DESPIAD TRIAL STUDY PARTNER (CARER) INFORMATION SHEET

Full Trial Title: Depletion of Serum Amyloid P Component in Alzheimer's disease: DESPIAD. Double-blind randomised trial of SAP depletion by CPHPC in mild Alzheimer's disease.

Short Trial Title: DEpletion of **S**erum amyloid **P** component In **A**lzheimer's **D**isease: DESPIAD

Invitation to take part in research trial

We would like to invite you to take part in our research trial as a study partner or caregiver of someone who has mild Alzheimer's disease, and who has expressed a wish to participate in this study. We will refer to participants with Alzheimer's disease as the "main participants". Before you agree to participate, we want you to understand why the research is being done and what it would involve for you as a study partner. Part 1 of this document tells you about the purpose of this trial and what will happen to the main participant and yourself, if you take part. Part 2 gives you more detailed information about the conduct of the trial. Please feel free to talk with family, friends and your GP about the trial if you wish. Take time to decide whether or not you want to take part as a study partner. One of our team will go through the information sheet with you and answer any questions you have. Please ask us at any time if anything is unclear.

PART 1

What is the purpose of the trial?

Alzheimer's disease is the commonest cause of dementia affecting around 30 million individuals worldwide. Alzheimer's disease is caused by the abnormal build-up of various proteins in the brain to form what are known as amyloid plaques. The plaques are toxic to brain cells, and eventually cause their death. This leads to the gradual decline in day-to-day memory and other mental functions. Serum amyloid P component (SAP) is a normal protein that occurs in everyone. It is manufactured in the liver and then travels in the blood stream to reach other organs including the brain. Although only very small amounts of SAP enter the brain, it binds to the abnormal proteins in the brains of patients with Alzheimer's disease. It forms part of the amyloid plaques and prevents them from breaking down. Therefore, preventing SAP from binding amyloid plaques may lead to faster breakdown of the amyloid plaques and so delay the progression of Alzheimer's disease. There is also evidence that SAP directly damages brain cells and may contribute to the development of Alzheimer's disease. Removal of SAP may reduce this damage to brain cells. A new drug has been developed, called CPHPC, which eliminates SAP almost completely from the blood and thereby stops SAP from reaching the brain. CPHPC may also remove the SAP already present in the brain. This may reduce the brain damage caused by the disease.

CPHPC has been given daily to about 100 individuals, including both normal healthy volunteers and patients with systemic amyloidosis, Alzheimer's disease and osteoarthritis, for periods of up to nearly 7 years, involving over 60,000 injections to date. Over 45 systemic amyloidosis patients have received the drug daily for at least one year. Systemic amyloidosis is a severe condition in which amyloid can affect the major body organs, heart, kidneys, liver, spleen, nerves, gut, skin and blood vessels and the patients are accordingly often very sick indeed. However there have been no side effects or adverse effects of the treatment other than mild temporary discomfort in the skin at the site of some of the injections. CPHPC was similarly well tolerated in 5 patients with Alzheimer's disease who were treated for 3 months in our preliminary study to confirm that CPHPC removed SAP from the brain.

This trial aims to add to our knowledge of the safety and side effects of CPHPC treatment in participants with mild Alzheimer's disease, and to determine whether CPHPC treatment for one year

provides clinical benefit as measured by the tests used to monitor the progression of Alzheimer's disease.

Why have I been invited to take part as a study partner?
You have been ask to participate in this study because you are a partner or carer of someone who has been diagnosed with mild Alzheimer's disease and their doctor believes that they could be eligible to take part in the trial. All the other main participants in the trial will have the same condition and they all need to have a study partner participating with them in the trial.

Do I have to take part as a study partner?
No. It is entirely your choice whether or not you would like to take part as a study partner. This information sheet should help you to make your decision. Please also ask us if anything is unclear or you have any questions.

If you decide not to take part, the main participant can still participate in the study if they can identify an alternative study partner. However, if no other study partner is identified, then the main participant will not be able to take part in the study. Main participants will still receive whatever treatment they and their doctors decide is best for them. Their medical and other care will not be affected in any way. If you agree to participate as a study partner, you will always remain free to withdraw at any time without giving a reason. The standard of care the main participant receives will not be affected in any way by withdrawal from the trial. However, the main participant may not be able to continue in the study, unless there is another designated study partner already participating in the study, or you are replaced by another study partner.

What will happen to me if I take part as a study partner?
If you decide to take part, we will ask you to sign a consent form as a study partner. The main participant will then undergo a screening process. This takes place over a period of up to four weeks to check that they are eligible for the trial. A member of the trial team will go through the initial assessment required to join the trial including collecting details of their medical history and checking that they meet the safety criteria. The research doctor will also ask you for information that you may have about the main participant's medical history and level of day-to-day function. If the research doctor still feels that it is satisfactory for them to enter the trial they will then be randomly allocated to one of the two groups to receive injections for a maximum of 12 months.

Arm A: Main participants in this active arm will receive the drug CPHPC at a dose of 60 mg (0.3 ml) three times daily by injection under the skin (subcutaneous) for the whole length of the trial.

Arm B: Main participants in this placebo arm will receive 0.3 ml of water for injection three times daily by injection under the skin (subcutaneous) for the whole length of the trial. The placebo does not contain the active component.

Sometimes we do not know which way of treating patients is best. To find out, we need to compare different treatments. In this trial there will be 2 groups of equal size, one receiving the active drug and one receiving an inactive placebo. Main participants will have an equal chance of being placed in one group or the other. Main participants are allocated to the CPHPC and placebo groups completely at random, like tossing a coin, and they will not know which group they are in. This trial is also 'double-blind', which means that neither main participants nor the research doctors will know which treatment group they are in. However, if the research doctor needs to find out for medical reasons they can always do so at any time.

The injections will be administered by the main participants or you as their study partner or carer. If you are going to administer the injections, it will be very important that you agree to administer the injections on a daily basis throughout the study, which will be a major commitment. You will be shown by the research team exactly how to administer the injections before you take over this role. Even if the main study participant will self-administer the injections, we will ask you to oversee the management of the injections. The study team will show you exactly how to do this. If a new study partner or carer becomes responsible for the injections then they will have to be shown by the research team exactly how to administer the injections before they can take over that role. At any one point, the main participant may have more than one designated study partner as long as they have all consented to be designated study partners. If you or any other study partner will be administering the injections, it is important to emphasize that the injections should not be administered against the main participant's will.

After the first week of the main participant receiving injections, you and the main participant will be contacted by the trial team to ask whether they have received all the scheduled injections, or have any problems or questions. If at this time the main participant no longer wishes to receive injections, then they will be withdrawn from the trial.

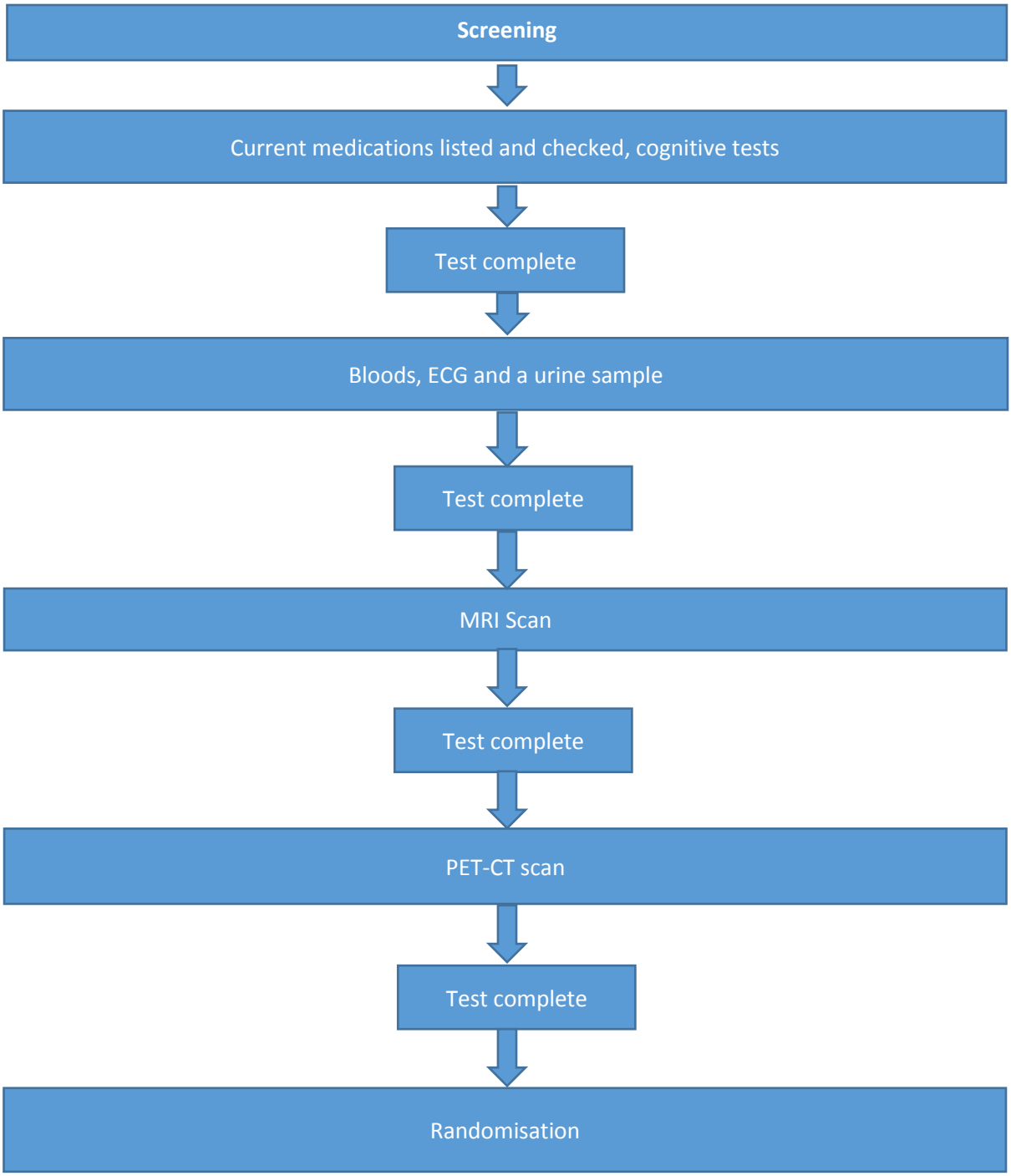
Between consent and screening there is a 4 week window to perform screening tests on the main study participant. After treatment has been completed for 12 months there is a 1 month follow up. Therefore, the maximum time in the trial from the day of consenting will be 14 months. There will be no long term follow up unless the research doctor feels this is appropriate, but, the research doctor will discuss this with you and the main participant if needed. There will be various assessments carried out before, during and after the trial, which can be found in the diagram below. There will also be visits to the research doctor at different points throughout the trial. You or other designated study partners will be asked to accompany the main participant during all study visits. The main participant will be asked at several points throughout the trial to complete questionnaires and tests to assess their mental capabilities. These tests help the research doctors to assess the status of their disease. Some of these questionnaires or tests require your input as someone who knows the main participant well. You will be asked standardised questions relating to your opinion and observation of the main participant's day-to-day function and mental capabilities. If there is more than one designated study partner, it will be important that the same study partner attends all visits that involve these questionnaires and tests.

<u>What will I have to do as a study partner?</u>

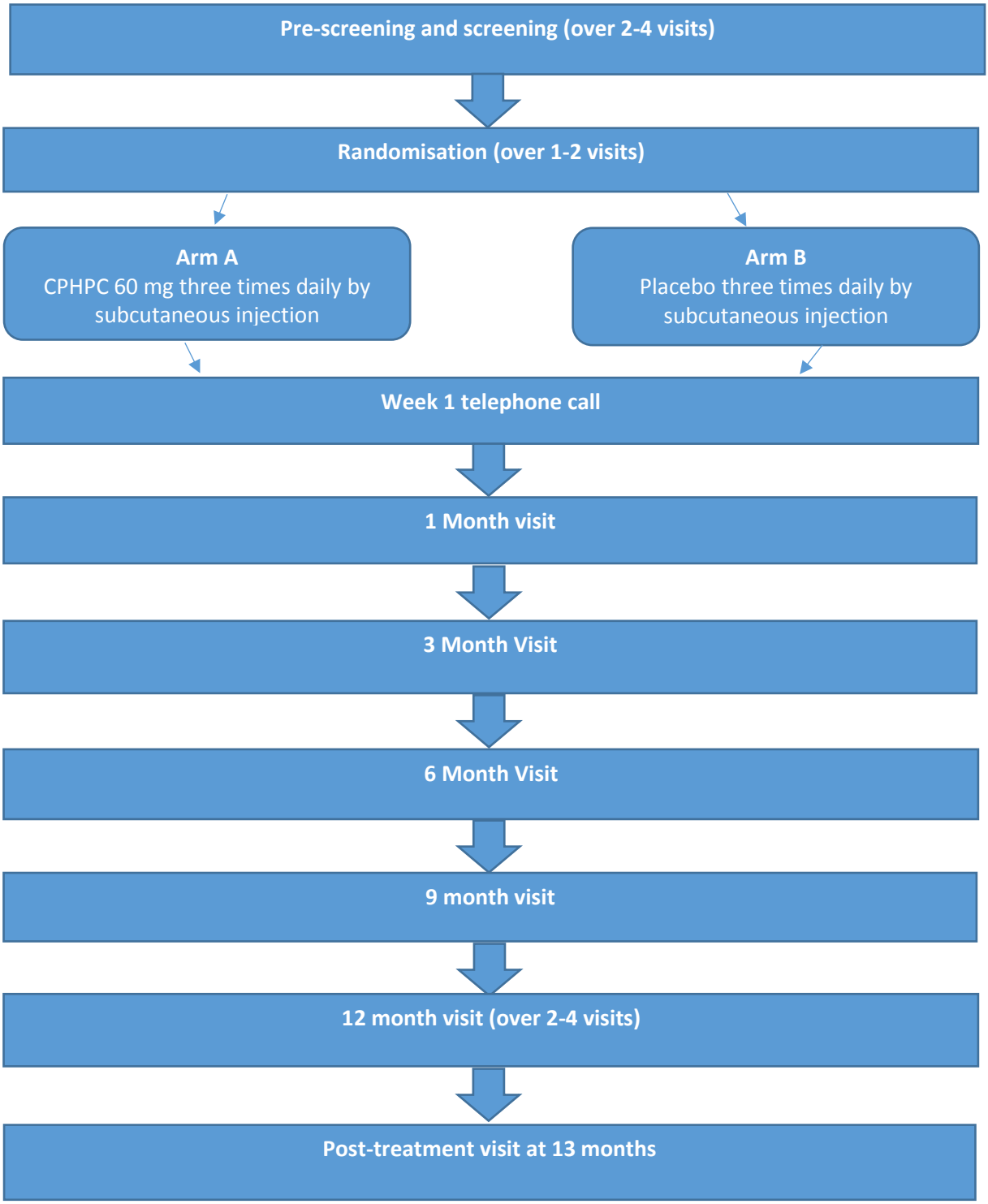
Diagrams of the trial visits and the assessments the main participants will be required to have at different times are shown on the following pages.

Screening for the trial

Screening assessments to determine whether the main participant can be accepted into the trial will involve 2-4 visits. The results from each visit must meet the trial criteria before they can proceed to the next visit. It is therefore possible that they may not complete the full assessment.



Trial Summary Flowchart



Once the main participant is in the trial they will need to attend the clinic at set times (1, 3, 6, 9 and 12 months after starting treatment and then one month after you finish treatment). You or any other designated study partners will need to accompany the study participant on all visits. The exact dates and times will be provided to you once the trial starts. During the study visits there will be various assessments carried out on main participants including: blood samples, urine samples, ECG (an electrical tracing of the heartbeat) and reviews by the research doctor to check for side effects. As

someone who has the opportunity to observe the main participant in his or her day-to-day settings, you will be expected to be alert to any new changes in the main participant's symptoms or behaviour and report them to the study team during study visits. The main participant will also be asked to have imaging scans on different visits, these include an MRI and amyloid PET-CT (both tests are a scan of the head). In addition, neurological tests on the main participant will be carried out at different visits. You or other designated study partners will be expected to accompany the main participant on all visits. Each trial visit will vary in duration depending on the assessments required; please discuss this with a member of the research team before consenting.

The main participant will also be asked to undergo a lumbar puncture (spinal tap) to collect a sample of spinal fluid on 2 occasions. This procedure involves having a needle inserted into the bottom of the spine to collect about two teaspoons (up to 10 ml) of spinal fluid. This will be performed by a research doctor who is trained and experienced in the procedure. Common complications include headache that worsens on sitting or standing, and pain, minor bleeding or bruising at the puncture site. The participant may need to lie down for a while after the lumbar puncture. Overnight care and observation can be provided, if necessary, after the lumbar puncture has been performed.

We will measure the main participant's memory, language and thinking, using different questionnaires and tests. These will take place throughout the trial to find out whether there have been any changes. Some of these questionnaires and tests require your input as someone who knows the main participant well. You will be asked standardised questions relating to your opinion and observation of the main participant's day-to-day function and mental capabilities. If there is more than one designated study partner, it will be important that the same study partner attend all visits that involve these questionnaires and tests.

The main participant will undergo three MRI scans and two PET-CT scans of the head as part of the trial. An MRI scan is a safe and painless procedure that uses magnetic fields to produce a detailed image of the head. There is no exposure to radiation (X-rays) during MRI scanning. The MRI scan involves the main participant lying still in a small noisy space for up to one hour; some people may feel claustrophobic. If at any point during the MRI scan the main participant wants to stop there is a button they can press to alert a member of staff. During a PET-CT scan the main participant is exposed to radiation from the X-rays of the CT scanner, and from the radioactive PET tracer injected into one of their veins through a small tube (cannula) just before scanning. The scan involves lying still in the scanner, which is larger and quieter than the MRI scanner. The whole process of obtaining a PET-CT takes about one hour.

There is also an optional transcranial magnetic stimulation (TMS) test. TMS is a safe and non-invasive method for assessing brain cell function. It involves the stimulation of a small area of the brain by applying a localised pulse of magnetic field using a small hand-held coil device over the head. In this experiment, the part of the brain controlling specific hand muscles will be stimulated. This results in a brief (one fifth of a second) painless twitch of hand muscles. Each TMS measurement study takes about 1 hour to complete and involves administering 70-80 pulses. The TMS experiments will be conducted by trained technicians in Professor John Rothwell's TMS laboratory at Queen Square, UCL. It is completely the main participant's choice whether they want to undergo this test or not.

The trial will involve 100 main participants and, although each individual is studied for 14 months, recruitment and completion of all main participants will take 3 years in total, including the time required to analyse the results. If the main participant, for any reason, is unable or unwilling to undergo all the required investigations they may be withdrawn from the trial and you will no longer be required to participate as a study partner.

Expenses and Payments

You and the main participant will be reimbursed for any reasonable extra expenses, e.g. cost of travelling to attend study visits as needed to take part in this trial. We are unable to make any payment for participation in this trial.

What is the treatment?

The new drug being tested here, CPHPC, is in the early stages of development but has already been used in about 100 people over the past 15 years, both normal healthy volunteers and patients with various diseases, including some with Alzheimer's disease. The purpose of CPHPC treatment is to remove a protein called serum amyloid P component (SAP) from the brain. The drug has been shown to do this, both in experimental studies and in 5 patients with Alzheimer's disease. The purpose of this trial is to confirm the safety and side effects, if any, of the treatment and to see whether it helps patients with Alzheimer's disease.

The placebo is pharmaceutical 'water for injection', specifically prepared for injection into patients. Both the CPHPC and the placebo will be administered by three small daily injections under the skin of the lower tummy. The clinic team will teach you, any other designated study partners and/or the main participant how to do the injections.

If, at any time, the main participant no longer wishes to receive injections, they will be asked if they are willing to continue attending for some or all of the trial assessments, but there will be no obligation to do so. You are also free to withdraw from acting as a study partner at any time without giving any reason. However, the main participant may not be able to continue in the study, unless there is another designated study partner already, or you are replaced by another study partner.

What are the possible disadvantages and risks of taking part to main participants and study carers?

It is not anticipated that there are any significant risks. However this is a trial of a new experimental drug so we cannot be sure that there will be no side effects.

Any new drug being investigated at an early stage of development can potentially cause side effects. All main patients in the trial will be watched carefully for any side effects. You will be asked to remain vigilant for any new symptoms or side effects that the main participant experiences during the study and report them to the research team. Side effects can be mild or serious. If the main participant experiences a side effect, the trial staff may give them medicines to help lessen these effects. Some side effects may go away as soon as the study participant stops taking the drug. In some cases, side effects can be serious, long-lasting or may never go away.

- You will need to consider the clinic visit and investigation schedule which is potentially tiring and time consuming both for you, any other designated study partners and the main participant.

- Administration of the trial medication requires three (3) daily injections under the skin of the tummy (abdomen). Although the amount injected each time and the needles used are very small, the injections may cause moderate temporary discomfort and occasionally bruising. Tolerance of these injections varies between individuals but many patients have taken them for years at a time without problems. As the trial medication involves injections, there is a risk of needle stick injury either to yourself or the main participant. The study team will show you and your partner exactly how to prepare, handle the injections and dispose of the needle in order to minimise this risk and what to do if any of you sustains a needle stick injury. You, any other study partners and/or the main participant will be asked to administer all injections throughout the study. This will be a major commitment and undertaking for all of you.

- The only side effect definitely caused by CPHPC has been related to the injections. Injection of CPHPC under the skin (subcutaneous injection) is sometimes associated with stinging and discomfort, which lasts for up to a few minutes. It is important not to inject the same area twice in a row to help reduce the chances of discomfort at the site of injection. This has not been a problem for most people but a few patients receiving the drug have discontinued treatment for this reason. If after starting the injections you, any other designated study partners or the main participant have any concerns about side effects, please contact the trial team immediately.

- The lumbar puncture procedure can be uncomfortable. Local anaesthetic is used to make the area numb but if the main participant experiences discomfort they should inform the research doctor performing the procedure and she/he will use additional local anaesthetic. After the lumbar puncture, the main participant may be asked to remain lying down for a while. Some patients experience headache that can last up to a week after a lumbar puncture.

- The amount of radiation from the PET radioactive tracer is very small and it does not make the main participant feel unwell. The radiation goes away very quickly and drinking plenty of fluids after the scan helps flush the tracer out of their system but they should keep away from pregnant women and young children for six hours after the scan. The radiation from the radioactive tracer and from the CT part of the scan is also kept to the minimum necessary and is similar to the background radiation each of us is exposed to on a daily basis over two years. The risk of the radiation causing any problems in the future is very small. The MRI scan does not involve any radiation.

- Some subjects may report a mild headache from the TMS, but this resolves with non-prescription medication. Some subjects may experience discomfort from pressure applied to the skin in order to attach recording leads on the head or arm. TMS at very high intensities and at frequencies that will not be used in the study, has been reported to induce seizures. However we will follow internationally published safety guidelines to avoid this. To minimise the risk further, subjects who have had seizures in the past will be excluded. The TMS laboratory is located on the Hospital's premises and has well established standard operating procedures for dealing with any medical emergencies including seizures.

- If the main participant is a woman of child bearing potential or a male with a partner of child bearing potential they will be required to use contraception during the trial and for 30 days after the trial end of treatment. Contraception includes oral, injected or implanted hormonal methods, placement of an intrauterine device (IUD) or intrauterine system (IUS); female or male condom with spermicidal gel, true abstinence or male sterilisation.

- Warfarin or any other anticoagulant drug is prohibited at the time of the main participant's enrolment and throughout the trial (due to an increased risk of bleeding from the lumbar puncture). Cholinesterase inhibitors, memantine and antidepressant drugs are prohibited unless the main participant is maintained on a stable dose for at least 3 months prior to randomisation.

<u>What are the possible benefits of taking part?</u>

Taking part in this trial may not benefit you or the main participant directly. If the main participant is in the active treatment group the drug will reduce the amount of SAP in their blood and remove the SAP from their brain throughout the period of treatment. Although the purpose of the trial is to see whether this affects the severity and progression of the main participant's Alzheimer's disease, we

cannot promise that the treatment will improve their condition. Nevertheless, everyone who enters the trial will contribute very useful information about the treatment of Alzheimer's disease and thus help future developments. An independent group of experts will be reviewing the results and observations throughout the trial to ensure safety and maintenance of the highest standards of care.

What happens when the research stops?

CPHPC treatment is still experimental and the drug will not be available to patients participating in this trial after its completion. The main participant will revert back to their normal treatment.

What if there is a problem?

Any complaints about negative experiences related to the trial or any possible harm you might suffer will be addressed. The detailed information concerning this is given in Part 2 of this information sheet. If you, any other designated study partners or the main participant have any concerns or complaints you should contact the research doctor in the first instance.

Will my taking part in the trial be kept confidential?

Yes. We will follow ethical and legal practices and all information about you, any other study partners and main participants will be handled in confidence. The details are included in Part 2.

If the information in Part 1 has interested you and you are considering participation in the trial as a study partner, please read the additional information in Part 2 before making any further decisions.

PART 2

What if relevant new information becomes available?

Sometimes we get new information about the treatment being studied. If this happens, the research doctor will tell you and the main participant and discuss whether you both should continue in the trial. If the main participant decides not to carry on, the research doctor will make arrangements for their usual care to continue. If the main participant wishes to continue but you do not, then they can continue in the study as long as there is another designated study carer who agrees to take over your role. If you both decide to continue in the trial, your research doctor may ask you both to sign an agreement outlining the discussion. On receiving new information the research doctor might advise you and the main participant to withdraw from the trial. She or he will explain the reasons and arrange for the main participant's care to continue.

What will happen if I or the main participant do not want to carry on with the trial?

If you wish to withdraw from the trial as a designated study partner, the main participant can continue in the study as long as there is another designated study partner who agrees to take over this role.

If the main participant withdraws from the clinical trial it can affect how the results are analysed, so we ask you both to think carefully about participating and attending for all visits before you agree to take part. However, the main participant will be free to stop receiving injections at any time without giving a reason. Information collected about the main participant during the trial may still be used (although they can request that their information is not used). If they do not wish to continue follow up, we will request to see them for an exit check-up within 1 week. This exit check-up would involve all the tests planned for the 12 month visit such as lumbar puncture, MRI, PET CT etc. If they wish, any stored samples that can still be identified as theirs will be destroyed.

What if there is a problem?

If you or the main participant have any concerns you should discuss them with your local study team first. You can also contact the Chief Investigator, Prof Martin Rossor, on 0203 549 5438 who will be happy to discuss any of your concerns. If you would like to discuss your concerns with someone not involved in the study, you can contact your local Patient Advice and Liaison Service (PALS) (information on how to contact your local PALS can be found at the end of this information sheet).

Notwithstanding the absence of legal commitment, UCL will pay compensation to patient-volunteers suffering bodily injury (including death) when, on the balance of probabilities, the injury was attributable to the administration of a medicinal product under trial or any clinical intervention or procedure provided for by the clinical trial protocol that would not have occurred but for the inclusion of the patient in the trial. After discussing with your study doctor, you should make the claim in writing to Professor Rossor who will then pass the claim to the Sponsors. You may have to bear the costs of the action initially, and you should consult a lawyer about this. Main participants (and study partners/carers) may be able to claim compensation for injury caused by participation in this clinical study without the need to prove negligence on the part of University College London or another party.

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

Will my taking part in this trial be kept confidential?

Yes, if you and the main participant consent to this trial, the records obtained while you are in this trial as well as related health records will remain strictly confidential at all times. The information will be held securely on paper and electronically at the Leonard Wolfson Experimental Neurology Centre under the provisions of the 1998 Data Protection Act. Your and the main participant's names will not be passed to anyone outside the research team or the Sponsor (UCL). You and the main participant will be allocated trial numbers, which will be used as codes to identify you on relevant trial forms. Any information about you or the main participant that leaves the hospital will have your names and addresses removed so that you cannot be identified.

Your and main participant's records will be available to people who work on the trial but may also need to be made available to people authorised by the Sponsor, which is the organisation responsible for ensuring that the trial is carried out correctly. By signing the consent form you agree to this access for the current trial and any further research that may be conducted in relation to it, even if you or the main participant withdraw from the current trial. This will include safety information that is collected about the trial medication that will be sent to the supplier of the medication.

The information collected about you or the main participant may also be shown to authorised staff from the UK Regulatory Authority (the Medicines and Healthcare Products Regulatory Authority) and the relevant Research Ethics Committee; this is to ensure that the trial is carried out to the highest possible scientific standards. All will have a duty of confidentiality to you and the main participant.

If, having started in the trial, the main participant withdraws consent from further trial treatment, their data and samples will remain on file and will be included in the final trial analysis unless they object. At the end of the trial, in compliance with Good Clinical Practice guidelines, their data will be securely archived for a minimum of 10 years. Arrangements will then be made for confidential destruction.

Will the main participant's GP be informed of their involvement?

With the main participant's consent, their GP and other doctors treating them will be notified that they are taking part in this trial. If there are any changes in their care requirements as a result of taking part in the trial, their GP will again be informed.

What will happen to any samples the main participant gives?

Blood samples and urine samples will be collected at eight points during this trial. The main participant will also be asked to provide samples of spinal fluid at two trial visits. These will be used to establish a baseline assessment of their health and check for any changes that may occur during treatment. If it is clinically necessary, they will be contacted by a member of the research team with the results. Their samples will be tested at specified central laboratories and then securely stored in case any need arises to test them as part of future research. The samples will be accessible the staff of UCL hospital laboratories, Royal Free hospital laboratories and GSK laboratories. They will be labelled with their month and year of birth and unique participant identification number to ensure that they can be accurately identified. They will not be transferred out of the UK.

What will happen to the results of the research trial?

The results of the trial will be available after it finishes and will usually be published in a medical journal and/or be presented at scientific conferences. The data will be anonymous and none of the main participants or study partners involved in the trial will be identified in any report or publication. Should you or the main participant wish to see the results, or the publication, please ask the research doctor.

Who is organising and funding the research?

This trial is being managed by the UCL Comprehensive Clinical Trials Unit (CCTU). University College London is the trial sponsor. Funding for the trial has come from the National Institute for Health Research (NIHR). The sponsor of this trial (UCL) will pay the Leonard Wolfson Experimental Neurology Centre for including the main participant and you in this trial.

Who has reviewed this trial?

All research in the NHS is looked at by an independent group of people called a Research Ethics Committee to protect your interests. The DESPIAD trial, including patient information sheet version 2.0, has been reviewed and formally considered acceptable by Berkshire B Research Ethics Committee.

Further information and contact details

You and the main participant are encouraged to ask any questions you may have before, during and after treatment. If you or the main participant have any questions please speak to the research nurse or research doctor who will be able to provide you with up to date information about the trial and treatment. If you or the main participant wish to read further about the research on which this trial is based, please also ask your research nurse or research doctor. For any further information on this trial please contact one of the following people:

Research Doctor
XXXXX

Research Fellow
XXXXXX

Research Nurse
XXXXXX

Emergency Contact Number
XXX

PALS contact:
XXXXXXXXXXX

The main participant will be given a copy of the patient information sheet and informed consent form to read before deciding to take part, and a signed copy if they decide to proceed and consent.

You will be given a copy of the study partner (carer) information sheet and consent form. Before you sign the informed consent form, you should ask questions about anything that you do not understand.

Thank you for taking the time to read this information sheet.