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PARTICIPANT INFORMATION SHEET

Spinal Accessory Nerve Electrical Stimulation in Neck Dissection (SANE): A randomized, single blind, single centre external pilot study

We would like to invite you to take part in our research study. Before you decide, it is important you understand why the research is being done and what it would involve for you. Please take time to read this information and discuss it with others if you wish. If there is anything that is not clear or if you would like more information, please ask us.

Invitation

You are being invited to take part in a research study because you are a patient with head and neck cancer and are due to have an operation called a neck dissection.

What is the purpose of the study?

The purpose of this study is to see whether it is feasible to run a larger trial investigating whether short pulses of electricity applied to a nerve in the neck (the spinal accessory nerve) during surgery can help improve recovery of shoulder function after neck dissection.

Every year, around 12,000 people in the UK are diagnosed with head and neck cancer, and an increasing number are being diagnosed at a younger age. As treatments improve, survival rates are rising, which means that more people are living with the long-term side effects of surgery.

About 5,000 patients undergo a neck dissection each year to remove lymph nodes that may be affected by cancer. During this procedure, the spinal accessory nerve, which controls shoulder movement, is at risk of injury. Damage to this nerve often leads to pain and weakness in the shoulder, and about half of affected patients are unable to return to work. At present, physiotherapy is the only treatment available, but this usually leads to only modest improvement.

This study is investigating a new approach: applying small pulses of electricity to the spinal accessory nerve during surgery to encourage nerve regeneration. Earlier studies suggest that this treatment can improve shoulder recovery, but the stimulation has traditionally lasted an hour in the operating theatre, which is difficult to deliver routinely. More recent evidence shows that just 10 minutes of stimulation may be equally effective and more practical for use in the NHS.

In this study, participants will either receive standard treatment with no stimulation, or standard treatment combined with 10 minutes of nerve stimulation while asleep during surgery. Everyone taking part will also complete questionnaires and undergo assessments of shoulder and nerve function, in addition to their usual care.

Do I have to take part?

It is up to you to decide whether or not to take part. If you do decide to take part you will be given this information sheet to keep and be asked to sign a consent form. If you decide to take part you are free to withdraw at any time and without giving a reason. Withdrawing from the study will not affect the healthcare you receive or your legal rights.

What will happen to me if I decide to take part?

- This study will be conducted at Churchill Hospital, Oxford. Participation will involve a telephone pre-screening followed by five in-person visits.
- The in-person visits will coincide with your routine clinical appointment to minimise inconvenience to you.
- During the first visit, you will be asked to complete questionnaires and undergo tests for shoulder and nerve function. Additionally, a blood sample will be collected.
- Subsequent visits will involve similar questionnaires and shoulder and nerve function assessments.
- You will be blinded to your allocation within one of two study arms: routine care (no nerve stimulation) or 10 minutes of nerve stimulation.
- Your involvement in the study will last approximately 15 months and each visit is expected to take approximately 2-3 hours.

The following provides a simplified sequence of activities that will occur during each visit.

Time Frame	Your Involvement
Telephone Pre-Screening	Telephone call made 2-7 days after you decide to take part in the study. This can be 14 days to 160 days before your operation date.
Visit 1	• Pre-assessment clinic • Screening to assess for eligibility and reasons for exclusion • Consent to be part of the study • Questionnaires (baseline)

	• Neurophysiology testing (test for nerve function) (baseline) • Goniometry (test for shoulder function) (baseline) • Blood test (approximately 5ml) - We will take a small extra amount of blood for the study, but this will be done at the same time as your routine blood tests, so you will not need any additional needle sticks. One sample will be taken before your operation at your pre-operative appointment, and another will be taken 24 hours after your operation.
Visit 2	Day of surgery. You would be randomised to receive standard care (no nerve stimulation) or 10 minutes of nerve stimulation. Nerve stimulation will be done under general anaesthetic by your operating surgeon and a trained member of the research team.
Visit 3	• 3 months post-surgery • Questionnaires • Neurophysiology testing • Goniometry
Visit 4	• 6 months post-surgery • Questionnaires • Neurophysiology testing • Goniometry
Visit 5	• 12 months post-surgery • Questionnaires • Neurophysiology testing • Goniometry

What will the nerve stimulation involve?

If you are randomly chosen to receive the treatment as part of the study, the following steps will take place during your operation:

While you are under general anaesthetic (fully asleep), as part of the standard surgical procedure, the surgeon will remove your lymph nodes and carefully identify and preserve a nerve in your neck called the spinal accessory nerve. We will use a nerve stimulator device on your nerve to electrically stimulate it for 10 minutes, using a safe and controlled electrical current. Once the stimulation is complete, the surgery will be finished as planned.

The equipment used is a CE-marked medical device, approved for use in nerve stimulation during surgery. All surgeons delivering this part of the treatment will be specially trained and supported by expert trial surgeons to make sure it is done safely and effectively.

How will I be allocated to receive the nerve stimulation, and when will I find out which group I am in?

You will be randomly assigned (by chance) to one of the treatment groups. This randomisation is done using secure online software to make sure the process is fair and unbiased. The study team will be notified automatically when a new participant has been randomised.

In research, "blinding" means keeping certain information is hidden from people involved in the study. This helps to make sure the results are fair and not influenced by what anyone expects to happen. In this study, you will not be told which treatment group you are in — whether you receive the nerve stimulation or not — because the stimulation happens while you are asleep during surgery. This means you won't know which group you were assigned to until the study is finished.

After your operation, you will be followed up by your surgeon or other members of the surgical team as part of your routine care. The clinical team will be given clear instructions on how to avoid accidentally revealing your treatment group during these visits.

It is not possible to keep the surgical and anaesthetic teams blind to the treatment during your operation. For this pilot study, the study assessments (such as nerve tests and questionnaires) will be done by research staff who know which group you are in.

At the end of the study, after your final visit, we will check how well the blinding worked to make sure the process was fair. After this, you and your General Practitioner (GP) will be sent a letter to explain which treatment group you were in.

What do the questionnaires and other assessments involve, and how long will they take?

As part of the study, you will be asked to complete several questionnaires and take part in a physical assessment. These help us understand your recovery, shoulder function, and general well-being.

Shoulder Movement Assessment (Goniometry)
We will measure how far you can move your shoulder in different directions using a simple tool called a goniometer. This will take less than 5 minutes.

Questionnaires
You will be asked to complete the following questionnaires at different time points during the study:

- **NDII (Neck Dissection Impairment Index)** – Assesses any changes or difficulties with your neck, shoulder, and daily activities.
  Takes around 5 to 10 minutes.

- **SPADI (Shoulder Pain and Disability Index)** – Measures shoulder pain and how it affects everyday tasks.
  Takes around 5 to 10 minutes.
- **EORTC QLQ-C30 and H&N35** – Cancer-specific questionnaires that explore your overall well-being, symptoms, and quality of life related to head and neck cancer.
  Together, these take about 30 minutes.
- **EQ-5D-5L** – A brief questionnaire about your general health, including mobility, mood, and pain.
  Takes around 5 minutes.

Overall, each assessment session will take approximately 2 – 3 hours. You can take breaks if needed, and you may skip any questions you do not feel comfortable answering.

Will Any Blood Samples Be Taken?

We will take a small extra amount of blood for the study (about 5 ml = 1 teaspoon), but this will be done at the same time as your routine blood tests, so you will not need any additional needle sticks:

- One at your pre-operative assessment
- One about 24 hours after surgery.

This pre-operative blood sample will be used to look at a specific gene that may affect how people respond to the electrical nerve stimulation used in this study. Research in animals suggests that a protein called *brain-derived neurotrophic factor* (BDNF) may help nerves heal after electrical stimulation. A common variation in the BDNF gene — called *Val66Met (rs6265)* — appears to reduce this healing effect in animals, but it has not yet been studied in humans.

Around 20% of people carry this variation. By analysing this gene in our study participants, we hope to learn whether it influences the response to treatment. This could help guide how we design future research or personalise treatment in the future.

In addition to looking at the BDNF gene, we are also measuring something called NFL in your blood. NFL stands for neurofilament light chain, which is a protein released when nerve cells are damaged. By measuring NFL levels in both the pre-operative and post-operative blood samples, we can get an idea of whether the nerves are being affected by the treatment and how much.

This helps us understand not just how the treatment works overall, but also whether it's helping the nerves heal or if there is any stress or damage happening. This information could help improve future treatments and make them safer and more effective.

What Will Happen to My Blood Sample?

Your sample will be frozen and securely stored at the Botnar Research Centre or at an approved Biobank at the Nuffield Department of Orthopaedics, Rheumatology and Musculoskeletal Sciences

(NDORMS), in line with the Human Tissue Act. The DNA will be extracted and tested in one batch later in the study. For this study only the Val66Met (rs6265) variant in the BDNF gene will be looked at. No other genetic variants will be analysed. We will ask for your permission to store any remaining sample for future ethically approved research.

If you agree to long-term storage, your anonymised sample may be used by researchers at Oxford or internationally, but only in studies that have received approval from a Research Ethics Committee. If you do not consent to long-term storage, your sample will be safely destroyed at the end of this study.

To help keep your information confidential, your sample and any information recorded about you in this study will be assigned a study code that is used instead of your name or other identifiers. However, your DNA is unique to you so it can never be completely anonymous.

Are there any possible disadvantages or risks from taking part?

If you are allocated to the treatment group, the additional procedure will increase the total time you are under general anaesthetic by just over 10 minutes. While longer anaesthetic times can carry a slightly higher risk, the actual risk from an additional 10 minutes is extremely low. The anaesthetic team will monitor you closely throughout your surgery to keep you safe, and the surgical team is fully trained to deliver the treatment efficiently and carefully.

As part of the study, we will also need to take blood samples. This may cause some minor side effects such as bruising or, occasionally, feeling faint.

You will also be asked to complete a series of questionnaires and attend assessments, including nerve function (neurophysiology) tests. These are not part of routine care and may take over 2.5 hours per session.

Previous clinical trials using similar electrical nerve stimulation have reported no serious side effects. Based on this, it is very unlikely that the treatment used in this study will cause any harmful reactions.

Will my General Practitioner (GP) be informed of my participation?

To ensure continuity of care, your GP will be notified if you choose to take part in this study. Your GP will not be informed which intervention group you have been allocated to until after the final follow-up appointment.

Will my taking part in the study be kept confidential?

Yes. All study records and samples will be identified only by a code. We will use your name, date of birth and NHS number where this is necessary (e.g. to link to your NHS records or to contact you). Information that can identify you will only be held securely by the lead investigator for the purposes of the study.

Confidentiality will be maintained as far as it is possible, unless you tell us something which implies that you or someone you mention might be in significant danger of harm. In this case, we would have to inform the relevant agencies, but we would discuss it with you first.

Responsible members of the University of Oxford, regulatory authorities and Oxford University Hospital NHS Trusts may be given access to data for monitoring and audit of the study to ensure that the research is complying with applicable regulatory requirements.

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 you and your hospital records for this research project. We will share your information related to this research project with the following types of organisations: University of Oxford, regulatory authorities, and Oxford University Hospitals NHS Trust**.** This information will include your trial ID number that is linked to your name, NHS number, date of birth, and contact 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:

- All trial data will be entered into an electronic case report form (eCRF) on the REDCap database, which is a secure web application.
- Within REDCap, you will be identified only by a unique trial-specific number or code.
- Your data can only be accessed by members of the study team.
- When the study is complete, the data will be exported and the REDCap database will be deleted.
- Your trial ID number will be linked to your name, hospital number, and email address in a password-protected Excel spreadsheet.
- This spreadsheet will be stored securely on a study-specific University of Oxford Microsoft SharePoint account.
- Access to this file will be restricted to authorised members of the research team.

  Your personal data will not be shared outside the UK.

After the study ends, the retention period (this means the length of time we keep your data for) will begin and we will keep your data for a minimum of 3 years in line with the University Policy on Management of Data. Once the retention period has finished, the study data will be kept in a way that does not identify you.

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 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.

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, Dr Yuri Hirayama (yuri.bow-liu@msd.ox.ac.uk)
- sending an email to yuri.bow-liu@msd.ox.ac.uk
- calling us on 01865 227374
- contacting the University's Data Protection Officer data.protection@admin.ox.ac.uk
- looking at the University's privacy notice available at: https://compliance.admin.ox.ac.uk/research-data.

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: https://www.hra.nhs.uk/planning-and-improving-research/policies-standards-legislation/data-protection-and-information-governance/gdpr-guidance/templates/template-wording-for-generic-information-document/.

What are the possible benefits of taking part?

This study is a feasibility study, which means its main purpose is to find out if it is possible and acceptable to carry out a larger trial in the future. The larger trial would look at whether electrical stimulation can help improve recovery after injury to the spinal accessory nerve during neck surgery.

This current study is not designed to provide a definite answer about how well the treatment works. However, some participants may experience short-term benefits. Those who are randomly assigned to receive the nerve stimulation during surgery might have better shoulder function afterwards, based on results from earlier similar studies.

While we cannot guarantee that you will personally benefit, early research suggests that electrical stimulation of nerves may help the nerve heal and improve recovery.

Will I be reimbursed for taking part?

Participants will attend five clinic visits in total as part of the study. As one of these visits is the surgery itself, reimbursement of £50 will be provided for each of the four clinic visits (i.e. the pre-operative assessment and follow up visit at 3, 6 and 12 months).

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

Participation is entirely voluntary, and participants may change their minds at any point during the study. You are not obligated to provide a reason for withdrawal. Withdrawal will not affect the care you receive from the NHS.

If you withdraw from the study, unless you state otherwise, any blood sample collected to that point will be used for research as detailed in this participation information sheet. You are free to request that your blood samples are destroyed. Data collected up to your withdrawal will be used in the study.

What will happen to the results of this study?

At the end of the study, the results will be published in scientific journals, presented at scientific conferences and be freely available to researchers around the world. You will not be able to be identified from these reports. We will also provide a summary to participants who indicate they would like to be contacted with results.

What if there is a problem?

If you have any concern about any specific aspect of the study, please speak with the research team. They will do their best to answer any questions

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 study. 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. The study doctor can advise you of further clinical action and refer you to a doctor within the NHS for treatment, if necessary.

NHS indemnity operates in respect of the clinical treatment provided.

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 study, contact Dr Yuri Hirayama via email on yuri.bow-liu@msd.ox.ac.uk or you may contact University of Oxford Research Governance, Ethics & Assurance (RGEA) at rgea.complaints@admin.ox.ac.uk.

The Patient Advisory Liaison Service (PALS) is a confidential NHS service that can provide you with support for any complaints or queries you may have regarding the care you receive as an NHS patient. PALS is unable to provide information about this research study.

If you wish to contact the PALS team please contact:

- Tel: **01865 221473**
- Email: PALS@ouh.nhs.uk

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

This study was designed together with the Heads2Gather, a national patient group for people living with head and neck cancer. They have formed a group to advise our study.

Who is organising and funding the study?

The University of Oxford is sponsoring the study. The Chief Investigator is Mr Akira Wiberg.

Funding has been provided by Oracle Head and Neck Cancer UK.

Who has reviewed the study?

All research in the NHS is looked at by an independent group of people, called a Research Ethics Committee, to protect participants' interests. This study has been reviewed and given a favourable opinion by the National Health Service Research Ethics Committee.

Participation un future research:

All contact will initially be made by the research team for this study. Agreeing to be contacted does not mean you are obliged to take part in any future research. If you change your mind, you can ask to be removed from the register at any time.

Further information and contact details:

For any further queries, please email Dr Yuri Hirayama (yuri.bow-liu@msd.ox.ac.uk).

Thank you for taking the time to consider participating in this study. Your involvement is greatly valued and will contribute to improving care for future patients.