PARTICIPANT INFORMATION SHEET

FOCUS: The efficacy of xanomeline-trospium in treating cognitive impairment in psychosis: A randomised, double-blind, active-controlled clinical trial

Introduction

You are being invited to take part in a research study which is part of a clinical trial aiming to find out if taking xanomeline-trospium (Cobenfy) can improve concentration and memory in patients with psychosis. The full scientific name of the trial is "The efficacy of xanomeline-trospium in treating cognitive impairment in psychosis: A randomised double-blind active-controlled clinical trial". As part of this, we would also like to recruit healthy control participants who will not receive any treatment but will undergo some brain scans. We will then compare with the brain scans obtained from patients with psychosis who are participating in the active treatment part of the trial.

Why have I been invited?

You are being invited as one of the healthy control participants. We aim to recruit 30 healthy volunteers aged 18 to 55.

Before you decide whether to take part, you need to understand why the research is being done and what it would involve for you. Please take time to read the following information carefully. Talk to others about the study if you wish. Ask us if there is anything that is not clear, if you have any questions, or if you would like more information.

What is the purpose of the trial?

The aim of the FOCUS trial is to see if xanomeline-trospium can improve concentration and memory in patients with psychosis. The purpose of the brain imaging part of the FOCUS trial is to predict response to xanomeline-trospium using information from Magnetic Resonance Imaging (MRI) and Magnetoencephalography (MEG) brain scans. In order to make a good comparison of the effect of xanomeline-trospium on the brain, we would like to compare the brain scans of the patients treated with xanomeline-trospium, and those treated with a regular antipsychotic (risperidone or lurasidone), with those from a healthy group of volunteers for comparison.

Do I have to take part?

No, participation is entirely voluntary. Your decision will not affect your clinical care or legal rights in any way. If you decide to take part, you are free to withdraw at any time; your decision to do so will not affect the care that you receive. You will be asked to inform the study doctor should you decide to withdraw, and you do not have to give a reason for your withdrawal.

What does the trial involve?

You will be asked to attend a screening visit and one or two more visits to have the MRI and MEG scan. The trial visits will be performed in a private room within your local trial site. If you are eligible and are still willing to participate after visit 1 (the screening visit), you will be contacted by telephone to arrange the scanning visits.

You can take breaks during the visits and visits can be split over multiple days if you prefer. The visits will take about 1-4 hours each and include various activities, consisting of:

- Interviews and questionnaires about your health, medications, and experiences
- Completing tasks/assessments on an iPad/tablet: the ''CANTAB' and 'VRFCAT'.

Completing a questionnaire to determine if you can take part in the MEG/MRI-scanning.
Two sessions for brain scans, one for Magnetic Resonance Imaging (MRI) and one for Magnetoencephalography (MEG) brain scans. These take a maximum of 90 minutes each, and together take a maximum of 3 hours. These scans can either take place on the same day or can be planned on separate days.

MRI

During the MRI scan, you will be asked to lie still on your back in the MRI scanner for up to 90 minutes. The MRI scanner will take some images of your brain structure and activity and will also measure the concentrations of some naturally occurring brain chemicals.

MEG

During the MEG scan, you will be asked to sit still in the MEG scanner for up to 90 minutes. Similar to the MRI scanner, the MEG scanner will take some images of your brain, focusing more on brain activity. It will also measure naturally occurring chemicals in the brain.

More information about each visit and procedures is provided below. For further information on the MRI/MEG brain scans please see Appendix 1 (MRI scans) and Appendix 2 (MEG scans).

You will be reimbursed for your travel expenses, time, and inconvenience related to the study activities/visits. This will be arranged by your local trial team. Details are provided below (see "Will I be reimbursed for taking part in this trial?").

Summary of trial procedures		
When?	**What will happen?**	**Duration**
Visit 1 (Screening)		
	Informed consent process: • explanation of what the trial involves including potential risks • opportunity to ask questions • written consent form if you agree to participate confirming that you understand the trial and agree to take part	4h 15m
	Assessment to ensure the trial is suitable for you	
	Questions and questionnaires about: • symptoms • medical/psychiatric/medication history • demographics • cognition	
	Computer-based tests of cognition (e.g. memory and concentration) and a test of reading ability	
	Safety checks with doctor/nurse: urine sample for drug use screening test	
Visit 2		
1 week after visit 1	Questions and questionnaires about: • symptoms of psychosis • overall functioning • daily activities • quality of life • medication use	4h 00m
	Computer-based tests of cognition (e.g. memory and concentration)	

	MRI and MEG brain scans (90 minutes each)	3h 00m

What should I consider?
This trial will not be suitable for you if any of the below apply to you:

- You are pregnant or breastfeeding.
- You have participated in another clinical trial in which you received an experimental or investigational drug or agent within 2 months.
- You have a diagnosis of a psychiatric disorder other than previous episode(s) of depression or anxiety.
- Current active suicidal ideation within the last 2 weeks, defined as a score of 1 or higher on CDSS question 8, followed by an assessment by the treating clinician who determines it is not safe for the patient to participate in the trial.
- You are not willing or able to participate in the MEG/MRI scanning.
- You are not willing to undergo a urine drug screening test

What are the possible benefits of taking part?
There will be no direct benefits to yourself. However, by participating in this trial, you would be making a significant contribution to helping to develop potential new treatments for patients with psychosis, which may help improve the future treatment of those with psychosis.

What are the possible risks of taking part?
In this section, all known risks are described. You will be informed of any new risks/information by the trial team during the trial where this is relevant to you.

Potentially upsetting conversations
If there are questions that you do not want to answer, or if you wish to stop or pause these conversations at any time, please let the researcher know. In the event that you experience distress, the visit may be paused or stopped and we also have procedures in place to ensure appropriate support is provided.

MRI scans
The MRI scanner is like a long metal cylinder (see Figure 1) and most of your body will need to go into it. Some people may find that slightly claustrophobic. As it involves magnets, people with metal in their body cannot participate. We will be able to see and talk to you throughout the scan and we will provide you with a call button, which you can press at any time if you want to come out of the scanner. The scanner makes a loud knocking noise when it is running, so you will be given properly fitted earplugs and protective headphones during the scan. For further information about the MRI scans, please read Appendix 1.

MEG scans
The MEG scan (see Figure 2) has no clear risks associated with it. Like the MRI scan, this scan also involves magnets. Therefore, people with metal in their body cannot participate. We will ask you some brief questions to make sure it is safe for you before each MEG scan. For further information about the MEG scan, please read Appendix 2.

Will I be reimbursed for taking part in this trial?
You will be reimbursed for taking part in this trial. The total amount will depend on how many visits you attend (see below).

- £20 for the screening visit
- £50 per MRI scan
- £50 per MEG scan

The maximum possible reimbursement for attending the screening visit and the brain scans is £120. Additionally, travel expenses will be reimbursed based on the number of miles travelled or upon submission of public transportation tickets/receipts.

You will be paid via BACS transfer or vouchers.

What happens if there are incidental findings?
It is possible that the physical health examination may detect an unexpected finding that is relevant to your health. In this event, we will discuss this to you and recommend that you contact your GP.

It is important to note that we do not carry out brain scans for diagnostic purposes, only for research. Our scans are not routinely looked at by a doctor and are therefore not a substitute for a doctor's appointment. Occasionally, however, a possible abnormality may be detected. In this case, we would have the scan checked by a doctor. If the doctor considers the finding to be clinically important for your current or future health, you will be contacted directly and advised to discuss it with your GP. You would not be informed unless the doctor considers the finding has clear implications for your current or future health. All information about you is kept strictly confidential.

What will happen if I do not want to continue?
If you decide to take part, you can still withdraw at any time without giving a reason. Information collected up to that point will still be used in the trial. If you wish to withdraw from the trial, please contact the trial team using the contact details at the end of this document. If you decide to withdraw, we will ask for a reason behind your decision, but you are not obligated to provide one. The decision to withdraw will not affect the standard of care you receive from the healthcare organisations in any way, now or in the future.

Who is organising and funding the trial?
The FOCUS trial is being carried out by researchers at the University of Oxford and is part of a project involving several other institutes in the UK, where a total of 150 participants with early psychosis and 30 healthy participants will be recruited. As the University of Oxford is the research sponsor, it is legally responsible for the trial organisation and for overseeing the work of the researchers. The trial is funded by the Wellcome Trust, a charity in the UK. If you choose to participate, you will be part of the control group in the study. This group will serve as a comparator for the active treatment group in the trial. For the active treatment part of the trial, the medications that are investigated are xanomeline-trospium, risperidone and lurasidone. Xanomeline-trospium is manufactured and provided free of charge for the active treatment part of the trial by Karuna Therapeutics, a Bristol Meyers Squibb company. The regular antipsychotics (risperidone and lurasidone) are existing medications for the treatment of psychosis. None of the investigators are employed by Karuna Therapeutics. One of the investigators received speaker/consultancy fees from Karuna Therapeutics and several other pharmaceutical companies (Janssen, Boehringer Ingelheim, and Otsuka). One of the investigators involved in this trial co-directs a company that creates digital tools to help treat mental illness.

Has the trial been approved by an ethical committee?
The South West – Central Bristol Research Ethics Committee has reviewed the trial for compliance with medical and ethical standards and for scientific value.

Will the GP be informed of my participation in the trial?
No, your General Practitioner (GP) will not be informed of your participation. If the physical health examination or brain scan detect an unexpected finding that is relevant to your health, we will discuss this with you and recommend that you contact your GP (please see the section 'What happens if there are incidental findings?' for further information on this).

Will my taking part in the trial be kept confidential?
Yes. Generally speaking, trial records and samples will be identified only by a trial code that will replace your name and address at the start of the trial. During the study, research data is collected using different forms which will all be gathered in an electronic data collection system. In this system, your name and address are not mentioned, but your unique trial code is mentioned instead. This process is called 'pseudonymisation'. For example, the questionnaires you complete will be labelled with your code number instead of your name. It can be matched up with the rest of the data relating to you by the code number. Only members of the trial team, and designated individuals such as the trial monitor know which code corresponds to which participant. According to local hospital requirements, additional codes or identifiers may be used for MRI/MEG scans at local hospital sites, which will be removed before transferring to the Central Trial Team (University of Oxford server). Your age, sex (as assigned at birth) and your level of education will be collected for the trial. These data will also be labelled with your trial code number and not with your name and/or address. For demographic purposes, we would also like to ask for information such as race, country of birth, marital status, and occupation. These will not be used for the purpose of identifying you and you do not have to provide these data to take part in the trial.

Responsible members of the University of Oxford, sponsor and site representatives and regulatory authorities may be given access to data for monitoring and/or audit of the trial to ensure that the research is complying with applicable regulations.

The results of this trial will not include any personal details that could be used to directly identify you.

What will happen to my data?
Data protection legislation requires that we, the University of Oxford (whose legal name is The Chancellor Masters and Scholars of the University of Oxford), state the legal basis for processing information about you. In the case of research, this is a 'task in the public interest'. The University of Oxford is the sponsor for this study and is responsible for looking after your information and using it properly.

We will need to use information from your GP/hospital medical records for this research project. We will share your information related to this research project with the following types of organisations: NHS Trust trial sites; Medicines and Healthcare Products Regulatory Agency. This information will include your:

- Name
- Date of birth
- NHS number
- Contact details
- GP details

People will use this information to do the 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 by:

- Using secure storage systems
- Following strict data protection policies
- Complying with legal and ethical requirements

We may share data about you outside the UK for research related purposes to:

- Support future research.

If this happens, we will only share the data that is needed. We will also make sure you can't be identified from the data that is shared where possible. This may not be possible under certain circumstances – for instance, if you have a rare illness, it may still be possible to identify you. If your data is shared outside the UK, it will be with the following sorts of organisations:

- Research organisations.

We will make sure your data is protected. Anyone who accesses your data outside the UK must do what we tell them so that your data has a similar level of protection as it does under UK law. We will make sure your data is safe outside the UK by doing the following:

- Some of the countries your data will be shared with have an adequacy decision in place. This means that we know their laws offer a similar level of protection to data protection laws in the UK
- We use specific contracts approved for use in the UK which give personal data the same level of protection it has in the UK. For further details visit the Information Commissioner's Office (ICO) website https://ico.org.uk/for-organisations/uk-gdpr-guidance-and-resources/international-transfers/

- We do not allow those who access your data outside the UK to use it for anything other than what our written contract with them says
- We need other organisations to have appropriate security measures to protect your data which are consistent with the data security and confidentiality obligations we have. This includes having appropriate measures to protect your data against accidental loss and unauthorised access, use, changes or sharing
- We have procedures in place to deal with any suspected personal data breach. We will tell you and applicable regulators when there has been a breach of your personal data when we legally have to. For further details about UK breach reporting rules visit the Information Commissioner's Office (ICO) website https://ico.org.uk/for-organisations/report-a-breach.

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.

We will keep your study data for the minimum period of time required by the UK Clinical Trial Regulations.

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. You have the right to ask us to remove, change or delete data we hold about you for the purposes of the study. We might not always be able to do this if it means we cannot use your data to do the research. If so, we will tell you why we cannot do this.

If you choose to stop taking part in the study, we would like to continue collecting information about your health from your GP and/or hospital medical records. If you do not want this to happen, tell us and we will stop.

You can find out more about how we use your information, including the specific mechanism used by us when transferring your personal data out of the UK, by:

- asking one of the research team via FOCUS@psych.ox.ac.uk
- sending an email to **FOCUS@psych.ox.ac.uk**
- calling us on [study team number to be confirmed]
- contacting the University's Data Protection Officer data.protection@admin.ox.ac.uk
- looking at the University's privacy notice available at: How we use your personal data for research purposes | Compliance.

If you would like to find out more about the use of confidential data in research, the HRA has developed a general information leaflet which is available at: Patient data and research leaflet - Health Research Authority.

Authorised MRI/MEG scanning centre personnel at the NHS Trust where the research site is based and the research team will have access to the MRI/MEG imaging data. MRI/MEG imaging data is assigned a unique ID as it is collected, and stored in a secure database on University managed IT systems. Due to the nature of the MRI/MEG images, they remain potentially identifiable, even after we destroy your personal details. The images will be de-faced and any identifiable information erased before storing. Imaging data will be stored on archive tapes at the MRI/MEG location and the neuroimaging computer network at the University of Oxford and may be kept indefinitely, for quality control, and to facilitate further use of the scans where permission has been given (even if you withdraw from this research).

Your bank details will be stored for 7 years in accordance with University of Oxford financial policy.

A copy of the consent form from this study will be kept in your medical records for as long as those records are retained. They will keep any other identifiable information about you from this study for up to 25 years after the study has finished.

We may use third party service providers or subcontractors to help with some of the research activities we carry out (e.g., IT provision, survey provision, transcription services etc.). We may therefore share your personal data with these providers when it is necessary to do so to allow them to carry out the services we require them to provide. However, we require all our third-party providers to have appropriate security measures in place to protect your data and we only allow them to process your data for the specific purposes we have stated in our instructions.

What will happen with the results of the trial?
A description of this clinical trial will be available on the UK's Clinical Study Registry, ISRCTN. The website will include a summary of the results. You can search this website at any time. The results of the trial will also be published on the trial website (https://). None of these websites will include information that can identify you.

Who do I contact if I need further information?
If you have any questions about the research, your rights as a participant, or would like to report any problem or injury arising from the research, please contact:

Name doctor, the investigator _____
Telephone number _____

You can also ask to speak to an independent doctor who is not part of the trial but who has enough knowledge about the trial to answer your questions.

Name of independent doctor _____
Telephone number _____
You can find out more about how we use your information on:
www.hra.nhs.uk/information-about-patients/

What if there is a problem?
If you have a concern about any aspect of this trial, you should ask to speak to the researchers who will do their best to answer your questions [contact number].
The investigators recognise the important contribution that volunteers make to medical research, and will make every effort to ensure your safety and wellbeing. The University of Oxford, as the research sponsor, has appropriate insurance in place in the unlikely event that you suffer any harm as a direct consequence of your taking part in this trial. If something does go wrong, you are harmed during the research, and this is due to someone's negligence, then you may have grounds for a legal action for compensation. While the Sponsor will cooperate with any claim, you may wish to seek independent legal advice to ensure that you are properly represented in pursuing any complaint.

If you wish to complain about any aspect of the way in which you have been approached or treated, or how your information is handled during the course of this trial, contact <name of investigator> <contact details (phone number & email)> or you may contact University of Oxford Research Governance, Ethics & Assurance (RGEA) on 01865 616480, or the director of RGEA at rgea.complaints@admin.ox.ac.uk.

If you want to complain about how researchers have handled your information, you should contact the research team. If you are not happy after that, you can contact the Data Protection Office at the University of Oxford: data.protection@admin.ox.ac.uk

If you are not happy with their response or believe they are processing your data in a way that is not right or lawful, you can complain to the Information Commissioner's Office (ICO) (www.ico.org.uk or 0303 123 1113).

How have patients and the public been involved in this trial?
Members of the public were involved in reviewing this Participant Information Sheet. In designing this trial, we have received patient advice on the frequency of participant visits and the tests that we will carry out. Potential participants were involved in describing the inclusion and exclusion criteria and monitoring for this trial.

Thank you for considering participating in the FOCUS trial. As a participant, you will be given a copy of this information sheet and your signed consent form to keep.

Appendix 1: SUPPLEMENTARY INFORMATION REGARDING THE MRI SCAN

MRI is safe and non-invasive and does not involve any ionising radiation (x-rays). However, because they use a large magnet to work, MRI scans are not suitable for everybody. Because of this, you will be asked pre-screening safety questions to help determine if you are able to take part, as per your local hospital policy. Other procedures depending on your hospital's MRI safety review may apply. Please let us know beforehand if you wear contact lenses or glasses.

The MRI scanner is like a long metal cylinder and most of your body will need to go into it (see Figure 1). Some people may find that slightly claustrophobic. Therefore, if you suffer from claustrophobia, MRI is unlikely to be suitable for you.

As the MRI involves magnets, people with metal in their body cannot participate. Normally, MRI scanning for research purposes would not be performed without further investigation if you have a heart pacemaker, mechanical heart valve, mechanical implant such as an aneurysm clip, hip replacement, or if you carry other pieces of metal that have accidentally entered your body.

As some of the scans are noisy, you will be given earplugs, head padding or headphones to make this quieter for you.

Preparation for the MRI may vary according to your local hospital's requirements. However, as an example you might be asked to change into pocketless and metal free "pyjama-style" top and trousers. You might be asked to remove underwired bras (if applicable to you) although if you have a suitable sports type bra, it might be possible to wear this instead. Metal jewellery, including body piercing, must also be removed. Generally speaking, eye shadow and mascara must also be avoided, since some types contain materials that can interact with the magnetic field produced by the MRI scanner. Lockers may be provided to secure your personal belongings and clothing; however, arrangements may vary between hospitals. Please consult your local hospital team for further details.

It is important to note that these research scans are not a substitute for a doctor's appointment, and the trial scans are not taken for diagnostic purposes. Depending on your hospital's usual procedures, the scans may be clinically assessed by a radiologist. However, this may not always be the case, as conducting a clinical assessment of your scans is not part of the research procedures. If it is local policy for a clinical review to take place and a medically-relevant finding is detected, this finding could then be passed on to your doctor. Your local trial team will explain the procedure at your participating hospital.

Figure 1: An MRI scanner

Appendix 2: SUPPLEMENTARY INFORMATION REGARDING THE MEG SCAN

MEG is safe and non-invasive and does not involve any ionising radiation (x-rays). Similar to MRI, MEG scans involve magnets. MEG scans are therefore not suitable for everybody. Because of this, you will be asked pre-screening safety questions to help determine if you are able to take part, as per your local hospital policy. Other procedures depending on your hospital's MRI safety review may apply.

The MEG system contains very sensitive detectors arranged around a helmet shaped hollow (see Figure 2). Brain activity is measured from a participant as they sit with their head inside this hollow. Because the magnetic signals produced by brain activity are tiny compared to those produced by the earth and electrical equipment, the scanner is in a specially built room that keeps out magnetic fields from the environment. During the MEG scan you will be in a quiet, dark room.

Figure 2: a MEG scanner