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 13.0 01-Mar-2021
Sponsor	UCL JRO
Sponsor protocol number	15/0592
Funder(s)	NIHR HTA
EudraCT number	2017-001950-33
IRAS ID	215297
ISRCTN number	79478762
Active IMP(s)	methylphenidate
Phase of trial	III
Sites	Multiple sites
Chief Investigator	Prof. Patrick Stone Marie Curie Palliative Care Research Department Division of Psychiatry, UCL 6th Floor Maple House 149 Tottenham Court Road London W1T 7NF
Sponsor Representative	Anne Marie Downey PRIMENT Clinical Trials Unit Research Department of Primary Care and Population Health UCL Medical School, Royal Free Campus London NW3 2PF

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: 01-Mar-2021

Sponsor Representative: Anne Marie Downey

Sign: 

Date: 01-Mar-2021

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	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. 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. 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.
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	1. Section 3 (Trial personnel); details of IMP manufacturer have been entered. 2. Summary; has been amended to refer to 5 (rather than 4) pilot sites. 3. Section 8.1.1; a ± 2 week window for collection of the primary outcome has been introduced. 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. 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. 6. Section 9.1.4 (Dose titration); this section has been modified to include collection of data about concomitant medication. 7. Section 9.4 (Tapering); the tapering schedule has been altered to allow longer period on lower doses prior to stopping. 8. Section 11.5.1 (Patient identifiers and contact details); now includes mention that data on ethnicity will be collected from study participants.

		9. Section 11.8 (Treatment procedures); the flexibility around the weekly assessments has been increased from ±3 to ±4 days. 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. 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. 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. 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. 14. Section 12.1 (Treatment of participants); the table showing the standard titration schedule has been amended to be consistent with Section 11.8. 15. Section 13.9 (Source of IMPs including placebo); this section has been updated to include the name of the manufacturer. 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. 17. Sections 14.3 (Trial database) and Section 14.4 (Data collection and handling) have been added to the protocol. 18. Section 16 (Statistical considerations); variables has been changed to outcomes. 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 6 weeks are missing. 20. Section 16.1.3 (Secondary outcome analysis); variables has been changed to outcomes. 21. Section 17.1 (Trial Management Group); junior statistician has been changed to trial statistician.
5.0	08 –Dec-2017	Added in 2 more side-effects for consistency with Medikinet SmPC.
6.0	30-Jan-2018	Changes made in response to MHRA review.

		1. Section 4 (Summary) updated to conform with other changes made to the protocol (see below). 2. Section 5 (Trial flow chart) updated to conform with other changes made to the protocol (see below). 3. Section 6.5.2.10 (Pregnancy and lactation); Section 10.2 (Exclusion criteria); Section 11.3 (Screening period); Section 11.9 (Table of study assessments) have been altered to clarify that pregnancy is an exclusion criterion but that females or male partners of females of childbearing potential are not excluded from the study provided that they agree 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. It has also been indicated that females of child-bearing potential will have a pregnancy test scheduled seven days or fewer prior to first dose administration and at every physical visit during the study. 4. Section 6.5.2.12 (Avoiding use in patients with thyrotoxicosis); this is a new section of the protocol which specifies that patients with clinical hyperthyroidism will be excluded from the study. Other patients must have a thyroid function test result available demonstrating no evidence of hyperthyroidism in the three months prior to administration of the first dose of study medication. 5. Section 8.2 (secondary outcomes); Section 9.1.3 (Duration of treatment); Section 9.1.4 (Dose titration); Section 9.4 (Tapering) Section 9.5 (Trial schematic); Section 11.8 (Treatment procedures); Section 11.9 (Table of study assessments) and other relevant parts of the text have all been amended to indicate that the last face-to-face visit will now occur at week 10, and that an additional telephone assessment will now occur at week 9. 6. Section 10.2 (Exclusion criteria); in addition to the changes described above related to pregnancy, the exclusion criteria have been amended to indicate that a white blood count less than 1.5 x 10^9/litre; or an AST or ALT or ALP or GGT > 2 x ULN or bilirubin > 1.5 x ULN; will result in a patient being ineligible for the study. In addition any evidence of severe or uncontrolled infection that in the view of the investigator makes it undesirable for the patient to participate in the trial will result in exclusion. Patients with clinical hyperthyroidism or thyrotoxicosis will be excluded. Patients must have a thyroid function test (T4 and TSH) showing no evidence of hyperthyroidism in three months prior to first dose administration of study medication.

		7. Section 11.2 (Consent for screening) has been amended to indicate that if no recent thyroid function test result is available (within 3 months of screening) then a fresh blood specimen will be obtained. 8. Section 11.3 (Screening period) and Section 11.10.1 (Laboratory procedures) have been amended to specify what measures are included in the FBC and biochemistry, and to include the requirement for a thyroid function test. When relevant blood tests are available from within the previous two weeks (full blood count and biochemistry) or within previous three months (thyroid function tests), no further blood tests will be necessary. 9. Section 11.7.1 (Emergency unblinding) has been amended to make it clear that the investigator cannot be required to discuss unblinding if he or she feels that emergency unblinding is necessary. 10. Section 11.9 (Table of study assessments) has been amended to indicate that thyroid function tests are required. 11. Section 11.12.3 (Withdrawal of individual participants at their own request) has been amended to make it clear that if a participant withdraws from the study they will be asked to attend at least one face-to face meeting (one week after cessation of the study therapy) at which, fatigue, adverse events, blood pressure and pulse will be recorded. 12. Section 11.12.4 (Distinction between stopping study IMP and withdrawal from the study) have been amended to indicate that participants who stop taking the study medication will remain in the study for the full ten week period, unless they ask to be withdrawn (see 11.12.3 above). They will also be asked to attend at least one face-to face meeting (one week after cessation of the study therapy) at which, fatigue, adverse events, blood pressure and pulse will be recorded. 13. Section 11.12.5 (Withdrawal due to the inability to tolerate the lowest dose of study medication) and Section 11.12.6 (Withdrawal of individual participants due to adverse effects) have been amended to indicate that treatment will be discontinued for any patient who develops an SAE, or who develops increased frequency or new onset of seizures; or who develops suicidal tendencies or other psychiatric conditions; or who becomes pregnant. 14. Section 11.12.7 (Withdrawal of individual participants due to pregnancy); a new section has been included in the protocol to indicate that if a trial participant reports that they are pregnant the

		trial medication will be stopped, but they will remain on study follow-up. 15. Section 18.4 (Procedures for reporting and recording serious adverse events) has been amended to indicate that the responsibility to inform the sponsor of an SAE applies to any member of the study team within 24 hours of becoming aware of the event.
7.0	19-Mar-2018	Changes made to protocol following feedback from Trial Steering and Data Monitoring committees and from trial collaborators. 1. Section 4 (Summary); an omission has been corrected regarding the frequency with which secondary outcomes will be measured (at 3, 6 and 10 weeks, rather than just at 3 and 10 weeks). 2. Section 6.5.1.13 (Skin and subcutaneous tissue disorders) was amended (in version 5) by the inclusion of an additional side-effect with unknown frequency (dry skin) in order to be consistent with the Medikinet SmPC. However the amendment was not detailed in the Version History table at that time and thus has been included here for completeness. 3. Section 6.5.1.16 (Reproductive system and breast disorders) was amended (in version 5) by the inclusion of additional side-effects with unknown frequency (priapism, erection increased and prolonged erection) in order to be consistent with the Medikinet SmPC. However the amendment was not detailed in the Version History table at that time and thus has been included here for completeness. 4. Section 8.2 (Secondary outcomes) has been altered on the advice of the TSC to make it clearer that FACIT-F will be analysed at other time points (as well as at 6 weeks), as part of the assessment of secondary outcomes. The reference to measuring the satisfaction of carers was also removed on the advice of the TSC as this phrase had been left in the protocol in error from a previous version. 5. Section 8.2.1.5 (Satisfaction of patients and carers); this title has been corrected by removing “and carers”. Following advice from the TSC, the GBS has been changed from a 7-point score to a five-point score and the supporting references have been accordingly amended. 6. Section 8.3.1 (Sample size calculation) has been altered to remove reference to a Global Benefit Score (GBS) to avoid confusion with the GBS score used as a measure of patient satisfaction in this study. 7. Section 9.1.4 (Dose titration); the list of concomitant medications has been modified to make it clear that, “this will include the recording of any non-drug treatments that are specifically directed at relieving fatigue (e.g. blood transfusion)”. In addition the section on the GBS has been amended in order to harmonise with Section 8.2.1.5.

		8. Section 9.1.4.1 (Responsibility for dose titration) has been modified to make it clear that dose titration can also be undertaken by another physician delegated by the PI. The dose titration instructions will be communicated to the patient by telephone and also either by text message (if patient agrees) or by a letter sent by first class mail. 9. Section 10.1 (Inclusion criteria); an error in the duration of the study was corrected (from 9 weeks' to 10 weeks' duration). 10. Section 11.1 (Participant identification); this has been amended to state that "a video will be produced to complement the information provided in the Patient Information Sheet". 11. Section 11.2 (Consent for screening); this section has been modified by addition of "or delegate". 12. Section 11.7.1 (Emergency unblinding) has been amended to state that "Trial participants will be provided with a card which can be given to attending medical staff and which explains whom to contact in an emergency". 13. Section 11.12.6 (Withdrawal of individual participants due to adverse events); for consistency the phrase "mild or moderate side-effects" has been replaced with "dose-limiting side-effects". 14. Section 18.2 (Recording adverse events) has been amended to clarify that recording of adverse events occurs after randomisation rather than after consent. The sentence, "If the results are not expected as part of disease or IMP, these will also be recorded as unexpected" has been removed. 15. Section 18.3C (Expectedness) was amended (in version 5) by clarifying that the reference document to be used to assess expectedness against the IMP is Section 4.8 "undesirable effects" of the SmPC for methylphenidate (January 2017). However the amendment was not detailed in the Version History table at that time and thus has been included here for completeness. 16. Section 18.10 (Pregnancy) has been amended to clarify that if patients become pregnant then they will be withdrawn from the study.
8.0	28-Oct-2018	Changes made to the protocol after consultation with NIHR HTA in response to below expected accrual to the study during first few months of the pilot phase. 1. Front page; name and contact details of Sponsor's Representative have been changed to Anne Marie Downey. 2. Section 3 (Trial personnel); name and contact details of Sponsor's Representative have been changed to Anne Marie Downey. 3. Section 4 (Summary) has been amended to reflect changes elsewhere in the protocol (see below). 4. Section 5 (Trial flow chart) has been amended to reflect changes elsewhere in the protocol (see below). 5. Section 6.5.2.1 (Cardiovascular status) has been amended to reflect changes in exclusion criteria (see Section 10.2). This now

		includes a statement that, "In the context of a palliative treatment for advanced incurable cancer in adults a more pragmatic approach is judged to be justified. The risk benefit balance is somewhat different to that of a paediatric population given that many of these patients will have had some past history of heart failure, angina or myocardial infarction, but at the time of recruitment to the study will have these conditions currently well managed and stable". The text has been changed to indicate that it is only patients with *uncontrolled* heart failure, *uncontrolled* angina, or myocardial infarction (*within last one year*) who will be excluded. 6. Section 6.5.2.2 (Cerebrovascular disorders) has been amended to reflect changes in exclusion criteria (see Section 10.2). This now includes a statement that, "The data supporting these cerebrovascular contraindications are based on the licensed use of methylphenidate in children and adolescents and therefore, exclusion in children is recommended. However in the context of a palliative treatment for advanced incurable cancer a more pragmatic approach is proposed, as the risk benefit balance is somewhat different to that of a paediatric population, and many palliative care patients may have had pre-existing cerebrovascular conditions or risk factors that are well managed and/or stable". The text has been changed to indicate that it is only patients who have had a stroke (*within last one year*) who will be excluded. 7. Section 6.5.2.5 (Abuse, misuse and diversion) has been amended to reflect changes in exclusion criteria (see Section 10.2). Rather than excluding patients with any history of drug or alcohol abuse, the text has been amended to indicate that only patients with a history of drug or alcohol dependency *within the last one year* will be excluded. This has been justified on the basis that, "It is recognised that a one year limit on past substance abuse is relatively short. However, given the limited longevity of the patient population, that the dose of study medication is being titrated weekly, that all participants are being weaned off the medication before the end of the trial and that palliative care patients are routinely administered drugs with far higher risks of dependence (e.g. opioids) we believe that a one year limit is reasonable". 8. Section 6.5.2.7 (Renal and Hepatic insufficiency) has been amended to only refer to renal insufficiency and to reflect changes in exclusion criteria (see Section 10.2). The text has been amended to include the information that, "the SPC reports that haematuria is an uncommon side effect (≥ 1/1000 to <1/100) but does not report any other effects on the renal or urinary systems". The rationale for reducing the eGFR level that results in exclusion to <45mls/min is that prescribing information for methylphenidate notes that, "renal insufficiency is expected to have minimal effect on the pharmacokinetics of methylphenidate

		since less than 1% of a radio-labeled dose is excreted in the urine as unchanged compound, and the major metabolite (ritalinic acid), has little or no pharmacologic activity". The protocol has therefore been amended to state that we will exclude patients, "with an estimated glomerular filtration rate [eGFR] of <45 ml/minute per 1·73 m^2. The rationale for this limit is based on the fact that many elderly palliative care patients have mild/moderate renal impairment but are routinely prescribed other drugs for which caution should be exercised (e.g. opioids). The dose of methylphenidate in this study is being individually titrated, which reflects the way that this medication would be prescribed in clinical practice in the circumstances of impaired renal function. The starting dose is low and, in patients with renal impairment, the local PI will individually adjust the dose; either titrating upwards slowly according to response/adverse effects, or staying at the lowest dose level". 9. Section 6.5.2.8 (Hepatic insufficiency); this section has been newly added. The text has been altered to state that, "The SPC notes that, there is no experience with the use of methylphenidate in patients with hepatic insufficiency. The SPC reports that elevation in hepatic enzymes in response to methylphenidate is uncommon (≥ 1/1000 to <1/100), and that abnormal liver function or hepatic coma are very rare (< 1/10,000). Prescribing information for methylphenidate notes that, "hepatic insufficiency is expected to have minimal effect on the pharmacokinetics of methylphenidate since it is metabolized primarily to ritalinic acid by non-microsomal hydrolytic esterases that are widely distributed throughout the body". *In this study the risk associated with using MPH in patients with hepatic insufficiency will be minimised* by excluding patients with severe liver impairment (as judged by the results of clinical biochemistry tests). We will exclude patients who have AST or ALT or GGT > 2 x ULN or bilirubin > 1.5 x ULN. Patients with abnormal ALP (in the absence of rises in AST, ALT or Bilirubin) will not be excluded from this study, as patients with advanced cancer often have a raised Alkaline Phosphatase (ALP) because of metastatic bone (rather than metastatic liver) disease". 10. Section 8.3.2 (Planned recruitment rate) has been amended to reflect newly agreed targets with NIHR. 11. Section 9.2 (Criteria for dose escalation) has been amended to accommodate those circumstance when participants experience adverse effects that prevent an increase in dose, but which are not judged by the PI to necessitate a reduction in dose. 12. Section 9.6 (Recruitment) has been amended to reflect changes described elsewhere in the protocol. 13. Section 10.1 (Inclusion criteria); the prognosis requirement (2-12 months) has been removed.

		14. Section 10.1 (Inclusion criteria); the requirement to be "under the care of a specialist palliative care team" has been replaced with the requirement to be, "receiving generalist or specialist palliative care". 15. Section 10.2 (Exclusion criteria); the cardiovascular exclusion criteria have been altered so that it is explicit that it is only patients with uncontrolled heart failure or angina who are excluded, and patients with a recent history (within last six months) of myocardial infarction. 16. Section 10.2 (Exclusion criteria); the cerebrovascular exclusion criteria have been altered to clarify that it is only patients with a recent history of stroke (within last six months), or with known high risk factors for cerebrovascular disorders who are excluded. 17. Section 10.2 (Exclusion criteria); the minimum eGFR permitted for study entry has been reduced from 60mls/min per 1·73 m^2 to 45mls/min per 1·73 m^2. 18. Section 10.2 (Exclusion criteria); the alkaline phosphatase (ALP) exclusion criterion has been removed. 19. Section 10.2 (Exclusion criteria); the requirement to exclude inpatients in hospitals or hospices has been removed. 20. Section 10.2 (Exclusion criteria); the exclusion criterion relating to substance or alcohol abuse has been modified to state, "current or previous substance or alcohol dependency within the last one year". 21. Section 11.1 (Participant identification) has been amended to reflect changes described elsewhere in the protocol. 22. Section 11.3 (Screening period) has been amended to reflect changes described elsewhere in the protocol. 23. Section 11.9 (Table of study assessments) has been amended because a few formatting errors had been detected in the previous protocol version, which made the Table difficult to interpret. 24. Section 11.12.1 (Internal pilot) has been amended to reflect the changes in accrual rates agreed with the NIHR. 25. Section 11.12.5 (Withdrawal due to inability to tolerate the lowest dose of study medication) has been amended to make it explicit that participants who reduce from Step 1 to Step 0 can be re-started on the medication during the titration phase.
9.0	20-May-2019	Changes made to protocol following feedback from Trial Steering and Data Monitoring committees and from trial collaborators. 1. Correction of formatting and spelling errors throughout the document. 2. Version History (Notes on v8.0, bullet point 15); in Protocol v8.0, the exclusion criteria (section 10.2) were updated to state that the definition for a recent history of myocardial infarction was 'within the last one year'. However, the Version History of v8.0 incorrectly noted that section 10.2 had been updated to state this definition as 'within the last 6 months'. Thus for completeness we are noting

		here that in Version 8.0 of this protocol, the definition of a recent myocardial infarction was updated to be 'within the last one year'. 3. Section 2 (List of abbreviations); the following abbreviations were added: blood pressure (BP), central nervous system (CNS), Hospital Anxiety and Depression Scale (HADS), Monoamine Oxidase (MAO), Minimal Clinically Important Difference (MCID) 4. Section 3 (Trial Personnel); the name and contact details of Dr Elli Enayat (Trial Manager); Dr Louise Marston (Statistician); Laura Hennelly (Research Nurse); Munirah Islam (Clinical Trial Practitioner) and Peter Buckle (Patient and Public Representative) have been added 5. Section 4 (Summary); the estimated trial duration was amended (in version 8.0) from 28 months to 42 months. However, the amendment was not detailed in the Version History table at that time and thus has been included here for completeness. 6. Section 4 (Summary); Section 8.3.2 (Planned recruitment rate); Section 9.6 (Recruitment); the total number of sites was changed from 17 to 20, to reflect the changes to total site numbers agreed with the NIHR in May 2019. 7. Section 5.0 (Trial flow chart); week of pre-screening/screening was changed from -1 to -2 for consistency with the timings shown in Section 11.9 (Table of study assessments). The lists of assessments carried out at each time point were also updated to more accurately reflect the time-points for each assessment as listed in Section 11.9 (Table of study assessments) and to harmonise with changes to the rest of the protocol (see below) 8. Section 6.5.2 (How main sources of risk will be minimised); the statement 'to exclude patients with severe untreated hypertension' was changed to 'to exclude patients with severe hypertension' to more accurately reflect exclusion criteria in 10.2. 9. Section 6.5.2 (How main sources of risk will be minimised); the statement 'all study participants will be reviewed by a study nurse or doctor on a weekly basis for the duration of the trial' was changed to reflect that it will be a 'team member' who will review study participants on a weekly basis, and the wording was updated throughout the section to reflect this 10. Section 6.5.2 (How main sources of risk will be minimised); the time points for BP and pulse assessment was corrected to 3,6 and 10 weeks (from 3, 6 and 9 weeks). 11. Section 6.5.2.7 (Renal insufficiency); Section 6.5.2.8 (Hepatic insufficiency); in-text references were changed to citations and full reference was moved to reference list. 12. Section 6.5.2.11 (Pregnancy and lactation); the clause (at the screening visit and again at the baseline visit, if it takes place more than 7 days after the last pregnancy test) was added to clarify exactly when pregnancy tests should be conducted for women of childbearing potential.

		13. Section 8.2 (Secondary outcomes) and section 8.2.1.6 (Need for other medication) were updated to clarify that need for other medication should be assessed weekly (not every 6 weeks) 14. Section 8.3.2 (Planned recruitment rate); this section was updated to reflect changes to the planned recruitment strategy approved by the NIHR in May 2019. The total number of sites has been changed from 17 to 20. The estimated recruitment rate when all 20 sites are opened has been changed to 0.85 from 0.88. The planned recruitment rate table has been deleted because it no longer reflects the revised recruitment targets agreed with the NIHR. It has been replaced by the sentence: "We anticipate opening all 20 sites by October 2019 and reaching the target total recruitment of 230 patients by June 2020." 15. Section 9.1.3 (Duration of treatment); 'by a research nurse' was deleted from the description of who should make the weekly telephone consultation to harmonise with the rest of the protocol 16. Section 9.1.4 (Dose titration); the sentence "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 specialty" was replaced with: "The telephone calls will be made by research staff at UCL or at the site from which they were recruited. The research staff responsible for making the telephone calls will have experience of oncology / palliative care or an associated specialty." Wording throughout this section was updated to reflect that research staff, rather than specifically research nurses, will make the telephone calls 17. Section 9.2 (Criteria for dose escalation); the dosing schedule in the standard titration schedule table was changed from ± 3 to ± 4 days. Explanations on how many pills should be take and what time(s) of day at each dose level have also been added for clarity: • Dose level 1: In two divided doses (morning and lunch) • Dose level 2: In two divided doses (morning and lunch) • Dose level 3: In two divided doses (morning and lunch) • Dose level 4: In two divided doses (morning and lunch) • Dose level 5: In three divided doses (4 tablets in the morning, 3 tablets at lunch and 3 tablets in early afternoon before 4pm) • Dose level 6: In three divided doses (morning, lunch and early afternoon before 4pm) 18. Sections 9.3 (Maintenance (or reduction)); 11.1 (Participant identification); 11.2 (Consent for screening) and 11.8 (Treatment procedures) were updated to reflect that a member of research team / study staff, rather than specifically a research nurse, would make the weekly telephone calls to participants 19. Section 9.4 (Tapering); the standard tapering schedule table was amended to include ± 4 days

		20. Section 9.5 (Trial schematic); the week of pre-screening was changed from -1 to -2, and screening was moved from wk 0 to wk -2, to more accurately reflect the time-points shown in section 11.9 (Table for study assessments) and 5.0 (Trial flow chart). 21. Section 10.2 (Exclusion criteria); the cerebrovascular criteria have been altered to clarify that it is only patients with a recent history of stroke (within last one year) or with pre-existing cerebrovascular disorders, cerebral aneurysm, vascular abnormalities including vasculitis or known high risk factors for cerebrovascular disorders who are excluded. This was incorrectly recorded as 'patients with a recent history of stroke (within last 6 months)' in v8.0 22. Section 10.2 (Exclusion criteria); criterion 22 was clarified to explain that patients who have participated in another research study involving any investigational agents within four weeks prior to registration should be excluded (changed from 'patients currently participating' in a research study involving an investigational agent) 23. Section 10.2 (Exclusion criteria); criterion 23 was changed from 'English not first language or unable to read English' to 'Insufficient English language skills to understand study documentation and complete assessments' 24. Section 10.2 (Exclusion criteria); the clause 'and that the expected prognosis is 2 – 12 months' was deleted from the text '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' as prognosis is no longer an exclusion criterion. 25. Section 11 (Study procedures); wording was updated throughout to clarify that a pregnancy test should be conducted at the screening visit (for women of child bearing potential) and again at the baseline visit, if it takes place more than 7 days after the last pregnancy test 26. Section 11.9 (Table of assessments); the formatting of the baseline column of the table was amended for clarity, and markers for 'perception of efficacy' and 'adverse event review' were removed from the baseline assessment column. A footnote was added to the pregnancy assessment at baseline, to clarify that the pregnancy test should be taken again if the last test was >7 days prior to baseline assessment/first dose administration (to harmonise with rest of protocol) 27. Section 11.12.1 (Internal pilot); the planned recruitment rate has been changed to 0.85 from 0.88 to reflect the new target recruitment rate agreed with NIHR in May 2019 28. Section 13.11 (Assessment of compliance) and Section 18.11 (Overdose) were updated to clarify that pill counts to assess

		compliance should be carried out at weeks 3, 6 and 10, not at weeks 3, 6 and 9. 29. Section 25 (References); the format and numbering of the references has been updated in the reference list and throughout the protocol to correctly reflect the order that citations appear in.
10.0	22-Aug-2019	1. Cover page; the ISRCTN number for the trial (79478762) has been added 2. Section 2 (List of abbreviations) has been updated to include Eastern Cooperative Oncology Group (ECOG) performance status scale. 3. Section 5 (Trial flow chart); section 9.6.1 (Screening); section 11.3 (Screening period); section 11.5.3 (Baseline assessment clinical assessment) and section 11.9 (Table of study assessments) were updated to reflect a new requirement that information on cancer diagnosis should be recorded at screening and ECOG performance status should be recorded at screening and baseline assessments, since it was recognised that this information is not currently being collected in the CRF. 4. Section 11.3; Bilirubin has been listed among the variables required as part of routine biochemistry assessment at screening 5. Section 5 (Trial flow chart); section 11.5.3 (Baseline assessment clinical assessment); section 11.9 (Table of study assessments) and section 18.2 (recording adverse events) were updated to reflect a new requirement that the adverse event review should be conducted at the baseline assessment, as well as at all other weekly assessments. The previous version of the protocol did not require adverse events data to be recorded at the baseline assessment. 6. Section 5 (Trial flow chart) and section 11.9 (Table of study assessments); the requirement for the withdrawal checklist to be completed at week 10 was deleted, as this form is only required when patients withdraw from the study. An explanatory footnote was added to the table of assessments: “The withdrawal checklist should be completed if and when a patient withdraws from the study”. 7. Section 18.2 (Recording adverse events); the wording has been corrected from “Adverse events (and their severity) will be recorded weekly on the case report form until each participant has stopped taking the trial medication” to “Adverse events (and their severity) will be recorded weekly on the case report form until each participant has completed their involvement in the trial”. This is to clarify that adverse events information should still be recorded for participants who remain within the trial even when they have stopped taking the trial medication. For example, during the tapering phase or in the event that the participant stops taking the IMP due to a dose-limiting side effect or other reason, but does not withdraw from the trial.

		8. Section 18.6 (Notification of deaths); the wording has been changed from "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" to "Only deaths that are assessed to be caused by the IMP will be reported to the sponsor. Deaths due to disease progression of cancer will not be reported unless it is felt that the IMP resulted in the disease progression occurring earlier than expected. Such deaths will be reported on the SAE form and will be immediate."
11.0	17-Mar-2020	1. An Appendix has been added to the protocol to document the mitigation measures that have been introduced to deal with the COVID-19 pandemic
		2. A typographical error in Section 11.5.3 was incorrectly incorporated into the heading of section 11.5.4 in the previous version of the protocol. This typographical error has now been corrected.
12.0	06-Jul-2020	1. Section 3 (trial personnel) - Laura Hennelly (Research Nurse) has been replaced by Hinal Lukha (Clinical Trial Practitioner). Contact number of Dr Elli Enayat (MePFAC Trial Manager) and Louise Marston (Statistician) has been updated. 2. Section 4 (summary) – the estimated length of the study has been increased to 64 months this is to account for both a slower than expected rate of recruitment (16-month extension) and an additional six month delay due to suspension of recruitment during the COVID-19 pandemic. The sample size has been changed to encompass a lower figure of 215-230. The text has been amended to indicate that screening and enrolment consent occur together. Other changes in the summary have been made to reflect changes elsewhere in the protocol. 3. Section 5 (Trial flow chart) – has been amended to reflect changes elsewhere in the protocol. 4. Section 6.5.1 (Assessment of risk related to COVID-19 pandemic) – a new section has been created to summarise the risks of conducting research in the light of the COVID-19 pandemic. 5. Section 6.5.2.5 (psychiatric disorders) – bruxism (teeth grinding) has been added as a common adverse effect in response to changes in SmPC. 6. Section 6.5.2.14 (musculoskeletal, connective tissue and bone disorders) – trismus has been added as an adverse effect with unknown frequency in response to changes in SmPC. 7. Section 6.5.2.15 (renal and urinary disorders) – incontinence has been added as an adverse effect with unknown frequency in response to changes in SmPC. 8. Section 6.5.2.21 (pregnancy) – has been expanded in response to changes in the SmPC. "Data from a cohort study of in total approximately 3,400 pregnancies exposed in the first trimester do not suggest an increased risk of overall birth defects. There was a

		small increased occurrence of cardiac malformations (pooled adjusted relative risk, 1.3; 95 % CI, 1.0-1.6) corresponding to 3 additional infants born with congenital cardiac malformations for every 1000 women who receive methylphenidate during the first trimester of pregnancy, compared with non-exposed pregnancies". 9. Section 6.5.3.1 (risks related to COVID-19) – This is a new section which has been created to summarise the changes made to the protocol to mitigate risks associated with COVID-19 10. Section 6.5.3.2 (Cardiovascular status) - This section has been amended to describe the option of home BP monitoring for participants who have remote (rather than face-to-face) assessments. 11. Section 6.5.3.9 (Hepatic insufficiency) – This section has been amended to indicate that the required liver function tests will be limited to ALT and Bilirubin in line with current local practice of testing liver function. 12. Section 8.3.1 (Sample size calculation) – additional text has been included to account for the change in sample size calculation introduced following a contract variation request to NIHR. "In December 2019, these assumptions were re-evaluated in the light of actual recruitment and retention figures. At that stage, attrition was running at approximately 13%. On the assumption that attrition over the course of the study was no worse than 20%, then the estimated sample size needed to accrue 172 evaluable patients would reduce from 230 to 215 randomised participants". 13. Section 8.3.2 (Planned recruitment rate) - additional text has been included to account for the change in planned recruitment rate following a contract variation request to NIHR. "In December 2019, these assumptions were re-evaluated in the light of actual recruitment figures. Rather than recruiting 17 patients per month, we aimed to recruit 7 patients per month once all sites were open". 14. Section 9.1.3 (Duration of treatment) – text changed to indicate that face-to-face assessments can be undertaken by telephone 15. 9.1.4 (Dose titration) – text changed to indicate that face-to-face assessments can be undertaken by telephone and that where re-supply of IMP is to be couriered or posted by site pharmacies, verbal consent from the participant will be obtained and recorded in the source data or medical records. Text has been clarified to indicate that the dose titration weeks are counted from the date on which the medication is received/collected by the participant. A change has also been made to the description of the skills and training of the research staff making the telephone calls. Rather than saying that staff will have oncology /

		palliative care experience the text now states that staff will have "appropriate training". 16. Section 9.5 (Trial schematic) – has been updated to reflect changes elsewhere in the protocol. 17. Section 9.6.1 (Screening) – has been edited to indicate that screening and enrolment can occur on the same day and that only one consent is required. 18. Section 9.6.1.1 (Pre-screening by clinical staff) – has been changed to indicate that only one written consent for screening/enrolment is required. Indicates that verbal consent will be sufficient to allow for blood tests and BP/pulse assessments to be undertaken to check for eligibility prior to obtaining written/informed consent. 19. Section 10.2 (exclusion criteria) – has been altered to indicate that only ALT and Bilirubin are required for assessment of liver function. 20. Section 11.1 (Participant Identification) – text changed to indicate that only one written consent will be obtained for participants to be screened/enrolled. Reference to a REC approved video has been removed, as this resource is not currently available. 21. Section 11.2 (Consent for Screening and Study enrolment) – The text has been amended to indicate that the two phase consent process has been removed and wording relating to enrolment consent (formerly Section 11.4) has been moved to this section. This section has also been amended to indicate that verbal permission may be granted by potentially eligible participants to undertake additional blood tests (or request additional analyses of existing samples) and BP/pulse assessment, as this may prevent potentially avoidable trips to the healthcare setting. 22. Section 11.3 (Screening period) – The text has been altered to clarify that screening and enrolment consent will occur on the same day and wording from the enrolment consent section relating to pregnancy testing timelines has been moved to the assessment list in this section. Text makes clear that screening and baseline assessments can occur on the same day or at separate visits and that IMP may be dispensed immediately or later. 23. Section 11.4 (Consent for study enrolment) - As screening and enrolment consent is now to be combined, this section has been deleted and relevant wording incorporated into sections 11.2 and 11.3. 24. Section 11.4 (Baseline assessment) – The section is now 11.4 and was previously section 11.5. Section updated to revise text to say that enrolment occurs 0-14 days after screening. 25. Section 11.4.1 (Patient identifiers and contact details) – the section is now 11.4.1 and was previously 11.5.1. Section updated to indicate that contact information is also needed to coordinate

		shipment of re-supply of medication where participants verbally consent to this. 26. Section 11.4.4 (End of baseline visit) – This section is now 11.4.4 and was previously 11.5.4. Section has been amended to indicate that IMP can be delivered to participants' addresses. 27. Section 11.7 (Treatment procedures) – The section is now 11.7 and was previously section 11.8. Text has been amended to indicate that week 3, 6 and 10 assessments can be by telephone, to indicate that IMP can be delivered to patients' homes and that verbal consent for posting/courier of IMP will be obtained from the participant. 28. Section 11.8 (Table of study assessments) – The section is now 11.8 and was previously section 11.9. The section has been amended to reflect changes elsewhere in the protocol. 29. Section 11.11.3 (Withdrawal of individual participants at their own request) – The section is now 11.11.3 and was previously section 11.12.3. Text has been amended to indicate that face-to-face assessments can also be undertaken remotely using the telephone. 30. Section 11.11.6 (Withdrawal of individual participants due to adverse events) – The section is now 11.11.6 and was previously section 11.12.6. The text has been altered to clarify that assessments do not need to be face-to-face 31. Section 13.8 (Drug accountability) – Text has been amended to indicate that IMP may be delivered to and from participants using a locally approved delivery method, if participants themselves are unable to attend the study site. Verbal consent for IMP to be delivered to their home will be obtained from the participant. 32. Section 26 (Appendix 1 – COVID19 mitigation arrangements) – Text has been amended to clarify that participants on trial during the pandemic were withdrawn from IMP but remained in the study.
13.0	01-Mar-2021	1. Section 6.5.2.6 (Nervous system disorders) – text has been altered to include dysphemia as an adverse effect with unknown frequency.

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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
BP	Blood Pressure
CA	Competent Authority
CI	Chief Investigator
CNS	Central Nervous System
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
ECOG	Eastern Cooperative Oncology Group performance status scale
eCRF	Electronic Case Report Form
eGFR	Estimated Glomerular Filtration Rate
EMEA	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
HADS	Hospital Anxiety and Depression Scale
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
MAO	MonoAmine Oxidase
Main REC	Main Research Ethics Committee
MCID	Minimal Clinically Important Difference
MePFAC	Methylphenidate versus Placebo for Fatigue in Advanced Cancer
MHRA	Medicines and Healthcare products Regulatory Agency
MPH	Methylphenidate
MS	Member State
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

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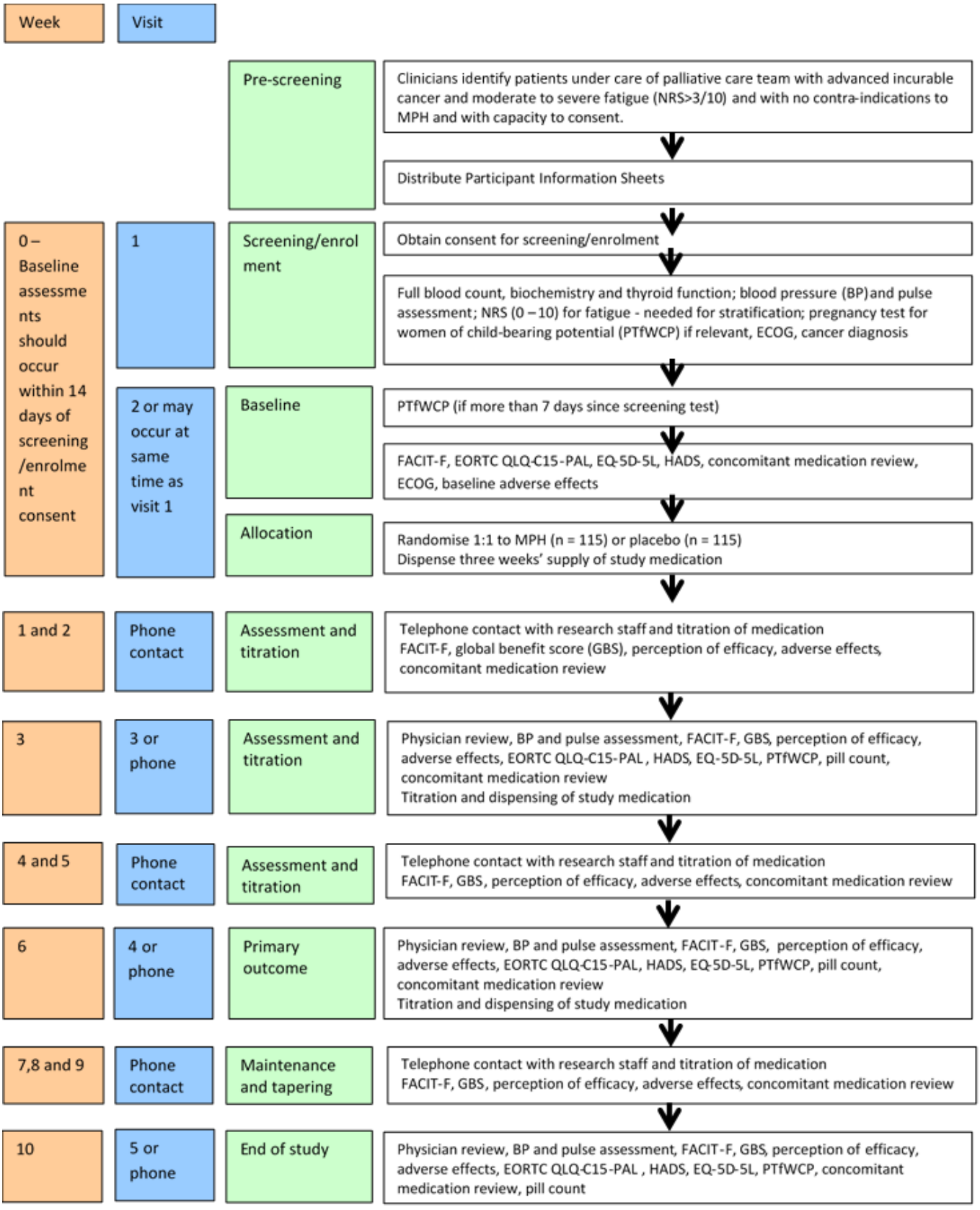
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4 SUMMARY

Title:	Methylphenidate versus placebo for fatigue in advanced cancer
Short title:	MePFAC
Trial medication:	Methylphenidate 5mgs tablets Matching Placebo tablets
Phase of trial:	III
Objectives:	To estimate clinical effectiveness of methylphenidate versus placebo for cancer-related fatigue in patients receiving palliative care
Type of trial:	Prospective, randomised, double-blind, placebo-controlled trial with internal pilot in palliative care patients with advanced cancer
Trial design and methods:	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, 6 and 10 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. Potentially eligible patients will be identified and provided with study information and asked for consent for screening/enrolment. At screening, if no recent blood results are available, a fresh specimen will be obtained (full blood count, liver and renal function, thyroid function) and blood pressure will be assessed. Patients who are confirmed as eligible will be invited for a baseline assessment and will be randomised. After randomisation, face-to-face (or telephone) assessments will occur at weeks 3, 6 and 10 and will include; completion of outcome measures and blood pressure (can be home monitored). 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 15 - 23) 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.
Trial duration per participant:	10 weeks
Estimated total trial duration:	64 months
Planned trial sites:	20
Total number of participants planned:	215 - 230
Main inclusion/exclusion criteria:	Patients with advanced cancer with cancer-related fatigue and receiving palliative care **Inclusions:** 18+ years; advanced incurable cancer of all tumour types; moderate or severe fatigue on numerical rating scale (>3/10); informed consent; receiving generalist or specialist palliative care **Exclusions:** Known sensitivity or contraindication to methylphenidate; severe anaemia; decompensated liver failure; current or previous psycho-stimulant use in last month
Statistical methodology and analysis:	With 215-230 randomised and 172 evaluable patients (20-25% 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). Randomisation will be computer generated and stratified by centre, by receipt of palliative cancer treatment, by baseline HADS depression score and by initial fatigue score >7.

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 (MPH) 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 MPH.

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. MPH did not affect reproductive performance or fertility at low multiples of the clinical dose. MPH 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 (MPH and dexamethylphenidate) in varied cancer populations.

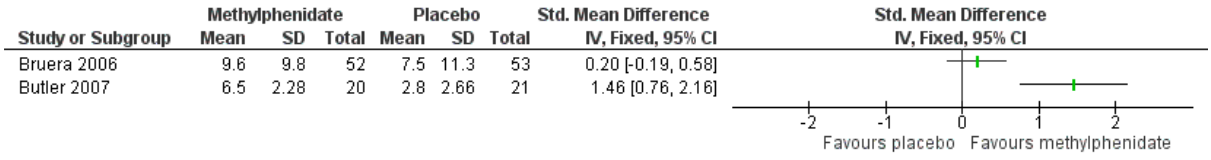
MPH is a central nervous system (CNS) stimulant (psycho-stimulant). It is an inhibitor of catecholamine re-uptake and increases central dopamine and noradrenaline levels [20]. It is a short-acting drug with a half-life of one to four hours. It has been widely used for decades

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 MPH 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 MPH in cancer-related fatigue in palliative care patients [SMD = 0.49, 95% CI 0.15 to 0.83] (see Figure 1).

In our systematic review of psycho-stimulants 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 MPH [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, MPH was well tolerated and no serious side-effects were observed. There was little information on long term safety. MPH 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 MPH 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 MPH 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, psycho-stimulants 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 MPH 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 MPH should play in the management of fatigue in the context of advanced cancer.

6.5 ASSESSMENT AND MANAGEMENT OF RISK

6.5.1 ASSESSMENT OF RISK RELATED TO COVID-19 PANDEMIC

Recruitment to the trial was temporarily halted in March 2020 due to global COVID-19 pandemic. Although there was no reason to believe that the IMP would have any effect on susceptibility to COVID-19, recruitment was suspended in order to reduce burden on the NHS, to reduce all but essential visits to research sites and to free up staff time and other resources to combat the pandemic.

Prior to re-starting recruitment some changes were made to the protocol to minimise exposure of participants to COVID-19 and to maintain social distancing.

6.5.2 MAIN SOURCES OF RISK ASSOCIATED WITH IMP

The active ingredient in the IMP is methylphenidate (the international non-proprietary name for α-Phenyl-2-piperidineacetic acid methyl ester hydrochloride). MPH is licensed for use as a

part of a comprehensive treatment programme for ADHD in children aged six 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.

MPH is a widely used medication in children and young adults. Following some concerns about possible adverse effects, the European Medicines Agency (EMEA) completed a review of the safety of medicines containing MPH 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 ADHD [33].

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

6.5.2.1 Infections and infestations

Common: Nasopharyngitis

6.5.2.2 Blood and lymphatic disorders

Very rare: Anaemia, leucopenia, thrombocytopenia, thrombocytopenic purpura
Unknown: Pancytopenia

6.5.2.3 Immune system disorders

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

6.5.2.4 Metabolism and nutritional disorders

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

6.5.2.5 Psychiatric disorders

Very common: Insomnia, nervousness
Common: anorexia, affect lability, aggression, agitation, anxiety, depression, irritability, abnormal behaviour, bruxism (teeth grinding)
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)

6.5.2.6 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 MPH is unclear).
Not known: Cerebrovascular disorders (including vasculitis, cerebral haemorrhages, cerebrovascular accidents, cerebral arteritis, cerebral occlusion), grand mal convulsions, migraine, dysphemia

6.5.2.7 Eye disorders

Uncommon: Diplopia, blurred vision
Rare: Difficulties in visual accommodation, mydriasis, visual disturbance

6.5.2.8 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

6.5.2.9 Vascular disorders

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

6.5.2.10 Respiratory, thoracic and mediastinal disorders

Common: Cough, pharyngolaryngeal pain
Uncommon: Dyspnoea

6.5.2.11 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

6.5.2.12 Hepatobiliary disorders

Uncommon: Hepatic enzyme elevations
Very rare: Abnormal liver functions, including hepatic coma

6.5.2.13 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
Not known: Dry skin

6.5.2.14 Musculoskeletal, connective tissue and bone disorders

Common: Arthralgia
Uncommon: Myalgia, muscle twitching
Very rare: Muscle cramps
Unknown: Trismus

6.5.2.15 Renal and urinary disorders

Uncommon: Haematuria
Unknown: Incontinence

6.5.2.16 Reproductive system and breast disorders

Rare: Gynaecomastia
Unknown: Erectile dysfunction, priapism, erection increased and prolonged erection

6.5.2.17 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

6.5.2.18 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

6.5.2.19 Pharmacokinetic interactions

The SmPC advises that there are reports indicating that MPH may inhibit the metabolism of coumarin anticoagulants, anticonvulsants (e.g. phenobarbitol, phenytoin, primodone) and some antidepressants (tricyclics and selective serotonin reuptake inhibitors).

6.5.2.20 Pharmacodynamic interactions

6.5.2.20.1 Anti-hypertensives

The SmPC advises that MPH may decrease the effectiveness of drugs used to treat hypertension.

6.5.2.20.2 Use with drugs that elevate blood pressure

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

6.5.2.20.3 Use with alcohol

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

6.5.2.20.4 Use with halogenated anaesthetics

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

6.5.2.20.5 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 MPH in combination with clonidine or other centrally acting alpha-2 agonists has not been systematically evaluated.

6.5.2.20.6 Use with dopaminergic drugs

Caution is recommended when administering MPH with dopaminergic drugs, including antipsychotics. Because a predominant action of MPH is to increase extracellular dopamine levels, MPH 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.

6.5.2.21 Pregnancy

Data from a cohort study of in total approximately 3,400 pregnancies exposed in the first trimester do not suggest an increased risk of overall birth defects. There was a small increased occurrence of cardiac malformations (pooled adjusted relative risk, 1.3; 95 % CI, 1.0-1.6) corresponding to 3 additional infants born with congenital cardiac malformations for every 1000 women who receive methylphenidate during the first trimester of pregnancy, compared with non-exposed pregnancies. 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.

6.5.2.22 Lactation

MPH has been found in the breast-milk of a woman treated with MPH. 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 MPH. A risk to the suckling child cannot be excluded.

6.5.2.23 Elderly

The SmPC advises that safety and efficacy of MPH have not established in the elderly.

6.5.3 HOW MAIN SOURCES OF RISK WILL BE MINIMISED IN THIS STUDY

6.5.3.1 Risks related to COVID-19

Changes to the protocol instituted following the COVID-19 pandemic were put in place to minimise the risk to participants from exposure to the virus and to maintain social distancing.

In summary these changes relate to reducing face-to-face assessments by: combining consent for screening/enrolment, facilitating the opportunity for the screening and enrolment visits to occur on the same day; by reducing the number of additional blood tests required at screening (and therefore reducing the need for repeat visits); and offering the option of telephone assessments (with home BP monitoring and delivery of IMP) rather than face-to-face assessments at weeks 3, 6 and 10. Staff at recruiting sites will also follow local infection prevention and control guidelines.

6.5.3.2 Cardiovascular status

The SmPC for MPH 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 MPH 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 the context of a palliative treatment for advanced incurable cancer in adults a more pragmatic approach is judged to be justified. The risk benefit balance is somewhat different to that of a paediatric population given that many of these patients will have had some past history of heart failure, angina or myocardial infarction, but at the time of recruitment to the study will have these conditions currently well managed and stable.

In this study cardiovascular risk will be minimised by excluding patients with known pre-existing cardiovascular disorders including severe hypertension, uncontrolled heart failure, arterial occlusive disease, uncontrolled angina, haemodynamically significant congenital heart disease, cardiomyopathies, myocardial infarction (within last one year), 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 hypertension (BP >160/100mmHg). All study participants will be reviewed by a study team member 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, 3, 6 and 10 weeks. If hypertension is detected 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.

If participants have the week 3, 6 or 10 assessment undertaken remotely rather than face-to-face then they will be supplied with a British Heart Foundation approved home BP monitor and instructed how to take their own BP and pulse rate measurements. At the end of their involvement in the study the BP monitor will be returned to the local study team and disinfected prior to being used again.

6.5.3.3 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 MPH 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 MPH and early treatment. The diagnosis should therefore be considered in any patient who develops new neurological symptoms that are consistent with cerebral ischemia during MPH therapy. These symptoms could include severe headache, numbness, weakness, paralysis, and impairment of coordination, vision, speech, language or memory.

The data supporting these cerebrovascular contraindications are based on the licensed use of MPH in children and adolescents and therefore, exclusion in children is recommended. However in the context of a palliative treatment for advanced incurable cancer a more pragmatic approach is proposed, as the risk benefit balance is somewhat different to that of a paediatric population, and many palliative care patients may have had pre-existing cerebrovascular conditions or risk factors that are well managed and/or stable.

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 (within last one year). After initial consent, potential participants will also be further screened by measurement of blood pressure – to exclude patients with severe hypertension (BP >160/100mmHg). All study participants will be reviewed by a study team member 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, 3, 6 and 10 weeks.

6.5.3.4 Psychiatric disorders

The SmPC 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 MPH 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 MPH 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 MPH treatment.

MPH is associated with the worsening of pre-existing anxiety, agitation or tension. Particular care should be taken in using MPH to treat ADHD in patients with comorbid 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 MPH, patients with comorbid 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 (HADS) to document the extent of any affective symptoms and to screen for any undiagnosed symptomatology. All study participants will be reviewed by a study team member on a weekly basis for the duration of the trial (either by telephone or face-to-face) and psychiatric side-effects will be monitored.

6.5.3.5 Seizures

The SmPC [16] states that MPH should be used with caution in patients with epilepsy. If seizure frequency increases or new-onset seizures occur, MPH 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 patients 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 team member on a weekly basis for the duration of the trial (either by telephone or face-to-face) and side-effects will be monitored.

6.5.3.6 Abuse, misuse and diversion

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

Rather than excluding all patients with any history of drug or alcohol abuse, *in this study the risk of abuse, misuse and diversion will be minimised* by excluding patients with known drug or alcohol dependency within the last one year. In addition we will only dispense three weeks' supply of IMP at each visit. All study participants will be reviewed by a study team member on a weekly basis for the duration of the trial and we will conduct pill counts at each face-to-face meeting.

It is recognised that a one year limit on past substance abuse is relatively short. However, given the limited longevity of the patient population, that the dose of study medication is being titrated weekly, that all participants are being weaned off the medication before the end of the trial and that palliative care patients are routinely administered drugs with far higher risks of dependence (e.g. opioids) we believe that a one year limit is reasonable.

6.5.3.7 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.

6.5.3.8 Renal insufficiency

The SmPC notes that, there is no experience with the use of MPH in patients with renal insufficiency. The SmPC reports that haematuria is an uncommon side effect (≥ 1/1000 to <1/100) but does not report any other effects on the renal or urinary systems.

Prescribing information for MPH notes that, "renal insufficiency is expected to have minimal effect on the pharmacokinetics of methylphenidate since less than 1% of a radio-labeled dose is excreted in the urine as unchanged compound, and the major metabolite (ritalinic acid), has little or no pharmacologic activity" [35].

In this study the risk associated with using MPH in patients with renal insufficiency will be minimised by excluding patients with an estimated glomerular filtration rate [eGFR] of < 45 ml/minute per 1·73 m^2. The rationale for this limit is based on the fact that many elderly palliative care patients have mild/moderate renal impairment but are routinely prescribed other drugs for which caution should be exercised (e.g. opioids). The dose of MPH in this study is being individually titrated, which reflects the way that this medication would be prescribed in clinical practice in the circumstances of impaired renal function. The starting dose is low and, in patients with renal impairment, the local PI will individually adjust the dose; either titrating upwards slowly according to response/adverse effects, or staying at the lowest dose level (see Section 9.2 for dose titration).

6.5.3.9 Hepatic insufficiency

The SmPC notes that, there is no experience with the use of MPH in patients with hepatic insufficiency. The SmPC reports that elevation in hepatic enzymes in response to MPH is uncommon (≥ 1/1000 to <1/100), and that abnormal liver function or hepatic coma are very rare (< 1/10,000).

Prescribing information for MPH notes that, "hepatic insufficiency is expected to have minimal effect on the pharmacokinetics of methylphenidate since it is metabolised primarily to ritalinic acid by nonmicrosomal hydrolytic esterases that are widely distributed throughout the body" [35].

In this study the risk associated with using MPH in patients with hepatic insufficiency will be minimised by excluding patients with severe liver impairment (as judged by the results of clinical biochemistry tests). Most patients will have routine liver function tests as part of their cancer treatment and we will exclude patients who have ALT > 2 x ULN or bilirubin > 1.5 x ULN. Patients with abnormal Alkaline Phosphatase (ALP) (in the absence of rises in ALT or bilirubin) will not be excluded from this study, as patients with advanced cancer often have a raised ALP because of metastatic bone (rather than metastatic liver) disease. We will no longer include AST or GGT among the "liver function tests" as these tests are not routinely measured at most participating centres and removing AST and GGT from the exclusion criteria would greatly simplify recruitment to the study (allowing patients to be excluded simply on the basis of blood results that are already routinely available in hospital records). This would reduce the number of visits which potential participants would need to make to the hospital/hospice and would not compromise patient safety. Advanced cancer patients frequently have liver function assessed prior to far more toxic therapies (e.g. chemotherapy) solely on the basis of "routine" liver function tests and so it does not seem necessary to require a higher standard for a relatively less toxic intervention. Moreover, there is potentially more risk associated with requiring patients to travel to and from the clinic for an additional blood test rather than using routine results that are already available.

6.5.3.10 Potential for gastrointestinal obstruction

MPH tablets should not ordinarily be administered to patients with 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.

6.5.3.11 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 MAO-inhibitors, or within a minimum of 14 days of discontinuing those drugs; patients currently receiving psycho-stimulants, 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 MPH. 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.

6.5.3.12 Pregnancy and lactation

In this study the risk associated with administration during pregnancy or lactation will be minimised by only including females of childbearing potential if they agree to use an effective method of contraception (hormonal or barrier method of birth control; abstinence) from the time consent is signed until six weeks after treatment discontinuation. Males who have sexual partners with child-bearing potential must also agree to use an effective method of contraception from the time consent is signed until six weeks after treatment discontinuation. A pregnancy test will be scheduled seven days or fewer prior to first dose administration (at the screening visit and again at the baseline visit, if it takes place more than 7 days after the last pregnancy test) and at every physical visit during the study for females of child-bearing potential. Females must not be breastfeeding.

6.5.3.13 Elderly

The SmPC advises that safety and efficacy of MPH have not been 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.

6.5.3.14 Avoiding use in patients with thyrotoxicosis

The SmPC advises that hyperthyroidism or thyrotoxicosis are contra-indications to MPH. Patients with clinical hyperthyroidism will be excluded from the study. Other patients must have a thyroid function test result available demonstrating no evidence of hyperthyroidism in the three months prior to administration of the first dose of study medication.

6.5.4 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 Functional Assessment of Chronic Illness Therapy (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 (± 2 weeks) measured by the fatigue sub-scale of the FACIT-F questionnaire [36]. The FACIT Measurement System is a collection of QOL questionnaires targeted to the management of chronic illness [37]. The fatigue sub-scale consists of 13-items specifically related to fatigue [36]. It is probably the best validated and most widely used cancer-related fatigue specific outcome measure [38] 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 [39] known-groups validity and sensitivity to change [40]

8.2 SECONDARY OUTCOMES

Secondary outcomes (measured at 3, 6 and 10 weeks) are other measures of quality of life, adverse events, activities of daily living, appetite, satisfaction of patients and carers, survival, need for other medication (assessed weekly) and FACIT-F (measured on a weekly basis). The FACIT-F will be analysed at each time point for which it is collected, and an

analysis will be undertaken in which all observations of the FACIT-F are included as repeated measures within a randomised subject.

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 [41] 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 (MCIDs) for the various symptom sub-scales of the EORTC QLQ-C15-PAL have recently been proposed [42].

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 five 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' [43, 44].

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

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[45]. The GBS is scored on a 5-point scale depending upon how the following statement is answered; "Overall with regard to fatigue, during the last week, I found that …" with responses ranging from "Things have got much better" to "Things have got much worse".

Once participants have completed the ten week follow-up they will be given the option to continue (or start) MPH 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 weekly assessments.

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. [46] and Cella et al. [47] reported a 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. [40] determined the MCID by relating changes in FACIT-F with changes in patient satisfaction and reported that a reduction of 10-points or more was associated with a subjective change that was, "moderately important, consistently beneficial". They also reported [40] that a median change of 7.5 points or a mean change of 9.3 points on the FACIT-F corresponded to a subjective change that was "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 MPH 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).

In December 2019, these assumptions were re-evaluated in the light of actual recruitment and retention figures. At that stage, attrition was running at approximately 13%. On the assumption that attrition over the course of the study was no worse than 20%, then the estimated sample size needed to accrue 172 evaluable patients could be reduced from 230 to 215 randomised participants.

8.3.2 PLANNED RECRUITMENT RATE

Initially we estimated that each site would recruit one patient per month during the pilot and the initial set-up phase of the full trial. Once the trial was fully established and recruiting at all 20 sites we estimated that the trial would recruit a total of 17 patients per month (at a recruitment rate of approximately 0.85 patients per site per month). We anticipated opening all 20 sites by October 2019 and reaching the target total recruitment of 230 patients by June 2020.

In December 2019, these assumptions were re-evaluated in the light of actual recruitment figures. Rather than recruiting 17 patients per month, we aimed to recruit 7 patients per month once all sites were open.

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 MPH 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 (weeks 1, 2, 4, 5, 7 and 8) or following face-to-face (or further telephone) assessment with a member of the study team (weeks 3 and 6). During 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 10 the study will end. At that point participants will be managed according to local clinical practice and circumstances. This may include the prescription of MPH 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, 8 and 9) or face-to-face or telephone (weeks 3, 6 and 10). The dose titration weeks will be counted from the date on which the study medication is received/collected by the participant. The telephone calls will be made by research staff at UCL or at the site from which they were recruited. The research staff responsible for making the telephone calls will have appropriate training. They will have (or will receive) training in communication skills. The research staff 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 research staff on the CRF.
- Global benefit score (GBS) – this is a measure of global perception of drug benefit. The GBS is scored on a 5-point scale depending upon how the following statement is completed; "Overall with regard to fatigue, during the last week, I found that…", with responses ranging from "Things have got much better" to "Things have got much worse". The questions will be read out to respondents over the phone and responses recorded on the CRF.
- Patient perception of efficacy - the research staff member 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 CRF and graded as mild, moderate or severe (see Section 18).
- List of concomitant medications - this will include the recording of any non-drug treatments that are specifically directed at relieving fatigue (e.g. blood transfusion).

At the face-to-face or telephone assessments (weeks 3, 6 and 10) these same questions will be posed by the research staff or by the PI (or delegate). Once again responses will be recorded on the CRF. Where re-supply of IMP is to be couriered or posted by site pharmacy, verbal consent from the participant will be obtained and recorded in the source data or medical records.

9.1.4.1 Responsibility for dose titration

At the first assessment study participants will be instructed by the PI (or another physician delegated 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 research staff at UCL or by the local PI/delegate). 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 dose titration instructions will be communicated to the patient by telephone and also either by text message (if patient consents to receiving texts) or by a letter sent by first class mail.

The decision about how to adjust the dose of medication will be made by the local PI (or another physician delegated by the PI) on the basis of the patient's responses to the questions described in 9.1.4 (above). The patient's responses will be communicated to the local PI (or another physician delegated by the PI) via the "Sealed Envelope" database, or by secure email (either using NHS mail if the PI/delegate 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/delegate 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 research staff at UCL or at the site from which they were recruited. If necessary, the PI/delegate 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/delegates 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 and there are no dose-limiting adverse effects
- To remain at the current dose level if
  - Fatigue is adequately controlled and there are no dose-limiting adverse effects
  - There are dose-limiting adverse effects that prevent an increase in dose, but which are not judged by the PI to necessitate a reduction in dose
- To reduce to the previous dose level (or stop study medication if only on level 1) if
  - There are dose limiting side-effects which in the opinion of the PI necessitate a dose-reduction

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" [48]. 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

Dose level	Days	Total daily dose of methylphenidate 5mg	Dose schedule
1	0 -7 (± 4)	2 tablets	In two divided doses (morning and lunch)
2	8 – 14 (± 4)	4 tablets	In two divided doses (morning and lunch)
3	15 – 21 (± 4)	6 tablets	In two divided doses (morning and lunch)
4	22 – 28 (± 4)	8 tablets	In two divided doses (morning and lunch)
5	29 – 35 (± 4)	10 tablets	In three divided doses (4 tablets in the morning, 3 tablets at lunch and 3 tablets in early afternoon before 4pm)
6	36 – 42 (± 4)	12 tablets	In three divided doses (morning, lunch and early afternoon before 4pm)

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 research staff.

Standard maintenance schedule

Days	methylphenidate 5mg tablets
43 - 49 (± 4)	Continue at level reached during dose titration or reduce due to adverse events
50 - 56 (± 4)	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 MPH abruptly (due to the risk of discontinuation phenomena), medication will be tapered during week 9 of the study (regardless of whether participants are receiving placebo or active medication). Participants will follow the following tapering schedule.

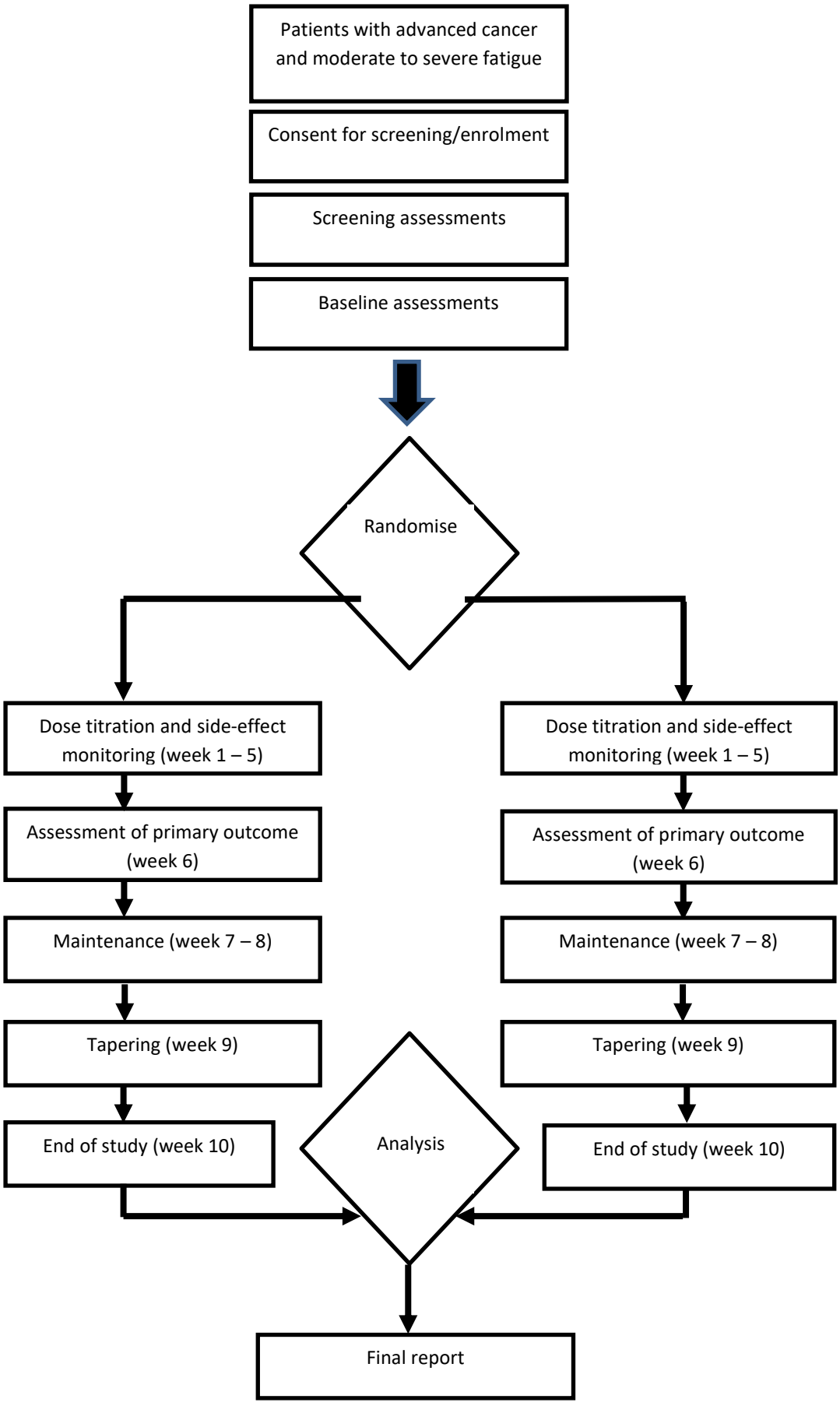
Standard tapering schedule

Days	methylphenidate 5mg tablets
57 (± 4) – 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 days 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 patients with advanced incurable cancer receiving palliative care.

It is planned that this study will take place at 20 different sites. It is planned that at least five sites will be involved during the internal pilot phase. The services themselves will span community services, hospital and hospice services (including day care and outpatients).

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, cancer diagnosis, ECOG performance status, extent of disease, estimated prognosis, whether patient was approached by a member of the clinical team about the study (if not, why not), whether patient agreed to speak to a member of the research team (no reasons 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 consented to screening/enrolment, whether or not they were eligible and whether or not they agreed to participate in the study (no reasons 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

Pre-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 MPH). In line with good clinical practice [49] 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?" [49]. 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 Participant Information Sheets (PIS) and will be invited to meet a member of the research team to discuss the study in detail. To avoid unnecessary additional visits to hospital/hospice, and prior to obtaining written informed consent for screening/enrolment, potential study participants may be asked to give verbal consent for blood tests to be undertaken (either using a fresh blood specimen or additional analyses of pre-existing samples) and for BP and pulse assessment to determine potential eligibility.

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. Able and willing to comply with all study requirements, including ability to participate in study for ten weeks
6. Participant is receiving generalist or specialist palliative care
7. Willing to allow his or her General Practitioner to be notified of participation in the study

10.2 EXCLUSION CRITERIA

1. Pregnancy
2. Females of childbearing potential and males who have sexual partners with child-bearing potential 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 six 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)
3. Females of childbearing potential must have a negative pregnancy test seven days or fewer prior to first dose administration and must be willing to have a pregnancy test at every physical visit during the study
4. Females must not be breastfeeding
5. Known sensitivity to methylphenidate or to any of the excipients
6. History of glaucoma
7. Known phaechromocytoma
8. Planned general anaesthesia in the next nine weeks
9. During treatment with non-selective, irreversible MAO-inhibitors, or within a minimum of 14 days of discontinuing those drugs
10. Clinical hyperthyroidism or thyrotoxicosis. Patients must have a thyroid function test (T4 and TSH) showing no evidence of hyperthyroidism in three months prior to first dose administration of study medication
11. Known diagnosis or history of severe depression, anorexia nervosa/anorexic disorders, suicidal tendencies, psychotic symptoms, severe mood disorders, mania, schizophrenia, psychopathic/borderline personality disorder

12. Known diagnosis or history of severe and episodic (Type 1) bipolar (affective) disorder (that is not well controlled)
13. Known pre-existing cardiovascular disorders including severe hypertension (BP >160/100mmHg), uncontrolled heart failure, uncontrolled angina, arterial occlusive disease, haemodynamically significant congenital heart disease, cardiomyopathies, myocardial infarction (within last one year), potentially life-threatening arrhythmias and channelopathies
14. Pre-existing cerebrovascular disorders, cerebral aneurysm, vascular abnormalities including vasculitis or stroke (within last one year) or known high risk factors for cerebrovascular disorders
15. Current or previous psycho-stimulant use in last month
16. Severe anaemia (haemoglobin < 80g/L)
17. Platelets $<50 \times 10^3/\mu L$
18. White blood count less than 1.5×10^9/litre
19. Any evidence of severe or uncontrolled infection that in the view of the investigator makes it undesirable for the patient to participate in the trial
20. Estimated glomerular filtration rate [eGFR] <45 ml/minute per 1·73 m^2
21. ALT > 2 x ULN or bilirubin > 1.5 x ULN
22. Participating in another research study involving any investigational agents within four weeks prior to registration
23. Insufficient English language skills to understand study documentation and complete assessments
24. Current treatment with clonidine, warfarin, monoamine oxidase inhibitors or modafinil
25. History of previous or current substance or alcohol dependency within the last one year
26. Unable to swallow tablets/capsules
27. History of poorly controlled epilepsy, or seizures related to underlying brain tumour
28. 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. 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 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 hospital or hospice 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 member of the research staff 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 the 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/enrolled in the study.

11.2 CONSENT FOR SCREENING AND STUDY ENROLMENT

Verbal consent for additional blood tests (or additional analyses of existing samples) and for BP/pulse assessment to assess eligibility, prior to seeking written consent, will be permitted in order to minimise avoidable additional hospital/hospice visits. However, before any other study-related procedures can be undertaken, written consent for screening/enrolment must be obtained. The Investigator, or a person delegated by the Investigator will obtain written informed consent from each participant, following adequate explanation of the aims, methods, anticipated benefits and potential hazards of the study. Consent will normally be taken by a member of the research staff who has been Good Clinical Practice (GCP) trained, is suitably qualified and experienced, and has been delegated this duty by the CI/PI on the delegation log. A copy of the signed "Informed consent for screening and 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.

If no recent full blood count or routine biochemistry result is available (within 14 days of screening) or no recent thyroid function test result is available (within three months of screening) then a fresh blood specimen will be obtained. Blood pressure will be recorded.

The PI or delegate will record when the PIS has been given to the participant. Screening and baseline assessments may, if the patient agrees, be undertaken at the same visit at which the patient gave consent for screening/enrolment. However, if the patient prefers, then they may return to see a member of the research team at a later date for the additional baseline assessments and collection of study medication.

11.3 SCREENING VISIT

After a potentially eligible patient has been identified by a member of the clinical team, and after they have provided written informed consent to screening/enrolment, 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
- Checking the results of, or obtaining new samples for a full blood count (haemoglobin, white cell count and differential, platelet count), routine biochemistry (creatinine and electrolytes, alanine aminotransferase, bilirubin) and thyroid function tests (TSH, T4). When relevant blood tests are available from within the previous two weeks (full blood count and biochemistry) or within previous three months (thyroid function tests), no further blood tests will be necessary.
- Measurement and documentation of pulse and blood pressure – to exclude patients with severe hypertension (BP >160/100mmHg)
- Recording cancer diagnosis and ECOG performance status
- Baseline assessments (see section 11.4) can be carried out at the same visit at which screening/enrolment consent is given, or within 14 days if it is more convenient for the participant to return at a later date.
- A negative pregnancy test must be obtained within seven days prior to the baseline assessment/first dose administration (if the woman is of child bearing potential).

Patients who (after providing informed consent for screening/enrolment) 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).

At the screening/enrolment visit potential participants may (if they wish) proceed immediately to the baseline assessments (Section 11.4) and if they are found to be eligible for the study then the study medication may also be dispensed at the same visit. If all of the eligibility assessment results are not available at the screening/enrolment visit then IMP will not be dispensed immediately. Participants may either return to the site to collect the IMP at a later date (within 14 days of the baseline assessments) or will provide verbal consent for the medication to be posted/couriered to their place of residence. If the participant prefers then they may return for the baseline assessment and dispensing of the IMP at a later date. The baseline assessment will occur between 0-14 days after the screening/enrolment visit at which consent was obtained.

11.4 BASELINE ASSESSMENT

The baseline visit will occur between 0-14 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;

11.4.1 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 numbers. 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. Contact information is also needed to coordinate shipment of re-supply of medication where participants verbally consent to this.

11.4.2 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 [37]. The fatigue sub-scale consists of 13-items specifically related to fatigue [36]. It is probably the best validated and most widely used cancer-related fatigue specific outcome measure [38] 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 [39], known-groups validity and sensitivity to change [40].

- The Hospital Anxiety and Depression Scale (HADS) [50] - 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 minimise the biological features of these conditions. It has been previously validated in patients with advanced cancer [51]. Scores on each sub-scale 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) [41] this is a well-validated modification of the larger 30-item EORTC QLQc30 questionnaire [42] 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 seven-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 [43].

- 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' [44, 52].

11.4.3 CLINICAL EXAMINATION

- BP and pulse measurement
- Pregnancy test for women of child bearing potential (if more than 7 days last test)
- Adverse events - adverse events or reactions will be documented on the case report form and graded as mild, moderate or severe (see Section 18)
- ECOG Scale of Performance Status [53] – this is a standardised 5-item scale that measures the functional status of cancer patients and is widely used by oncologists and in clinical trials [54]. It describes a patient's level of functioning in three domains: ability to care for themselves, daily activity, and physical ability. Scores range from 0 (fully active, able to carry on all pre-disease performance without restriction) to 4 (completely disabled; cannot carry on any self-care, totally confined to bed or chair), with a higher score representing a lower level of functioning. It has demonstrated good inter-rater and intra-rater reliability [55, 56]. The ECOG performance status will be used to describe the baseline characteristics of study participants.

11.4.4 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. If necessary, participants may return to the hospital/hospice at a later date to collect the study medication or they may give verbal consent for the medication to be delivered/couriered to their address.

11.5 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).

11.6 UNBLINDING

11.6.1 EMERGENCY UNBLINDING

Trial participants will be provided with a card which can be given to attending medical staff and which explains whom to contact in an emergency.

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. The treating physician/investigator 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 (DSMB) for review in accordance with the DSMB Charter.

11.6.2 UNBLINDING FOR THE SUBMISSION OF SUSAR REPORTS

The following procedure will be used to unblind for the submission of a Suspected Unexpected Serious Adverse Reaction (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 randomisation 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 Medicines and Healthcare products Regulatory Agency (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.

11.7 TREATMENT PROCEDURES

Methylphenidate 5mg tablets and placebo will be prepared by the IMP manufacturer. At weekly intervals (± 4 days) after study medication has been dispensed, participants will be contacted by telephone (weeks 1, 2, 4, 5, 7, 8 and 9) or face-to-face or telephone (weeks 3, 6 and 10) 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 or following the baseline assessment, and at or following the week 3 (± 4 days) and week 6 (± 4 days) assessments. If participants have opted for remote assessments, then the medication will be posted/couriered to the patient's home and verbal consent for posting / courier will be obtained from the participant. The four days' flexibility on either side of the scheduled assessment days is to allow for contingencies. At week 3, 6 and 10, pill counts will be performed to assess compliance to IMP (see Section 13.11). At the assessment at the end of week 10 (±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 MPH should be prescribed depending upon local clinical assessment and patient and physician preference.

11.8 TABLE OF STUDY ASSESSMENTS

Table of assessments	Pre-screening	Screening/enrolment visit[b]	Treatment period										Post-treatment follow-up
			Baseline visit[e]										Final visit
Week (±4days)		-2 to 0	-2 to 0	1	2	3	4	5	6	7	8	9	10
F2F or phone assess	X[a]	X	X	-	-	X	-	-	X	-	-	-	X
Tel contact	X[a]	-	-	X	X	-	X	X	-	X	X	X	-
NRS Fatigue	X	X	X	-	-	-	-	-	-	-	-	-	-
Medical history	X	X	-	-	-	-	-	-	-	-	-	-	-
Informed consent for screening and enrolment.	-	X	-	-	-	-	-	-	-	-	-	-	-
Formal eligibility determination	-	X	-	-	-	-	-	-	-	-	-	-	-
Pregnancy test (in women of child-bearing potential)	-	X	X[f]	-	-	X	-	-	X	-	-	-	X
BP	X[i]	X	X	-	-	X	-	-	X	-	-	-	X
Pulse	X[i]	X	X	-	-	X	-	-	X	-	-	-	X
Full blood count	X[i]	X[c]	-	-	-	-	-	-	-	-	-	-	-
Biochemistry	X[i]	X[c]	-	-	-	-	-	-	-	-	-	-	-
Thyroid function	X[i]	X[d]	-	-	-	-	-	-	-	-	-	-	-
Randomisation	-	-	X	-	-	-	-	-	-	-	-	-	-
IMP administration	-	-	X[h]	-	-	X[h]	-	-	X[h]	-	-	-	-
FACIT-F	-	-	X	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	X
Cancer diagnosis	-	X	-	-	-	-	-	-	-	-	-	-	-
ECOG	-	X	X	-	-	-	-	-	-	-	-	-	-

	Pre-screening	Screening/enrolment visit[b]	Treatment period										Post-treatment follow-up
			Baseline visit[e]										Final visit
Week (±4days)		-2 to 0	-2 to 0	1	2	3	4	5	6	7	8	9	10
Perception of efficacy	-	-	-	X	X	X	X	X	X	X	X	X	X
Adverse event review	-	-	X	X	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	X
Physician's withdrawal checklist[g]	-	-	-	-	-	-	-	-	-	-	-	-	-

Notes for 11.8 Table of Study Assessments

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

b The screening/enrolment visit may occur at the same time as identification or may occur at a later date, baseline assessments can also occur at the same time as the screening/enrolment visit.

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

d If thyroid function results are available from within the previous three months then no fresh blood test is required

e The baseline visit (can be done by face to face or by phone) may occur between 0 – 14 days after the screening/enrolment visit or at the same time as the screening/enrolment visit.

f Pregnancy test should be repeated at baseline visit if baseline assessments conducted more than seven days after last test

g The withdrawal checklist should be completed if and when a patient withdraws from the study

h With participants verbal consent, IMP can delivered to participants' homes by the site pharmacy

i With participants' verbal consent, these assessments can be undertaken prior to the screening/enrolment visit

11.9 METHODS

11.9.1 LABORATORY PROCEDURES

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

11.10 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.

11.11 DISCONTINUATION/WITHDRAWAL OF PARTICIPANTS AND 'STOPPING RULES'

11.11.1 INTERNAL PILOT

After initial start-up (i.e. during months 18-23 [beginning of Oct 2018 to end of Mar 2019]), 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 0.85 participants per centre per month. Therefore the stopping rules for the study at the end of the pilot phase are shown below.

Recruitment during months 18-23 of pilot phase (Oct 2018 to Mar 2019 inclusive)	**Action**
>38 patients	Proceed
27 – 37 patients	Consult with HTA
<27 patients	Stop

11.11.2 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).

11.11.3 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 participate in a withdrawal meeting (either face-to-face or by telephone) with a PI (or delegate) and any reasons for withdrawal that are volunteered will be documented. As a minimum they will also be asked to participate in at least one face-to-face or telephone assessment (one week after cessation of the study therapy) at which, fatigue, adverse events, blood pressure and pulse will be recorded.

11.11.4 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 ten 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. They will also be asked to attend at least one face-to face meeting (one week after cessation of the study therapy) at which, fatigue, adverse events, blood pressure and pulse will be recorded.

11.11.5 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, but will remain in the study, and will continue to be followed-up with or without taking further study medication (see Section 11.11.4). 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” [48]. This will include any “severe” adverse event, and may include “moderate” adverse effects (see Section 18). Participants who develop increased frequency or new onset of seizures; who develop suicidal tendencies or other psychiatric conditions; or who become pregnant will have treatment discontinued.

11.11.6 WITHDRAWAL OF INDIVIDUAL PARTICIPANTS DUE TO ADVERSE EVENTS

Participants who have progressed beyond the baseline dose level, if they subsequently develop dose-limiting side-effects, will be advised to return to the previous dose level of the study medication and to remain in the trial. However participants must stop taking or rapidly taper off the study medication if they develop a serious adverse event. Participants who develop increased frequency or new onset of seizures; who develop suicidal tendencies or other psychiatric conditions; or who become pregnant will have treatment

discontinued. Participants who stop taking the study medication will remain on study follow-up without taking the trial medication (see Section 11.11.4 above).
Participants will also have BP and pulse rate measured at baseline, 3, 6 and 10 weeks. If hypertension is detected at one of the 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.

11.11.7 WITHDRAWAL OF INDIVIDUAL PARTICIPANTS DUE TO PREGNANCY

If a trial participant reports that they are pregnant the trial medication will be stopped, but they will remain on study follow-up.

11.11.8 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

Dose level	Days	Total daily dose of methylphenidate 5mg	Dose schedule
1	0 -7 (± 4)	2 tablets	In two divided doses
2	8 – 14 (± 4)	4 tablets	In two divided doses
3	15 – 21 (± 4)	6 tablets	In two divided doses
4	22 – 28 (± 4)	8 tablets	In two divided doses
5	29 – 35 (± 4)	10 tablets	In three divided doses
6	36 – 42 (± 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 α-Phenyl-2-piperidineacetic acid methyl ester hydrochloride). MPH is licensed for use as a part of a comprehensive treatment programme for ADHD in children aged six 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.

MPH 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 (EMEA) completed a review of the safety of medicines containing MPH 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 ADHD[33].

MPH 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 lists the pre-clinical safety data relating to MPH.

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. MPH did not affect reproductive performance or fertility at low multiples of the clinical dose. MPH 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

MPH 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 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 MPH is detailed in the SmPC and in Section 6.5 of the protocol (above).

A systematic review of psycho-stimulants 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 MPH [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, MPH was well tolerated and no serious side-effects were observed. There was little information on long term safety. MPH 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 MPH 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 MPH 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 [57] and 54mgs/day [58]. The maximum daily dosage permitted for the licensed indication of MPH for ADHD in children aged six 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 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.

IMP will be dispensed at site pharmacies according to local policies and procedures. In the event that patients are unable to collect IMP in person then it may be delivered to them using a locally approved service. Verbal consent for IMP to be delivered will be obtained from participants.

All used/unused IMP will be collected from the patients by delegated site staff, who will then forward it onto the corresponding research site Pharmacy for updating the drug accountability log in the pharmacy file. If participants are unable to attend the site to return unused IMP, then the IMP may be delivered to the site using a locally approved delivery service. 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 10, 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 MPH 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 finalised before breaking the blind. Formal records will be kept of when the statistical analysis plan was finalised 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 and 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 ±2 weeks either side of the 6 week time point will be permitted. We will minimise 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 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 **is related** to any dose administered to that participant. *This includes medication errors, uses outside of protocol (including misuse and abuse of product)*
Serious adverse event (SAE), serious adverse reaction (SAR) or unexpected serious adverse reaction	Any adverse event, adverse reaction or unexpected adverse reaction, respectively, that: • results in death, • is life-threatening, • requires hospitalisation or prolongation of existing hospitalisation, • results in persistent or significant disability or incapacity, or • consists of a congenital anomaly or birth defect
Important Medical Event	These events may jeopardise 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: (a) in the case of a product with a marketing authorisation, in the summary of product characteristics for that product. (b) in the case of any other investigational medicinal product, in the investigator's brochure relating to the trial in question.
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 at baseline and at all weekly assessments following randomisation.

Clinically significant abnormalities in the results of objective tests will also be recorded as adverse events.

Adverse events (and their severity) will be recorded weekly on the case report form until each participant has completed their involvement in the trial.

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 definitions”.

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
Expected	An adverse event that is consistent with the information about the IMP listed in SmPC.
Unexpected	An adverse event that 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 MPH (latest available version).

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 or any delegated member of the study team will complete the sponsor's serious adverse event form and the form will be emailed to primentsafetyreport@ucl.ac.uk within 24 hours of any member of the study team 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 IMP dose administration.

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

Only deaths that are assessed to be caused by the IMP will be reported to the sponsor. Deaths due to disease progression of cancer will not be reported unless it is felt that the IMP resulted in the disease progression occurring earlier than expected. Such deaths will be reported on the SAE form and will be immediate.

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 seven 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 11.6.

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 the trial medication will be stopped, but they will remain on study follow-up. 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 10 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 seven 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, PIS's, consent forms, 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 one 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 PIS's. 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 in accordance 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).

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26 APPENDIX 1 COVID-19 MITIGATION ARRANGEMENTS

In response to the COVID-19 pandemic, temporary arrangements were instituted for participants already enrolled in the study.

- At week 3, week 6 and week 10 participants may now be contacted by telephone (rather than face-to-face). This is currently what already happens at weeks 1, 2, 4, 5, 7, 8, and 9 and therefore does not represent a significant change to usual practice. Those participants who are assessed remotely will be asked to record their own blood pressure at home (if they have a home monitoring device). If they do not have a home monitoring device, then their blood pressure will be measured on the next occasion at which they routinely visit the hospital/ hospice and this will be recorded in the CRF.
- At week 3 and 6 participants will have the option of having the IMP delivered to their house or to have the IMP collected by a delegate (relation or friend) if they verbally consent to do so. Participants must consent verbally to providing contact details for delivery purposes. Where participants are self-isolating or in quarantine, arrangements for a nominated person to collect product may be implemented with the participant's verbal consent.

On 19-Mar-2020, in the light of the escalating national health emergency, recruitment of new patients to the MePFAC trial was suspended. PIs were also instructed to withdraw existing participants from the IMP. The rationale for doing this was to minimise any additional potential burden to the health service that may have arisen as a result of avoidable visits to hospital occasioned by potential adverse effects from the IMP. All participants on the trial on that date had their medication withdrawn according to the dose tapering protocol. Participants remained on the trial and were followed up remotely by telephone until the end of the 10-week study period.