MePFAC
Methylphenidate vs Placebo for Fatigue in Advanced Cancer

Participant Information Sheet (study screening and enrolment)

Methylphenidate versus placebo for fatigue in advanced cancer (MePFAC)

You are being invited to take part in a research study. Before you decide whether to be screened for or take part in this study, it is important for you to understand why the research is being done and what it will involve. Please take the time to read the following information carefully and discuss it with others if you wish. Please ask us if there is anything that is not clear or if you would like more information. Please take time to decide whether or not you wish to take part.

What is the purpose of the study?

People who have been treated for cancer often find they experience tiredness or exhaustion (fatigue) that does not improve with rest. It is a widespread problem in people with cancer at all stages of their illness, whether they are receiving treatment or not, and is particularly common in patients receiving palliative care. There is no "standard" care pathway for the management of cancer-related fatigue and it is not routinely assessed or monitored by healthcare staff in the UK.

The purpose of this study is to determine whether a medication that has mood-enhancing and stimulant properties (methylphenidate) is effective, in comparison with a “dummy pill” that has no therapeutic properties (a placebo), in the treatment of cancer-related fatigue in patients receiving palliative care. Methylphenidate is currently used to treat children with Attention Deficit Hyperactivity Disorder (ADHD), in whom it has been shown to be a safe and effective medication. There is some reason to believe that it may also help adults with cancer-related fatigue, but it has not yet been adequately investigated for this purpose.

What will the main study involve?

If you are involved in the study you will be given either methylphenidate tablets or placebo for ten weeks. Which treatment you receive will be decided at random using a computer and neither yourself nor your doctors will know which treatment you are receiving. This is to make sure that the study is a “fair test”. During the ten week study

period you will be in contact with the research team on a weekly basis, either by telephone or at face-to-face meetings. The study will end after ten weeks. At that time, if you are still feeling fatigued, you will be able to discuss with your doctor whether any further treatment is advisable. This may or may not include use of methylphenidate depending upon your individual circumstances at that time.

Why have I been invited to take part in this study?

You have been invited because you have advanced cancer with moderate to severe cancer related fatigue. We are asking 230 patients over the age of 18 who have advanced cancer with moderate to severe cancer-related fatigue and who are receiving palliative care to participate in this research.

Before we can make a final decision about whether or not you would be suitable for the study we need to ask you some questions about your health, look through your medical records, take some blood tests and check your blood pressure and pulse. This process is known as "screening". If your screening shows you are suitable for the study and you still wish to take part, we will then enrol you onto the study and start your study treatment.

Do I have to take part in the study?

No, it is up to you to decide whether or not you wish to be screened/take part in the study. We will describe the study to you in detail and go over this information sheet. At this point you will also have the opportunity to raise any questions about the study. You do not have to take part unless you feel completely happy with what you are being asked to do. If you agree to be screened/take part, we will ask you to sign a consent form and you will be given a copy. We will then screen you to check that it is safe and suitable for you to take part in the study. You are free to change your mind at any time without giving a reason. Whatever you decide it will not affect the standard of care you receive.

Even if you agree to be screened and are found to be suitable to participate you are under no obligation to take part in the main study and are free to withdraw. However, if you know now that you definitely would not want to take part in the main study then there is no point in agreeing to be screened.

What will happen to me if I take part?

If you agree to take part, you will be asked some questions about your health, and will be asked to allow researchers to look through your medical records. If you have not already recently had a blood test which includes the relevant results, then you will need to provide a new 15 ml blood sample so that we can check whether your kidney

and liver function, blood count and thyroid function are good enough to take part in the study. You may also have to take a urine pregnancy test if relevant. You will also have your blood pressure and pulse measured. The whole process should take about 20-30 minutes.

You will be informed by a member of the research team about whether or not you are suitable to take part in the study. If you are not suitable then no further involvement in the research will be required and if you have any further queries about your health or the treatment of your symptoms then these should be directed to your medical team.

If you are found to be eligible to take part in the study (or while waiting for your screening results), you will be invited to complete the baseline assessments. This will occur within two weeks of being screened and may be done at the same time or at a separate face-to-face or telephone contact.

At the baseline assessment you will be asked to complete a number of questionnaires about your health and your fatigue levels. These will take approximately 20 minutes to complete. You may need your blood pressure, pulse and (if relevant) a pregnancy test repeated (depending on whether and how long a gap occurred between screening and baseline). At the end of the baseline visit you will be given either methylphenidate or an identical looking “dummy pill” (placebo). If you are having a phone assessment then the medication may be delivered to your house. In that case we would seek your verbal consent for allowing the pharmacy to have access to your contact details so that they could deliver study medication to your home. The whole baseline visit will take approximately 60 minutes. Neither yourself nor the medical or research team will know whether you have received the methylphenidate or the placebo. This is to make sure that the study is a “fair test”. Which treatment you receive will be decided randomly by a computer program. You will have a 50% chance of receiving either the methylphenidate or the placebo.

You will be instructed to take one tablet twice daily for at least one week. At the end of the first week, you will be contacted by telephone by one of our researchers. The researcher will ask you some questions about your fatigue, any side-effects you may or may not be experiencing and whether or not you feel that the tablets are helping. The telephone call will last approximately 15 minutes. The researcher will then communicate with your doctor and will call you back with advice about whether to continue on the current dose of the tablets or to change (or stop) the tablets altogether. After each phone call the advice will be confirmed either by a text message (if you agree to this) or by a letter sent in the post (whichever you prefer). If the doctor is unsure about what dose to advise then they may contact you directly to discuss things further (or to ask to see you again) before making a decision.

You will be contacted again after two weeks on the study tablets and the same procedures will be followed. On the third week you will either come back to the hospital/hospice to be seen by one of the doctors or you will be evaluated over the phone. On that occasion you will complete the same questionnaires as you did at the beginning of the study and will have your blood pressure and pulse rate checked again (this can be done at home if you are having a phone assessment). If relevant, the pregnancy test will also need to be repeated. You will be given another supply of tablets. If you are having a phone assessment then the medication may be delivered to your house. In that case we would seek your verbal consent for allowing the pharmacy to have access to your contact details so that they could ship study medication to your home. The assessment will last approximately 45 minutes.

You will be contacted by telephone again after four, five, seven, eight and nine weeks of treatment. After six and ten weeks of treatment you will be asked to come back to the hospital/hospice again for further assessments like the one you underwent at the beginning of the study or these assessments can also be undertaken remotely by phone. After each telephone call or visit you will be advised whether to continue on the same dose of the tablets or whether to increase, decrease or stop the tablets altogether. This advice will be given by telephone and either by text message or by letter (whichever you prefer). The most tablets that you will be advised to take will be four tablets three times daily. During the last week of the study the dose of the medication will gradually be reduced and at the end of the visit at week 10, your involvement in the study will be finished.

Travel expenses that you incur as a result of making additional visits to the hospital/hospice can be covered by the research team. Please let your research nurse know if you wish to claim back these expenses.

Are there any disadvantages in taking part?

Being screened to see if you are suitable for the study will take 20-30 minutes of your time, and at the end of it, you may not be found suitable to participate and so you may feel that this has been a waste of your time. There may also be some slight discomfort associated with having a blood test.

Like all medicines, methylphenidate can cause side-effects, but not everybody gets them. The side-effects are described later in this information sheet.

In addition to the possibility of developing side-effects, involvement in the study may be an added inconvenience for you. You will need to stay in regular contact with the research and clinical team. You will need to be available for a weekly telephone call or visit to the hospital/hospice, and you will need to take the time to answer questions

on the phone or complete questionnaires about your health and fatigue levels. You will need to have your blood pressure and pulse monitored (and you may need a pregnancy test).

Does the treatment have any side-effects?

Methylphenidate is generally safe when given to children with hyperactivity (ADHD). However, it is not known how safe it is in people with cancer who are experiencing fatigue. There is therefore a risk that you may develop side-effects or complications from the tablets.

Very common side-effects (affecting more than 1 in 10 people) are: difficulty sleeping; nervousness; and headache.

Common side-effects (affecting more than 1 in 100 people) are: cold or flu-like symptoms; loss of appetite; mood swings; aggression; agitation; anxiety; depression; irritability; abnormal behaviour; dizziness; abnormal movements; bruxism (teeth grinding); hyperactivity; drowsiness; abnormal heart rhythms; fast heart rate; palpitations; high blood pressure; cough; sore throat; abdominal pain; diarrhoea; nausea; stomach discomfort; vomiting; dry mouth; hair loss; itch; skin rashes; urticaria (raised, red itchy skin bumps); joint pains; fevers; and weight loss.

Uncommon side-effects (affecting more than 1 in 1000 patients) are: allergic reactions such as angioneurotic oedema (swelling affecting lips, tongue, hands, feet, rashes and breathing difficulties); anaphylactic reactions (severe allergic reactions); swelling of the ears; blistering skin conditions; exfoliative (peeling) skin conditions; urticaria (raised, red itchy skin bumps); itch; rashes; psychosis (hearing, seeing or feeling things that aren't really there); anger; suicidal ideas; alteration in mood; mood swings; restlessness; tearfulness; tics (fast, repetitive muscle movements that result in sudden and difficult to control body jolts or sounds); worsening of pre-existing tics or Tourette's syndrome (a neurological condition, characterised by a combination of involuntary noises and movements called tics); hypervigilance (a state of high alert); sleep disorders; sedation; tremors; double vision; blurred vision; chest pain; constipation; abnormalities in liver function blood tests; muscle pains; muscle twitching; blood in the urine; chest pain; fatigue; and heart murmurs.

Rare side-effects (affecting more than 1 in 10,000 patients) are: mania (abnormally elevated mood); disorientation; libido disorder (abnormally high or low sex drive); difficulty focusing vision; dilation of the pupil; visual disturbances; angina (chest pain on exercise); breathlessness; excessive sweating; macular (small flat) skin rashes; erythema (red skin rash); and gynaecomastia (swelling of the breasts in men).

Very rare side-effects (affecting fewer than 1 in 10,000 patients) are: anaemia (lack of red blood cells); lack of white blood cells (thereby increasing risk of infection); lack of platelets leading to easy bruising; suicide attempts or suicide; short-lived depressed mood; abnormal thinking; apathy; repetitive behaviours; over-focussing; fits; involuntary movements; reversible mini-strokes; cardiac arrest; myocardial infarction (heart attack); cerebral arteritis or occlusion (stroke); peripheral coldness; Raynaud's phenomenon (poor blood flow to fingers and toes); abnormalities in liver function; coma due to liver failure; exfoliative (peeling) dermatitis (eczema); erythema multiforme (severe skin rash); fixed drug eruptions (skin lesions which recur in the same area when the same drug is given); muscle cramps; sudden cardiac death; and increase in blood alkaline phosphatase or bilirubin level (liver enzymes).

Side-effects about which the frequency is unknown (cannot be estimated from available data) are: lack of all components in blood (red cells, white cells and platelets); delusions; thought disturbances; confusion; drug abuse and drug dependence (addiction); excessive incoherent and uncontrollable talkativeness; problems with blood circulation in the brain leading to stroke; fits; migraines; dysphemia (stammering or stuttering); abnormal heart rhythms (fast and slow rhythms, extra beats); dry skin; difficulty obtaining or maintaining erections; priapism (persistent erections); increased and prolonged erections; chest discomfort; trismus (painful restriction in opening the mouth due to muscle spasm); incontinence (urinary incontinence); and very high temperatures.

All side-effects will be listed on the leaflet accompanying the treatment when prescribed and your doctor will be happy to discuss these with you. You will also be given a telephone number to contact the research team if you are concerned.

A member of the research team will be in contact with you every week (either by telephone or at a face-to-face visit) and will closely monitor you for any side-effects. If any side-effects are detected then this information will be communicated to the clinical and research team and appropriate actions will be taken. This may include reducing or stopping the study medication or other interventions to address specific problems.

What are the possible benefits of taking part?

There are no direct benefits to taking part in screening. However, if you are found to be suitable, then you will be invited to participate in the study.
If you are on the study and if the methylphenidate is effective, then there may be some benefit in terms of reducing your fatigue. Some people may also find that their fatigue improves even if they are given the "dummy pills" (placebo).

Some people find it reassuring to be in regular (weekly) contact with a member of the research or clinical team for the duration of the trial.

It is important to remember that we cannot promise that the study will help you. However the information that we get from this study may help improve the treatment of other people with cancer-related fatigue. We will ensure that your treatment is delivered to the highest clinical standard and quality standards and we will be monitoring your progress throughout.

What are the alternatives for treatment?

No other medicine has consistently been proven to be effective for cancer-related fatigue. Patients who experience cancer-related fatigue are usually advised to take regular aerobic exercise and to maintain a healthy diet.

What if relevant new information becomes available?

Sometimes we get new information about the treatments being studied. We don't think this is very likely to be the case, but if it happens, we will tell you about it and discuss whether you want to, or should, continue in the study. If you decide not to carry on, we will make arrangements for your care to continue. If you decide to continue in the study we will ask you to sign an updated consent form. If the study is stopped for any other reason, we will tell you why and arrange your continuing care.

Will my GP be informed of my involvement?

We will not inform your GP about the screening unless you are found suitable to take part in the main study and agree to do so. If you are involved in the main study then with your permission, your GP, and other doctors who may be treating you, will be notified that you are taking part in this study.

Will my taking part in this study be kept confidential?

Yes. All information collected about you during the study will be kept strictly confidential and in accordance with the Data Protection Act 1998 and the General Data Protection Regulation 2018. The blood results, blood pressure and pulse readings will be included in your medical record and shared with your health professionals and with the research team.

So that we can keep in contact with you during the study it will also be necessary to share your personal details (name, address, date of birth, telephone number, medical history) with members of the research team. This is so that we can contact you to let you know the results of the screening tests and whether you can be enrolled in the

trial. If you are enrolled onto the study we will still need this information so that so that we can safely advise you about the dose of medication to take and to organise for re-supply of your study medication to be delivered to your home if necessary. We will also need to share your personal details (including your National Health Service [NHS] number) with the NHS Information Centre so that we can keep track of what happens to you after your involvement in the study. The other forms that we use to record your information will not contain your name but will instead use your initials, date of birth and trial identification number, to minimise any risk to confidentiality.

However, once the trial has been completed, any information about you that we collect will have your name and any other identifiable details removed and will be given a special code number. This code number will also be used to identify the questionnaires that you are sent, and the key to the code will be kept in a locked cabinet at the research centre at University College London (UCL) and on a secure computer server. Any identifiable information will be stored separately and securely at the research centre at UCL and locally at the site at which you are recruited (hospital or hospice). The identifiable information which is stored electronically, will be on a secure online database hosted on a secure encrypted server in Ireland by a company called Sealed Envelope with access only authorised by the sponsor. Sealed Envelope will not have authorisation to use or share any data from this trial and UCL has entered into an agreement with Sealed Envelope to ensure your confidentiality is protected. Sealed Envelope will act only on instructions from UCL and have in place appropriate technical and organisation security measures to prevent unauthorised access and processing of this data. Only members of the research team and responsible people authorised by the Sponsor, regulatory authorities or from the NHS Trusts / hospices involved will have access to this data. The Chief Investigator is responsible for the secure archiving of essential trial documents (for each site) and the trial database as per their trust policy. All essential documents will be archived for a minimum of 25 years after completion of the trial.

Although your GP will be aware that you are taking part in the study, (s)he will not know which treatment you are receiving and (s)he will not have access to any other data you provide as part of the research study (e.g. your answers to the questionnaires).

Data Protection Privacy Notice

The data controller and the data processor for this project will be University College London (UCL). The UCL Data Protection Office provides oversight of UCL activities involving the processing of personal data, and can be contacted at data-protection@ucl.ac.uk. UCL's Data Protection Officer is Lee Shailer and he can also be contacted at data-protection@ucl.ac.uk**.**

Your personal data will be stored for up to five years after the study has ended (in line with UCL data retention policies). Your personal data will be processed for the purposes outlined in this notice. The legal basis that will be used to process your personal data will be the conduct of a "public task". Your rights to access, change or move your information are limited, as we need to manage your information in specific ways in order for the research to be reliable and accurate. If you withdraw from the study, we will keep the information about you that we have already obtained. To safeguard your personal data it will be processed so long as it is required for the research project. Whenever possible we will pseudo-anonymise your personal data and we will endeavour to minimise the processing of personal data.
If you are concerned about how your personal data will be processed, please contact UCL in the first instance at data-protection@ucl.ac.uk. If you remain unsatisfied, you may wish to contact the Information Commissioner's Office (ICO). Contact details, and details of data subject rights, are available on the ICO website at: https://ico.org.uk/for-organisations/data-protection-reform/overview-of-the-gdpr/individuals-rights/.

What happens when the research study stops?

At the end of the week 10 assessment, your involvement in the study will be finished. At that point you will be treated and monitored in exactly the same way as if you had not been on the study. Your doctor may or may not consider that it is advisable to try using methylphenidate or any other treatment to help with fatigue. This decision will depend upon your medical condition at that time.

What will happen to the results of the research study?

The study results will be presented at conferences and published in relevant medical journals. None of the people taking part in the study will be identified in reports or publications. If you wish we will send you, or your friends or relatives, a brief summary of the results at the end of the study. Copies of any publications can be obtained from the study organisers and sent to any study participants and GPs who wish to have them.

What happens after screening?

You will be contacted by a member of the research team a few days after the screening to let you know whether or not you are suitable to take part in the main study. If you are not suitable then no further involvement in the research will be required and if you have any further queries about your health or the treatment of your symptoms then these should be directed to your medical team. If you are found to be eligible to take part in the study then you will be invited back to the hospital/hospice for a further

visit to discuss the study in more detail and to start the study treatment if you are agreeable.

Who is organising and funding the research?

The study is being organised by the Marie Curie Palliative Care Research Department, Division of Psychiatry, University College London. Funding is from the National Institute for Health Research (NIHR) Health Technology Assessment. Some staff working on the project are supported by Marie Curie funding and infrastructure support.

Who has reviewed this study?

This study has been reviewed and approved for its scientific methods by independent researchers in the field appointed by the research funder.

In addition, all research in the National Health Service (NHS) is looked at by an independent group of people, called a Research Ethics Committee, to protect your interests. This study has been reviewed and given a favourable opinion by London - City & East Research Ethics Committee (REC reference 17/LO/0871).

What if there is a problem?

If you have a concern about any aspect of this study, you should ask to speak with the researchers who will do their best to answer your questions - please see details below. If you remain unhappy and wish to complain formally, you can do this by contacting:

[local site to insert local contact details for complaints service].

Every care will be taken in the course of this study. However, in the unlikely event that you are injured by taking part, compensation may be available. If you suspect that the injury is the result of the Sponsor's (University College London) negligence then you may be able to claim compensation.

After discussing this with a member of the research team, please make the claim in writing to Professor Patrick Stone who is the Chief Investigator for the clinical trial and is based at the Marie Curie Palliative Care Research Department, Division of Psychiatry, University College London. The Chief Investigator will then pass the claim to the Sponsor's Insurers, via the Sponsor's office. You may have to bear the costs of the legal action initially, and you should consult a lawyer about this.

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. You should discuss this possibility with a member of the research team (details given at the end of this letter) in the same way as above.

Regardless of this, if you wish to complain, or have any concerns about any aspect of the way you have been approached or treated by members of staff or about any side effects (adverse events) you may have experienced due to your participation in the clinical trial, the normal NHS complaints mechanisms are available to you. Please ask your study doctor if you would like more information on this. Details can also be obtained from the Department of Health website: http://www.dh.gov.uk.

What if there is an emergency?
You will be provided with a card which can be given to attending medical staff and which explains whom to contact in an emergency.

What if I have any questions or concerns about the study?

We are providing contact details and telephone numbers and email addresses so you can contact us if you have any questions at any point. We will be happy to ring you back if you wish.

Thank you for taking the time to read this.

Local Principal Investigator	**Local research nurse**

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