DESPIAD TRIAL PATIENT 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. Before you agree to participate, we want you to understand why the research is being done and what it would involve for you. Part 1 of this document tells you about the purpose of this trial and what will happen to you 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. 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.

Patient Information Sheet
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?
You have been chosen for this trial because you have been diagnosed with mild Alzheimer's disease and your doctor believes that you could be eligible to take part in the trial. All the other patients in the trial will have the same condition as you.

Do I have to take part?
No. It is entirely your choice whether or not you would like to take part. 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, you will still receive whatever treatment you and your doctor decide is best for you. Your medical and other care will not be affected in any way. If you agree to participate, you will always remain free to withdraw at any time without giving a reason. The standard of care you receive will not be affected in any way by withdrawal from the trial.

What will happen to me if I take part?
If you decide to take part, we will ask you to sign a consent form. You will then undergo a screening process. This takes place over a period of up to four weeks to check that you 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 your medical history and checking that you meet the safety criteria. If the research doctor still feels that it is satisfactory for you to enter the trial you will then be randomly allocated to one of the two groups to receive injections for a maximum of 12 months.

Arm A: 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: 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. You will have an equal chance of being placed in one group or the other. Participants are allocated to the CPHPC and placebo groups completely at random, like tossing a coin, and you will not know which group you are in. This trial is also 'double-blind', which means that neither you nor your research doctors will know which treatment group you are in. However, if your doctor needs to find out for medical reasons they can always do so at any time.

The injections will be administered by you or your carer(s). If your carer is going to administer the injections, it will be very important that they agree to administer the injections on a daily basis throughout the study, which will be a major commitment. Your carer(s) (and you, should you decide to administer yourself) will be shown by the research team exactly how to administer the injections. In any case we will ask your carer to oversee the management of the injections. If you have a new carer who becomes responsible for your injections then he/she will have to be shown by the research team exactly how to administer the injections before they can take over that role.

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

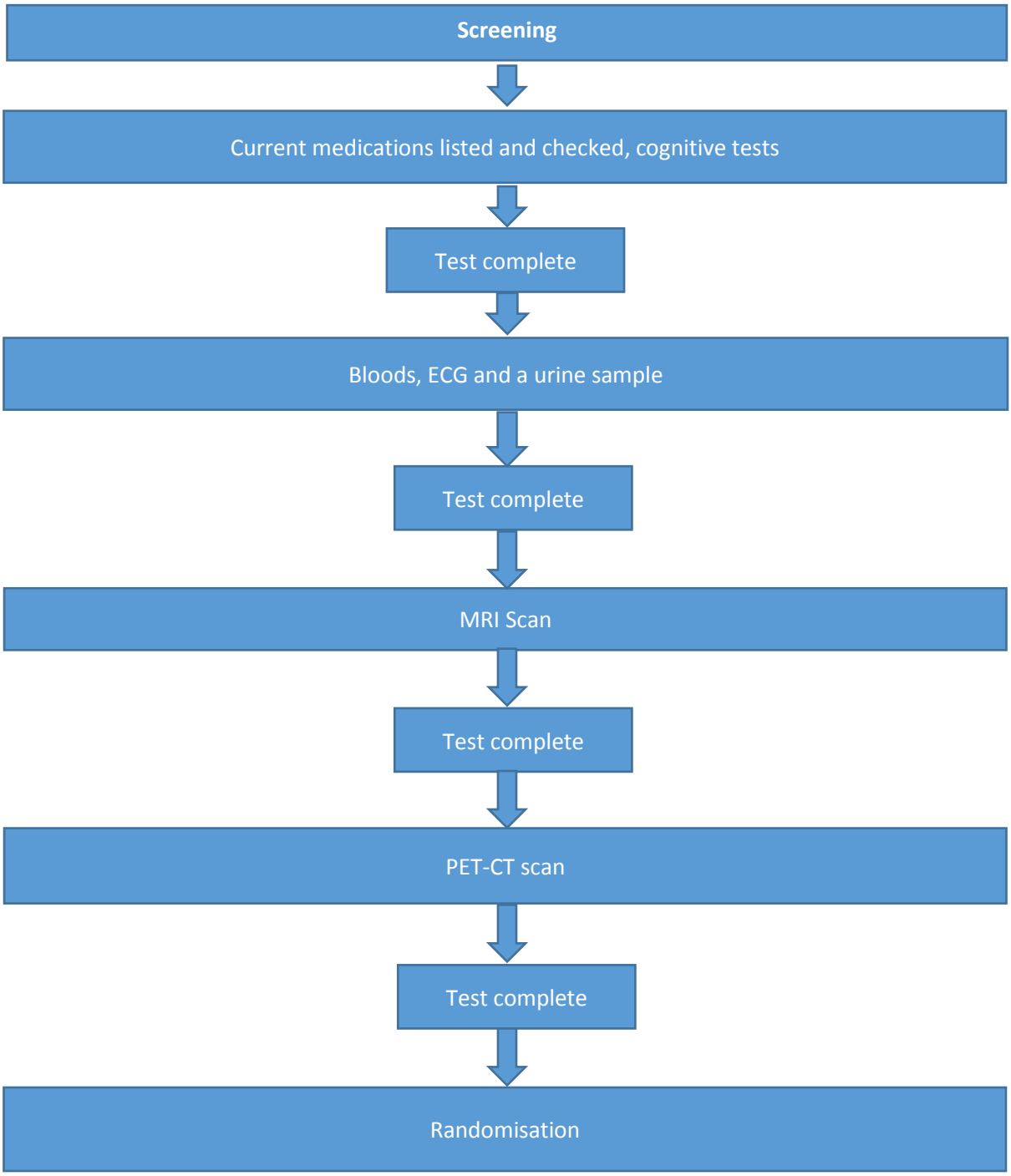
Between consent and screening there is a 4 week window to perform screening tests. After treatment has been completed for 12 months there is a 1 month follow up. Therefore, the maximum time in the trial from the day of consenting will be 14 months. There will be no long term follow up unless your research doctor feels this is appropriate, but, your research doctor will discuss this with you 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 your research doctor at different points throughout the trial. You will be asked at several points throughout the trial to complete questionnaires and tests to assess your mental capabilities. These tests help the research doctors to assess the status of your disease.

What will I have to do?

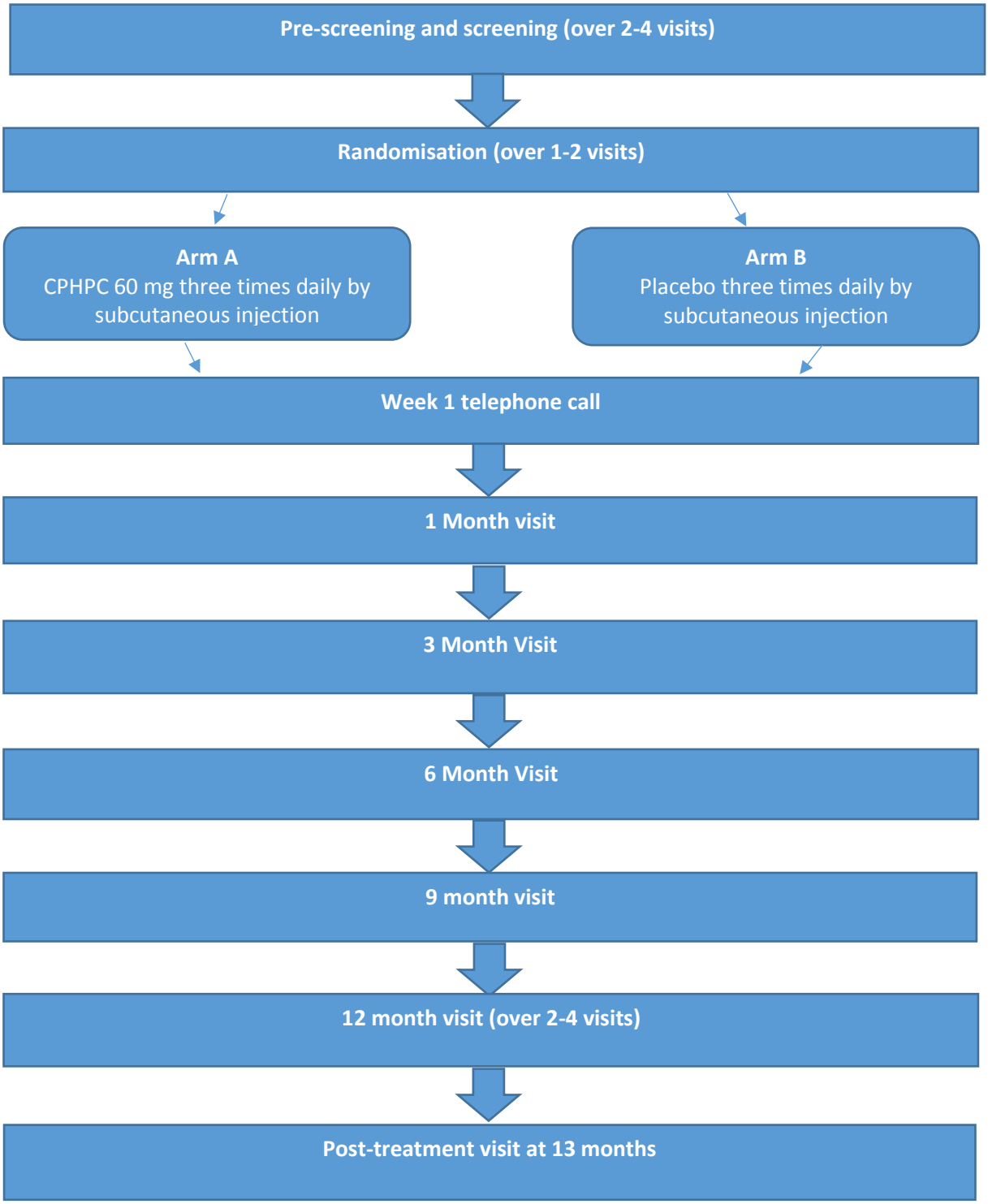
Diagrams of the trial visits and the assessments you will be required to have at different times are shown on the following pages.

Screening for the trial

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



Trial Summary Flowchart



Once you are in the trial you 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). The exact dates and times will be provided to you once you start the trial. During your clinic visits there will be various assessments carried out including: blood samples, urine samples, ECG (an electrical tracing of the heartbeat) and reviews by the research doctor to check for side effects. You 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 your head). In addition, neurological tests will be carried out at different 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.

You 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. You 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 your memory, language and thinking, using different tests. These tests will take place throughout the trial to find out whether there have been any changes.

You 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 your head. There is no exposure to radiation (X-rays) during MRI scanning. The MRI scan involves 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 you want to stop there is a button you can press to alert a member of staff. During a PET-CT scan you are exposed to radiation from the X-rays of the CT scanner, and from the radioactive PET tracer injected into one of your 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 your choice whether you want to undergo this test or not.

The trial will involve 100 participants and, although each individual is studied for 14 months, recruitment and completion of all participants will take 3 years in total, including the time required to analyse the results. If you, for any reason, are unable or unwilling to undergo all the required investigations you may be withdrawn from the trial.

<u>Expenses and Payments</u>

You and your carer will be reimbursed for any reasonable extra expenses, e.g. cost of travelling to the clinic 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 show you, your carer, relative and/or partner exactly how to do the injection. If, at any time, you no longer wish to receive injections, you will be asked if you are willing to continue attending for some or all of the trial assessments, but there will be no obligation to do so.

What are the possible disadvantages and risks of taking part?

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 patients in the trial will be watched carefully for any side effects. Side effects can be mild or serious. If you experience a side effect, the trial staff may give you medicines to help lessen these effects. Some side effects may go away as soon as you stop 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 and your partner, relative and/or carer who will need to attend all these visits with you.

- 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. You or your carer(s) will be asked to administer all injections throughout the study. This will be a major commitment and undertaking for both 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 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 you experience discomfort you should inform the research doctor performing the procedure and she/he will use additional local anaesthetic. After the lumbar puncture, you 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 you feel unwell. The radiation goes away very quickly and drinking plenty of fluids after the scan helps flush the tracer out of your system but you 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 kept to the minimum necessary and is similar to the background radiation you are 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 you are a woman of child bearing potential or a male with a partner of child bearing potential you 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 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 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 directly. If you are in the active treatment group the drug will reduce the amount of SAP in your blood and remove the SAP from your brain throughout the period of treatment. Although the purpose of the trial is to see whether this affects the severity and progression of your Alzheimer's disease, we cannot promise that the treatment will improve your 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.

<u>What happens when the research stops?</u>
CPHPC treatment is still experimental and the drug will not be available to patients participating in this trial after its completion. You will revert back to your normal treatment.

<u>What if there is a problem?</u>
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 have any concerns or complaints you should contact your 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 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, please read the additional information in Part 2 before making any further decisions.

Patient Information Sheet
PART 2

What if relevant new information becomes available?
Sometimes we get new information about the treatment being studied. If this happens, your research doctor will tell you and discuss whether you should continue in the trial. If you decide not to carry on, your research doctor will make arrangements for your usual care to continue, you will also be asked if you are willing to continue attending for some or all of the trial assessments, but there will be no obligation to do so. If you decide to continue in the trial, your research doctor may ask you to sign an agreement outlining the discussion. On receiving new information your research doctor might advise you to withdraw from the trial. She or he will explain the reasons and arrange for your care to continue.

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

What if there is a problem?
If you 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. Participants (and 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 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 National Health Service complaints

mechanisms are available to 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 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 name will not be passed to anyone outside the research team or the Sponsor (UCL). You will be allocated a trial number, which will be used as a code to identify you on all trial forms. Any information about you that leaves the hospital will have your name and address removed so that you cannot be identified.

Your 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 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 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 as a research participant.

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

Will my GP be informed of my involvement?

With your consent, your GP and other doctors treating you will be notified that you are taking part in this trial. If there are any changes in your care requirements as a result of taking part in the trial, your GP will again be informed.

What will happen to any samples I give?

Blood samples and urine samples will be collected at eight points during this trial. You will also be asked to provide samples of spinal fluid at two trial visits. These will be used to establish a baseline assessment of your health and check for any changes that may occur during treatment. If it is clinically necessary, you will be contacted by a member of the research team with the results. Your 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 your 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 patients involved in the trial will be identified in any report or publication. Should you wish to see the results, or the publication, please ask your 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 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 are encouraged to ask any questions you may have before, during and after treatment. If you 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 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

You 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 you decide to proceed and consent. 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.