funding and infrastructure support.

## **22 INSURANCE**

University College London holds insurance against claims from participants for injury caused by their participation in the clinical trial. Participants may be able to claim compensation if they can prove that UCL has been negligent. However, as this clinical trial is being carried out in an NHS organisation or an organisation contracted to the NHS, the NHS organisation or an organisation contracted to the NHS continues to have a duty of care to the participant of the clinical trial. University College London does not accept liability for any breach in the NHS organisation or an organisation contracted to the NHS's duty of care, or any negligence on the part of NHS organisation employees. This applies whether the NHS organisation is an NHS Trust or otherwise.

Participants may also be able to claim compensation for injury caused by participation in this clinical trial without the need to prove negligence on the part of University College London or another party. Participants who sustain injury and wish to make a claim for compensation should do so in writing in the first instance to the Chief Investigator, who will pass the claim to the Sponsor's Insurers, via Priment.

Organisations selected to participate in this clinical trial shall provide clinical negligence insurance cover for harm caused by their employees and a copy of the relevant insurance policy or summary shall be provided to University College London, upon request.

## **23 PUBLICATION POLICY**

Study results will be published in peer-reviewed, indexed, journals using an open access format, and the results will be presented at academic conferences. Authorship eligibility will be in accordance with The International Committee of Medical Journal Editors. All proposed publications will be accord with UCL publication policy.

## **24 STATEMENT OF COMPLIANCE**

The trial will be conducted in compliance with the approved protocol, the UK Regulations, EU GCP and the applicable regulatory requirement(s).

## 25 REFERENCES

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