

Information Leaflet: A multi-centre, placebo-controlled, double-blind, randomised controlled trial of the clinical and cost-effectiveness of sertraline in preventing depression in adults following a traumatic brain injury

We would like to invite you to take part in our research study. Before you decide we would like you to understand why the research is being done and what it would involve for you. Please take time to read the following information carefully. One of our team will go through the information sheet with you and answer any questions you have. Please talk to others about the study if you wish.

Part 1 tells you the purpose of this study and what will happen to you if you take part. Part 2 gives you more detailed information about the conduct of the study. Ask us if there is anything that is not clear.

PART 1

1. What is the purpose of the study?

Unfortunately, many people who suffer from a head injury (also called a 'traumatic brain injury, or 'TBI' for short) experience episodes of low mood (also called depression).

Depression after a head injury is very common and is often caused by many factors. These can include underlying brain damage, other health problems and the consequences of the injury such as financial or social changes.

Both drug and non-drug treatments are used to manage depression in people after a head injury, but preventing the depression from happening at all would be much better and easier. One drug that has shown to be effective in treating depression after a head injury is the anti-depressant sertraline (widely used). However, there is currently insufficient information to know how effective sertraline is for preventing depression after head injury in the first place.

We are carrying out a clinical trial of sertraline among people who are not currently experiencing depression following a head injury (TBI), to see if it helps long term to prevent them from getting depressed.

2. Why have I been approached?

As far as we know you have sustained a head injury and have not developed symptoms of depression, but this cannot be guaranteed in the future. For that reason, we would like you to consider taking part in the study.

3. Do I have to take part?

No, it is up to you to decide. If you do decide to take part, we will ask you to sign a consent form to show that you have agreed. Even if you do give consent, you are free to withdraw from the study at any time without giving a reason. This would not affect the standard of care you receive.

4. What will happen if I agree to take part?

Checking that it is safe for you to take part

Each person who gives consent to take part in the study will be assessed by the research team for their eligibility. This will involve talking to you and checking your medical records to check that there is no reason that you should not take part (for example being pregnant). Those who are identified as eligible will be entered into the study.

The treatment

If entered into the study, you will be randomly assigned by a computer program to receive either sertraline or placebo (a dummy capsule) added to any treatment that you are already receiving. The placebo capsules look exactly like the sertraline capsules but do not contain any medication. You would be asked to take the study medication for just over 12 months. The medication would need to be taken once a day and we will ask you to keep the medication diary (so that we can see there were any missed doses).

Please note, you should not consume grapefruit juice while taking the medication. This would be done without anyone involved (including you, your doctor, and the researchers) knowing whether you are taking the sertraline or placebo capsules. This allows for a fair assessment of the effectiveness of treatment with sertraline. However, your doctor will be able to find out quickly which treatment you are receiving if s/he needs to do so. Taking part in the study will not stop your doctor from changing any of your other treatments, or adding any new medication if this is considered the best thing to do.

Assessments

Baseline

At the beginning of the study (so-called Baseline), we will complete questionnaires with you to help us understand your mood, memory, health, and the way you feel about your life and health and take routine blood to check you don't have any health problems that would stop you taking sertraline (especially sodium levels).. We will ask about your social life and activity in the community. We may also look at your clinical records to add to our knowledge. We will also take some extra blood (3-4 tablespoons) and saliva samples to look for any changes in proteins (biomarkers) that could help us predict whether head injury causes any long-term health problems. This visit will take approximately 90 minutes.

2, 4, 12 weeks

At 2, 4, and 12 weeks we will repeat the blood test to check the sertraline is not causing any side effects. We will also take some extra blood (3-4 tablespoons) and saliva samples to look for any changes in proteins (biomarkers) that could help us predict whether head injury causes any long-term health problems. These visits will not take more than 30 minutes.

6, 12, 18 months

At 6, 12 and 18 months of study participation, we will assess your health again and complete the questionnaires exactly as during the Baseline visit. We will also take some extra blood (3-4 tablespoons) and saliva samples to look for any changes in proteins (biomarkers) that could help us predict whether head injury causes any long-term health problems. Each of the assessment meetings will take approximately 90 minutes.

With your permission, we will ask a carer or family member to complete some questionnaires. These carer questionnaires are about your health at the beginning of your study participation and then after 6, 12 and 18 months.

In addition to the assessments, we will also need to contact you regularly to check you are receiving the study medication at regular intervals. You will collect the medication during the clinical appointments at randomisation, and then 3, 6 and 9 months. Given this, it would be most helpful if you know you will be in the country for 12 months when you decide to part in this study.

We will provide a medication diary card to help you remember this, and we will ask you to note down each time you take a dose of your study medication on this diary card.

We will collect the Hospital Episodes Statistics data (information on all hospital appointments since joining the TBI study) with your permission- this is detailed in the Informed Consent Form. The collection of this data will help us with the evaluation of the cost-effectiveness of using sertraline.

Contacting you

With your permission, we may also contact a relative or friend solely to help the research team to get in contact with you, should we not be able to get in contact with you directly. If you don't want us to contact a relative or friend, this part of the study can be missed out.

5. What is the medicine that is being tested?

Sertraline is widely used in clinical practice to treat people with depression. However, this study will be the first properly designed clinical trial to investigate if sertraline helps prevent people from getting depression following head injury in the first place.

We will start you on a low dose of the medication (50mg a day), and this will be increased to 100mg a day after two weeks. We will ask you to remain on this dose for the next 12 months.

6. What are the possible benefits of taking part?

You may find that you are less likely to get depressed as a result of participating in the study, but we cannot guarantee the study will help you.

7. What are the possible disadvantages or risks of taking part?

If you decide to take part, one disadvantage is that you will be asked to give up some time to meet with a member of the research team over the 18 months for the assessments. Another disadvantage is the possible risk of side effects from the study treatment (detailed below). When we assess progress, we will ask carefully about any side effects that you may have experienced and discuss these with you to assess how we can deal with them. If the side effects are bad, we will inform your doctor who may decide to stop your study medication.

Side Effects

As with any medicine, side effects are possible with sertraline, however, not everyone who takes the medication will experience problems. To reduce the risk of side effects, we will use a low dose of the medication and increase the dose only once. Therefore, major side effects are unlikely although this cannot be guaranteed.

The most common side effects are sometimes feeling nausea, loss of appetite and headaches. These last for about a week and during this week they gradually subside and disappear. Another side effect is fatigue and numb feeling.

If you have any worries about side effects, you can speak with your doctor or a member of the research team (contact details are on the last page). If you feel unwell whilst taking part in the study and seek medical advice, you should mention that you are taking part in this study.

8. What happens when the research study stops?

Following the completion of the study, a formal letter will be sent to you informing you of the outcome of the trial. You will then remain under the care of your routine clinical team. We might contact you again after this time for a longer-term follow-up of the research.

If you feel that you may benefit from receiving the study treatment for longer (regardless of the arm), please contact your GP who will have all the information about the treatment.

9. Will my taking part in the study be kept confidential?

In this research study, we will use information from your medical records. We will only use the information that we need for the research study. We will let very few people know your name or contact details, and only if they need them for this study.

Everyone involved in this study will keep your data safe and secure. We will also follow all privacy rules.

At the end of the study, we will save some of the data in case we need to check it and for future research. We will make sure no one can work out who you are from the reports we write. Part 2 of this document tells you more about this.

If you take part, the information collected for the study may be looked at by members of the research team, representatives of the regulatory authority or the co-sponsors (Kings College London and King's College Hospital NHS Foundation Trust). All will have a duty of confidentiality to you and will handle your information in confidence and we will do our best to meet this duty.

If you tell us something and we believe that it is necessary to pass on that information to your clinical team or other authority to protect you or others from harm, we may do so even if you do not consent. We will inform you of our intention to pass on the information and why we are doing so.

10. Who has reviewed this study?

All research in the 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 favourable opinion by South Central - Oxford A Research Ethics Committee. It has also been approved by the Health Research Authority and each local hospital will also confirm that the study can go ahead.

11. Expenses and payments

If you do decide to take part, we will reimburse up to £15 for travel costs that you may incur in the process of travelling to and from study visits upon providing the receipts and filling out the expense form. The form can be obtained from your research team.

If the information in Part 1 has interested you and you are considering participation, please read the additional information in Part 2 before making any decision.

PART 2

1. What if relevant new information becomes available?

If any new information about sertraline becomes available during your participation in the study, a member of the research team will see you and fully explain this newly available information to you. At this point, if you wish to continue to be in the study, you may be asked to sign a further consent form. However, if you decide to withdraw from the study treatment your usual care will continue. We will ask you to complete the assessments even if you stop taking the study medication early, but this will also be up to you.

If the study is stopped for any other reason, we will tell you and arrange your continuing care.

2. What will happen if I don't want to carry on with the study?

You can withdraw from the study at any time without giving a reason. The information already collected may still be used, but if you do not want this to happen, tell us and we will stop.

We will publish the results in scientific journals and also produce a summary to send to those who have taken part. Neither you nor any other participant will be identified in any report or publication.

3. What will happen to any samples I give?

Samples collected for this study will be stored and analysed in the laboratories of your recruiting centre. In addition, specific analyses may be conducted in other UK laboratories. Samples may be used to conduct genetic analyses. Anything that can identify you will be removed and the samples will be labelled only with a study code number. Samples that have been collected from you will be stored and might be used in future studies. These future studies will be examined and approved by a qualified research ethics committee.

You will be asked to provide a blood sample of up to 70ml (approximately 4 tablespoons) at 6 visits after the Baseline (weeks 2, 4 and 12 and months 6, 12 and 18). Blood samples will be processed in the study laboratory and frozen as serum. Part of the blood sample will be used for genetic testing. The study is particularly interested in looking at segments of DNA, called genes, which may affect the chance that people will get certain diseases like Alzheimer's disease, but as we have described above, genes are just one of several factors. Genetic testing is for research purposes only and remains experimental. Therefore, we will not be feeding the results of the genetic testing back to you. Your overall genetic makeup will not be determined from these samples.

You will also be asked to provide a saliva sample (about 2 – 5ml - less than a teaspoon) at 7 study visits (Baseline, weeks 2, 4 and 12 and months 6, 12 and 18). This can be used to look at biomarkers. You should not eat, drink, smoke, chew gum, brush your teeth or use mouthwash for at least 30 minutes before providing your saliva sample.

The results from the blood and saliva samples will not be fed back to you, as all the results are for research purposes only and will only be analysed at the end of the study after the samples have been de-identified.

Please do not hesitate to ask any questions if you want to have more information about the sample collection and processing.

4. What if there is a problem?

An independent team of academics and patient representatives are in place to monitor the safety of the study. If there are any problems with the study you will be contacted by the study doctors.

Questions and Concerns – If you have a concern about any aspect of this study, you should ask to speak to the researchers who will do their best to answer your questions. Please contact:

Prof. Khalida Ismail (Khalida.2.ismail@kcl.ac.uk or +44 (0)20 7848 5131) or your local care team: Shu-Jen Leung (Research Assistant – shu-jen.leung@kcl.ac.uk)

Complaints – If you have a complaint, you should talk to your research doctors who will do their best to answer your questions. If you remain unhappy, you may be able to make a formal complaint through the NHS complaints procedure. Details can be obtained through the King's College Hospital Patient Advice and Liaison Service (PALS):

Email: kch-tr.palsdh@nhs.net, Tel: 020 3299 3601, 9 am to 4.30 pm, Monday to Friday (not bank holidays)

Post: Patient Advice and Liaison Service, King's College Hospital NHS Foundation Trust, Denmark Hill, London SE5 9RS. You can visit the PALS office, which is on the ground floor of Hambleden Wing, near the main Bessemer Road entrance. We're open from 9 am to 4.30 pm, Monday to Friday. If you are being treated on another King's site and cannot make it to our office, please phone us. We will arrange a time to visit you.

Harm – This trial is co-sponsored by King's College London and King's College Hospital NHS Foundation Trust. The sponsors will at all times maintain adequate insurance in relation to the study independently.

King's College London, through its professional indemnity (Clinical Trials) and no-fault compensation and the Trust having a duty of care to King's College NHS Foundation Trust patients via NHS indemnity cover, in respect of any claims arising as a result of clinical negligence by its employees, brought by or on behalf of a study patient. If something goes wrong, and you are harmed during the research due to negligence of study staff, then you may have grounds for legal action for compensation against King's College Hospital NHS Foundation Trust, but you may have to pay your legal costs.

If you have a concern about any aspect of this study, including the way you have been approached or treated by members of the study staff, you should ask to speak to your study doctor who will do their best to answer your questions [Shu-Jen Leung (Research Assistant – shu-jen.leung@kcl.ac.uk)]

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 study the normal NHS complaints mechanisms are available to you. Please ask your study doctor if you would like more information on this.

5. Will my taking part be kept confidential?

Yes. All information collected about you during the study will be kept strictly confidential. Any study information about you that leaves the hospital will have your name and address removed so that you cannot be recognized from it. In addition, a copy of your signed consent form will be sent to King's College London via a secure email system.

King's College London and King's College Hospital are the co-sponsor of this study based in the United Kingdom. We will be using information from you and your medical records to undertake this study and King's College London will act as the data controller for this study. This means that we are responsible for looking after your information and using it properly. King's College London will keep identifiable information about you for 10 years after the study has finished.

Your rights to access, change or move your information are limited, as we need to manage your information in specific ways 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 rights, we will use the minimum personally-identifiable information possible.

We have made sure that everyone involved in the study follows the laws and regulations that protect participant confidentiality (these regulations include the Data Protection Act 2018). Under this protection, only authorized representatives connected with the study are allowed access to the names of participants in the study. If we need someone else to access your details, we will ask for permission from you by writing. Your hospital notes will however be reviewed by representatives of the sponsor and regulatory authorities.

We will need to use information from your medical records for this research project.

This information will include your initials/ NHS number/ name/ contact details. People will use this information to do research or to check your records to make sure that the research is being done properly.

People who do not need to know who you are will not be able to see your name or contact details. Your data will have a code number instead.

We will keep all information about you safe and secure.

Once we have finished the study, we will keep some of the data so we can check the results. We will write our reports in a way that no one can work out that you took part in the study.

You can find out more about how we use your information by contacting the Chief Investigator Khalida Ismail Khalida.2.ismail@kcl.ac.uk

6. What are your choices about how your information is used?

You can stop being part of the study at any time, without giving a reason, but we will keep information about you that we already have.

We need to manage your records in specific ways for the research to be reliable. This means that we won't be able to let you see or change the data we hold about you.

If you agree to take part in this study, you will have the option to take part in future research using your data saved from this study.

7. Where can you find out more about how your information is used?

You can find out more about how we use your information

- at www.hra.nhs.uk/information-about-patients/
- our leaflet available from www.hra.nhs.uk/patientdataandresearch
- by asking one of the research team
- by sending an email to Data Protection Officer at KCL: info-compliance@kcl.ac.uk

You can also use the KCH Data Protection Officer if you wish: kch-tr.Information-Governance-Queries@nhs.net or

- by ringing us on 0203 299 1013.

If you consent to take part we will use your data to deliver this project as described in this Patient Information Sheet. If you would like to find out more, please read the supplementary leaflet provided, entitled 'How we use your data'

8. Involvement of the General Practitioner/ Family Doctor (GP)

If you agree, your GP will be informed that you are helping with the study. Your GP will also be notified if you decide to withdraw from the study for any reason, including the development of depression and requiring additional care. We may also request your GP to share the information about your medical

history. Other doctors not involved in the research, who may be treating you, may be informed of you being in the study.

9. Who is organising and funding the research?

The study is led by Professor Khalida Ismail at Kings College London and Dr Vanessa Raymont at Oxford University. The study is being sponsored by King's College Hospital NHS Foundation Trust and King's College London. The doctors looking after you are not being paid for their role in the study.

The only funding for this study comes from the Department of Health's NHS National Institute for Health Research (NIHR).

10. How have patients and the public been involved in this study?

We have held 2 PPI group meetings in London supported by 3 patient charities: Silverlining, Headways (national) and UDAV (East London). They supported us with the application to the funder and were involved in the study design. The group provided some very useful points to be included in the study protocol.

The patients and their carers who met with us before the submission were keen to remain involved. We will set up a PPI group in each of the 4 regions so that we can ensure there is diversity across the regions but also optimise the conduct of the study according to the local context. Their PPI representative will also attend our 6-monthly steering committee meetings. The PPI representatives reviewed this PIS and the consent forms.

11. Who has reviewed the study?

The NIHR reviewed the study before they funded it. Like all research in the NHS, it has been looked at by an independent group of people, called a Research Ethics Committee to protect your safety, rights, wellbeing and dignity. This study has been reviewed and given a favourable opinion by South Central - Oxford A Research Ethics Committee.

12. Further information and contact details

For specific information about this research study, please contact your local study team: Shu-Jen Leung (Research Assistant – shu-jen.leung@kcl.ac.uk). These are also the people to contact if you have any concerns during the study. Your participation is entirely voluntary. If you do decide to take part, you should keep this information sheet and you will be asked to sign a consent form. You are free to withdraw from the study at any time without giving a reason. Importantly, a decision to withdraw from the study or a decision not to take part will not affect the care that you receive ordinarily and regularly from your doctors and nurses. Please note that data and samples obtained during the period of your involvement in the study will be stored and used for analysis.

For any further discussions or queries about the study, you might want to talk to a member of your clinical team or Prof Khalida Ismail who can be contacted on Khalida.2.ismail@kcl.ac.uk.

13. Thank you

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

If you decide to take part in the study, we will give you a copy of the information sheet and a signed consent form to keep.