Home-based EEG neurofeedback to reduce chronic neuropathic pain

A cohort clinical trial

Research team Lead, Chief Investigator:

Research team Lead, Co-Principal Investigator:

Research Co-investigator:

Supervising Clinician:

Study aims:

This research aims to explore the feasibility, safety and efficacy of an 8-week home-based EEG neurofeedback training programme for a sample of 10 individuals living with severe chronic neuropathic pain within the NHS treatment framework.

Why have I been invited to take part?

We aim to invite 10 people with chronic neuropathic pain to participate in this study. We have invited you to take part in this study because you fulfil the eligibility criteria which are as follows:

- You are at least 18 years old
- You have experienced chronic neuropathic pain for 3 months or more that is moderate to severe in intensity, which must be rated on the Visual Analogue Scale (Pain) as being greater than 4 /10 and must also have had an average pain rating in the last week (prior to screening) of equal to or more than 4/10 on the Brief Pain Inventory outcome scale
- You must have a head circumference measurement of between 520 and 620 mm to enable comfortable fitment and wearing of the device
- You must have access to a reliable broadband internet connection and Wi-Fi at home

We will exclude people from this study who:

- Have previously undertaken neurofeedback training
- Have any of the following contraindications to neurofeedback training: recent serious head injury (within 12 months), traumatic brain injury, concussion, major neurological disorder (e.g. trigeminal neuralgia), history of seizures, or a major psychiatric disorder.
- Have an implanted electronic neuromodulation device (for example Deep Brain Stimulator device), heart pacemaker, or loop recorder
- Are not fluent in English
- Do not have access to a reliable broadband internet connection and Wi-Fi at home

If you meet the above eligibility criteria and agree to take part in the study you will be asked not to change any of your current treatments (e.g. medications, regular therapies and exercise) and asked not to start any new treatments for four weeks before the start of the study and throughout the duration of the study.

Do I have to take part?

No. Participation in this study is entirely voluntary (ie. your choice). You are free to decline to participate or to withdraw from the research at any time, without any disadvantage to you, or your ongoing health care.

What would my participation involve?

This Participant Information Sheet (PIS) explains the research and gives background information on what is involved to help you decide if you would like to take part. It sets out why we are doing this study, what your participation would involve, what the benefits and risks to you might be, and what happens after the study ends.

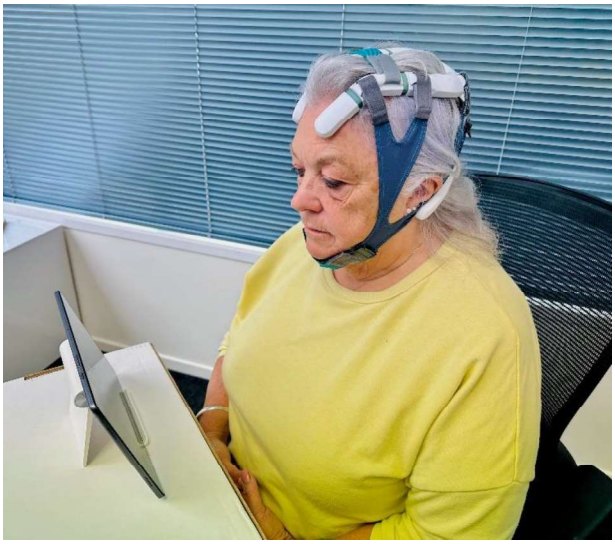
You do not have to decide today whether or not you will participate in this study. Before you decide you may want to talk about the study with other people, such as family, friends, or healthcare providers. Please feel free to do this. If you have any questions, then please contact us to further discuss (contact details are provided at the end of this document).

Participation depends on an individual candidate meeting all inclusion criteria as identified above. The Chief Investigator will screen all potential interested candidates to determine whether or not an individual candidate meets the relevant eligibility criteria for this study. Screening will include you taking head circumference measurements to enable the team to ascertain whether your measurements are within the relevant inclusion criteria.

If you are screened and identified as an eligible candidate, and you decide that you would like to take part in this study, you will be asked to complete, sign and date a consent form. You can do this either electronically and send us the completed consent form by email or if you would prefer, this could also be done in the first internet-based video call appointment with the team.

A member of the research team will also sign and date your completed consent form and return an electronic copy to you for your own records. After an individual has signed and dated the consent form, then the relevant equipment as identified in the picture below, will be couriered to your home address.

Figure 1: Individual wearing the Axon headset and taking part in a neurofeedback training session.



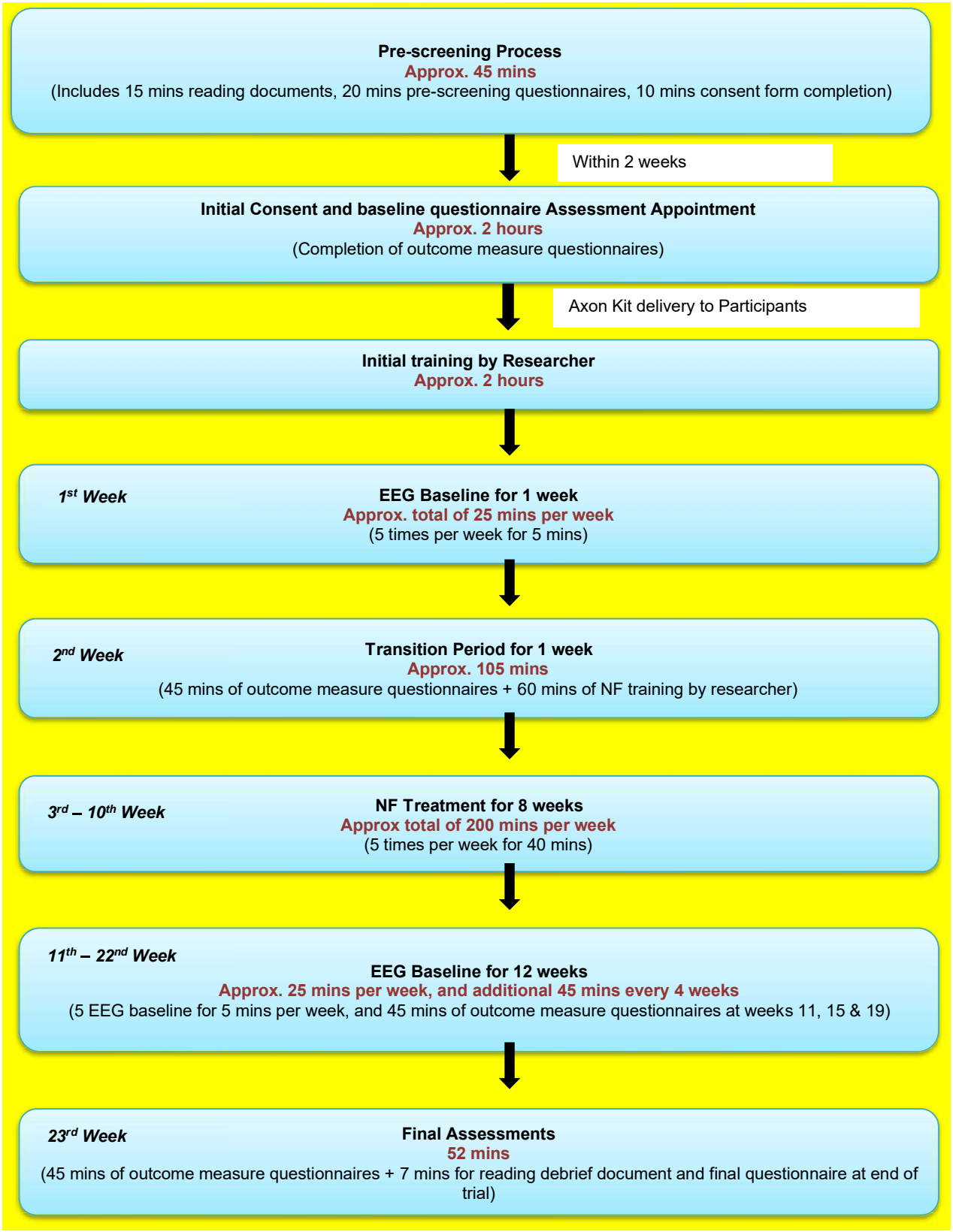


Figure 2: Study stages and time commitment required for this study

What is the purpose of this research study?

Chronic neuropathic pain is pain that lasts for 3 months. Chronic pain is very common, and current available treatments are usually only partially effective. Furthermore, many treatments have side effects that are hard to tolerate. The main purpose of this study is to see whether 8 weeks of neurofeedback training is a safe and effective non-pharmacological treatment for chronic neuropathic pain. The neurofeedback training will be delivered using an app on a tablet connected to your home broadband Wi-Fi, and a wireless headset. This means that the training can be done in the comfort of your own home, at a time that suits you.

What is neurofeedback training?

Neurofeedback training is a scientific way of training your brain. Your brain generates electrical impulses (or waves) which can be measured by the use of sensors (electrodes) placed in close contact with the scalp. This is known as an Electroencephalogram (EEG), which enables the recording of patterns of brain activity on the cerebral cortex – i.e., the surface of the brain.

Brain cells communicate with each other through electrical impulses. Changes in the patterns of recorded brain activity can give an indication of how your brain is working. For example, when you have chronic pain, your brain activity can change so that different areas of your brain are not communicating as well as they could with each other. Researchers believe that this may make the perception of your pain worse, potentially lower your mood, and interfere with your sleep.

During neurofeedback training, your brain activity is compared to your own personal baseline, and the training encourages your brain to spend more time in the frequency associated with relaxation and focus, and less time in frequencies associated with pain and anxiety. In this study you will be asked to wear a headset (as in above picture) that has sensors built into it, which will enable the recording and feedback of your individual EEG activity. When switched on, the headset connects to an app, enabling you to modulate your EEG activity.

In this trial, you will have the choice of playing 4 games (e.g. putting a jigsaw puzzle together or watching a balloon rise into the sky). When your EEG activity matches the target pattern the game will progress, and when you stay within the target pattern, you will hear a bell ring. This is enabling a type of learning known as 'Operant Conditioning' whereby the audio and visual feedback helps to redirect your brain to spend time in frequencies associated with relaxation and focus, and away from frequencies associated with chronic pain and anxiety.

Neurofeedback headset and tablet

The Axon headset will record your EEG brain activity and feed it back to the tablet in real time, and as your brain learns to match the target pattern of EEG activity, you may experience increased relaxation, focus and less anxiety and perception of pain. Much like exercise, it is considered that the more you practice and train your brain, the easier it gets to achieve the required target pattern. This concept is called neuroplasticity, which refers to the fact that the brain is constantly changing, and by training your neurons to fire at a particular frequency, you can alter the function and structure of your brain activity, thus creating neuroplastic changes to optimise your brain and reduce pain.

What if the equipment provided stops working?

If any of the equipment provided stops working, i.e. the Headset or tablet, then please email Exsurgo Limited Technical Support at the email address below and ensure that the Chief Investigator XX is copied into your email.

Exsurgo Ltd Technical Support:
support@exsurgo.com

What will my participation in the research study involve?

In order to participate in this trial, you will be asked to attend an initial baseline appointment via video conference software with one of the research team members. This appointment will be booked at a mutually convenient date and time. Within this first appointment, any queries relating to the trial will be addressed, headset measurement will be checked, and the consent form signed electronically. You will also be asked to complete seven outcome measure scale questionnaires:

The Visual Analogue Scale for rating pain (VAS - Pain)
The Brief Pain Inventory (BPI) scale
The Depression, anxiety, and stress outcome scale (DASS21)
The Pain Catastrophising Scale (PCS)
The Central Sensitisation Inventory scale (CSI)
The Pittsburgh Sleep Quality Index scale (PSQI)
The perceived health related quality of life scale (EuroQolEQ-5D-5L)

In addition, you will also be asked to record all analgesia that you are using (dosage and frequency).
Following consent, the research team will allocate you a Personal Identification Number (PIN) and Exsurgo Ltd.

will set up your individual app user profile and password in advance of your first training session. Exsurgo Ltd will arrange for your equipment to be couriered and delivered to your home address.

After you receive the equipment, a second video-based appointment with one of the research team members will be arranged at a mutually convenient date and time. In this session, you will learn how to use the headset and tablet-based application. You will be trained in all aspects of operating the equipment and how to self-administer the neurofeedback training by the research team. This training will include demonstration and instruction on Headset fitment and orientation, Headset use, tablet use and orientation, App orientation and set-up, post-session cleaning of equipment, charging and storing headset and tablet. All training will be conducted using remote video call-based sessions, enabling you to participate safely from home under the supervision of the research team. If you would like to book a further training session to practice during the transition period into the trial, then the research team will arrange and book a further training session into their research clinical diary in Week 2.

For the first week of the trial (the pre-intervention measurement phase), you will put your headset on, open the app on the tablet, answer some questions about your sleep, mood, and pain, and perform two EEG baseline measurements (2 minutes with eyes open followed by 2 minutes with eyes closed). You will do this 5 times during the first week. This establishes your EEG baseline before you start the active neurofeedback training phase.

During the second week of the trial (the transition period), you will have a video based appointment with the research team to practice training and answer any questions that you may have. You will also complete the 7 outcome measure assessments again (as per baseline appointment). From weeks 3 to 10, you will be asked to practice your training for 40 minutes per day to enable 5 X 40 minute sessions every week for a total of 8 weeks. In each session, you will put on the headset, open the app on the tablet, and answer some questions about your sleep, mood, and pain, followed by two EEG baselines (2 minutes with eyes open followed by 2 minutes with eyes closed). The session will then commence, and you will look at the screen, while interacting with a chosen 'game' selected from four available options. These games have been developed to encourage participants to upregulate their EEG activity in the alpha frequency band, while simultaneously downregulating beta and/or theta frequency bands, in accordance with the individual differences in EEG, observed in chronic pain.

Visual feedback will be provided on screen, representing your real time EEG activity measured by the

headset. Each session will be split into five blocks of five minutes each, with a one-minute rest period in between, in order to avoid fatigue and allow you to move around and adjust your position. After each rest block, you will be asked if you are ready to proceed and when ready, the next block can be started. After the end of the session (5 blocks) you will then be asked to perform a post-session eyes-open EEG recording, similar to the eyes-open baseline taken at the start of the session. We require you to complete 40-48 sessions over an 8-week period, to maximise the best chance of neuroplastic changes in your pain perception.

Whenever you perform a session, your EEG activity will be recorded automatically through the app software, allowing you to interact with your subconscious brain activity. If for some reason (for example, illness) you can't complete all the sessions in the eight weeks, we will give you another two weeks to complete them.

For the post intervention EEG baseline recording period (Weeks 11 - 22), you will perform 5 sessions of EEG baseline recordings during each week for a period of 12 weeks. Each session will take you approximately 5 minutes. For each session, you will put your headset on, open the app on the tablet, answer some questions about your sleep, mood, and pain, and perform two EEG baseline measurements (2 minutes with eyes open followed by 2 minutes with eyes closed). For each week, you will complete 5 sessions, so that at the end of these 12 weeks, you will have completed 60 EEG baseline recording sessions.

During this 12-week post intervention measurement period, you will also be asked to complete the same seven outcome measurement scales again in three separate follow up internet-based video call appointments with the research assistant, at Weeks 12, 16 and 24. In the final follow up assessment appointment in Week 24, you will also be asked to complete an additional two questions regarding your impression of change throughout the trial.

What are the possible risks of this study?

In the first few weeks, neurofeedback sessions will require mental effort and concentration, just like learning anything new. Some people with chronic pain have occasionally reported headaches and fatigue/drowsiness after undertaking neurofeedback training, which could be related to the mental effort and concentration needed. If you experience any adverse symptoms that you think might be related to using the equipment and taking part in this trial, then you should contact the Chief

Investigator by email to report it: XX

How would this be managed?

These symptoms are rare and when they do occur, they usually range from mild to moderate in severity and typically lessen or disappear over time. If you experience any of these symptoms, then you should report this to the research trial team and Chief Investigator. This enables the team to record this within the relevant study documentation.

The Chief Investigator, XX will then advise on what the most appropriate course of action should be. If you report any other health problems or issues during the training and trial, the Chief Investigator XX will be able to advise on what the most appropriate course of action should be. If necessary, XX would be able to refer you for appropriate medical care and/or you would also be free to seek this yourself at any time. If XX has any concerns for your safety, he will withdraw you from the study and in addition, you also always have the option of withdrawing from the study yourself.

There is a possibility that you may not experience any benefits from using the device and learning to practice the neurofeedback training, which may cause you to feel frustrated.

You would be informed of any new information about adverse effects related to the study if this became available during the study, which might have an impact on your health.

Please note that caffeine, sugary drinks and alcohol can cause the brain to change and will affect your results. You should wait for one hour before you start your neurofeedback training session after drinking any liquids containing caffeine (e.g. tea, coffee or energy drinks) or lots of sugar, such as soft drinks. Do not perform any neurofeedback training while under the influence of alcohol. If you have been drinking heavily the night before, the alcohol will still be in your system and you should not train the following day either, as your brain activity will still be affected.

Excessive Alcohol use: >14 Units / day for males and females.

Excessive caffeine Use:

Caffeinated drinks:

Caffeine is a stimulant. Drinks containing caffeine can temporarily make us feel more alert or less drowsy. Caffeine affects some people more than others, and the effect can depend on how much caffeine you normally consume.

Pregnant women should limit their intake of caffeinated drinks because of the caffeine content.

Caffeinated drinks are also unsuitable for toddlers and young children.

Drinks that contain high amounts of caffeine include coffee, tea, colas and energy drinks.

Reference: NHS Water, drinks and your health

Available at:

https://www.nhs.uk/live-well/eat-well/food-guidelines-and-food-labels/water-drinks-nutrition/

(Accessed August 2022).

What are the possible benefits of this research study?

Neurofeedback training may help to reduce your pain and could also potentially have other positive effects such as improving your mood and sleep. The effects detected usually vary from person to person but, based on a recent study in people with chronic pain (using the same neurofeedback training, the average reduction in pain intensity was just under 50%).

Data collection, management, storage and analysis.

XX will collect your name, email address, postal address, and telephone contact details in order to enable you to take part in this research study and these will be saved electronically in an Excel Workbook (Workbook 1). All participants will also be allocated a unique individual Participant Identification Number (PIN). These PINs will also be stored within Workbook 1 and will be used to enable linkage of PINs to the research team clinical trial diary of dates and appointment sessions during the trial, which will also be stored in Workbook 1. This Workbook will be saved and stored securely in the research repository system at XX IT Cloud system by the research team. The data stored in Workbook 1 will be stored for 3 years as per XX hospital policy and will then be destroyed.

Exsurgo Ltd will also need access to participant names and addresses in order to send the equipment kit to them in the post. Therefore, Exsurgo Ltd will also store a copy of Workbook 1 electronically in the cloud storage service used by Exsurgo Ltd.

The cloud storage service used by Exsurgo Ltd. is Amazon Web Services (AWS), who adhere to internationally recognized IT security and privacy standards. The AWS account belongs to Exsurgo Ltd and only staff who require access (i.e., for equipment deliveries, technical support, and some data analysis) will have access to the data.

Exsurgo Ltd will have access to this information in order to send equipment by post direct to each participant, and to contact participants should technical support be required.

With regard to Exsurgo Ltd, personally Identifiable Information including the participant's PIN will be stored in a separate data table to, for example, completed questionnaires and EEG data. The cloud storage service is designed to provide different levels of controlled access depending on the need, to maintain confidentiality

and data integrity.

The headset will stream EEG data to the tablet during the Neurofeedback training session. The tablet will be provided in a secure "Kiosk" mode, which will not allow access to its internal storage where the de-identified treatment data may be temporarily stored prior to being uploaded to the cloud storage service. The Axon App does not store any identifiable data. The tablet will continuously upload Headset data to Exsurgo's secure cloud service through an end-to-end encrypted internet connection.

How will the Sponsor (EKHUFT) use information about participants?

XX is the sponsor for this study in the United Kingdom. As the sponsor, XX will act as the data controller for this study. This means that we are responsible for looking after participant information and using it properly.

Exsurgo Ltd will have access to patient information for the delivery of equipment, joint data analysis, and technical support when required.

Individual participant rights to access, change or move information during trial participation are limited, as we need to manage participant information in specific ways in order for the research to be reliable and accurate. If participants withdraw from the study, personal information already collected will be kept for inclusion in the study results.

All personally identifiable data related to the trial will be securely stored by Exsurgo Ltd. for a period of 3 years, in alignment with XX policy, after which it will be destroyed.

The data gathered within this research will only be used for the purpose of health and care research and will not be used to contact participants or to affect their care in any way. Our research is conducted in accordance with the UK Policy Framework for Health and Social Care Research**.**

Data management

Confidentiality will be maintained throughout the trial. The CI and Co-PI Investigators involved in accessing health information are employees of XX and bound by its relevant privacy and confidentiality policies. Exsurgo Ltd have internal processes in place and have designed the data collection and retention system in accordance with the Data Protection Act 2018 as well as GDPR. De-identified (coded) data (i.e. questionnaire responses, EEG training data) will be collected by the tablet app and will be sent to a central data storage point maintained by AWS, using end-to-end encryption. This coded data will be kept by Exsurgo Ltd. in secure, cloud-based storage on a password protected database (AWS as previously detailed, on servers physically

located in the UK). Any data transferred/downloaded from the database during the study (e.g. for data safety monitoring and/or data analysis purposes) will be password-protected, remain de-identified and will be destroyed after the analysis has been completed. Data backups will be performed daily, and all data will be checked using range checks for data values prior to data analysis.

HRA General Data Protection Regulations (GDPR) transparency statement

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

You can find out more about how we use your information:

- by reading information at www.hra.nhs.uk/information-about-patients/
- by contacting either the Chief Investigator:XX or Co-Principal Investigator XX or by sending an email to the Research & Innovation Manager XX

What happens after the study or if I change my mind?

You may withdraw your consent for the collection and use of your information at any time, by informing the Chief Investigator and/or Co-Principal Investigator. If you withdraw your consent, your study participation will end, and the study team will stop collecting information from you.

Information collected up until your withdrawal from the study will continue to be used and included in the study. This is to protect the quality of the study.

After you complete the study, you will be provided with a Debrief document which outlines the conclusion of the research trial and gives you the option of obtaining a short research summary report after the whole trial is finished and data analysis has been completed.

After the study has ended, you will be allowed to continue to use the equipment provided by Exsurgo Ltd for this trial, through your regular healthcare provider, i.e. through the Out-patient clinics of Chief Investigator at XX Hospital.

If any of the equipment provided stops working, i.e. the Headset or tablet, then please email Exsurgo Limited Technical Support direct at the following email address:

Exsurgo Ltd Technical Support:
support@exsurgo.com

Can I find out the results of the research study?

As outlined in the Debrief document, should you wish to obtain a short summary report on the trial results, then if you inform the research team and give them your contact details, then they will send you a short 1-page summary report after trial completion and data analysis.

The results from this research study will be presented at meetings, academic conferences and written up for publication in international journals. No information that could personally identify you will be included. Please note that there may be a time period of up to three years from you taking part in this study to receiving the one-page summary.

What if there is a problem?

If any issue is raised, the research project team will address the issue at the earliest possible stage in order to resolve it and prevent adverse impact at any level. Please do not hesitate to speak with the research team at any stage about any concern that you might have.

Should you wish to make a formal complaint about any aspect of this research:

If you have a concern about any aspect of this study, you should initially ask to speak with the research team, who will do their best to answer your questions. If you remain unhappy and wish to complain formally, you can do this by contacting either the Chief Investigator or telephone on or the Co-Principal Investigator. Alternatively, you can contact the Patient Advice and Liaison Service (PALS) at the hospital, who can provide information on complaints procedures and independent help.

Who could answer any further questions?

Chief Investigator:

Co-Investigator: