Participant Information Sheet and Consent Form

Percutaneous Auricular Nerve Stimulation for Post-COVID Fatigue

What is the purpose of the study?

For most people, COVID only causes mild initial symptoms, which typically don't need hospitalisation. However, even after mild disease, many people (typically 20% or more) continue to suffer from symptoms. These can include fatigue and muscle weakness, a syndrome now known as Long COVID. For those who develop Long COVID, it has a significant impact on their quality of life and productivity.

Whilst post-viral fatigue is a well-recognized phenomenon, the mechanisms of fatigue are unknown. But there is growing evidence that non-invasive vagus nerve stimulation (nVNS) can improve symptoms of fatigue and reduce levels of inflammation in patients with chronic fatigue.

In this study, we plan to test the effects of nVNS on symptoms of fatigue. The vagus nerve will be activated via its branch supplying the skin around the ear canal. Stimulating the ear can be easily and safely done at home using a transcutaneous electrical nerve stimulation (TENS) device, available over the counter without prescription. The study will focus on people who have been diagnosed with COVID19 but did not require hospitalisation. Participants with pCF will be randomly assigned to one of three study groups. One group will be asked to stimulate the part of the ear containing the vagus nerve. The other two groups will either give sham stimulation to the same part of the ear or be asked to stimulate a part of the ear that does not contain the vagus. We will assess fatigue in all participants during their first visit to the lab with questionnaires and by performing a number of electrophysiological tests, and again after 8 weeks. From week 9, all participants will switch to receive active treatment (nVNS) and the fatigue measurements will be repeated at the end of week 16.

You are being invited to take part in this study. Please take time to read the following information carefully and discuss it with others if you wish. Ask us if there is anything that is not clear or if you would like more information. Take time to decide whether you wish to take part. Thank you for reading the document.

Why have I been chosen?

We have asked you to help us either as a normal, healthy volunteer or as someone who has had a verified COVID-19 test and who is now potentially experiencing some of the longer-term effects such as fatigue. If you have any history of neurological disease (for example epilepsy or Parkinson's disease), any implanted devices (e.g. a pacemaker), or are pregnant, you should decline to participate in this study. If you have never had COVID but belong to one of the high-risk categories, you should also not participate. People especially sensitive to loud noises should also not participate. You do not need to tell us the reason for your decision.

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. Please feel free to ask any questions at any time. If you decide to take part, you are still free to withdraw at <u>any time and without giving a reason</u>.

If at any point you feel uncomfortable during testing, please let the researcher know. If you aren't able to do a certain measurement, you will still be able to take part in the study.

What will happen to me if I take part?

You will be asked to attend our laboratories within the Medical School at Newcastle University, where we can discuss any further queries you may have regarding the study. Once you are happy to proceed and have signed the consent form we can begin. We will first ask you to fill in a brief questionnaire to allow us to quantify your self-assessment of fatigue. We will then carry out a number of experimental assessments, which will take less than 3 hours. We will use adhesive electrodes stuck to the skin in the forearm and lower leg to record your muscle activity. We will ask you to perform a task with your hand or arm or leg, in which you will be asked to respond to lights or sounds by moving in a particular way (e.g. reaching to press a button when it illuminates or asking you to move your ankle). We may also measure responses to different types of stimuli described in the paragraphs below. Stimuli will be given while you are at rest and also while you are making a movement.

One of the stimuli we might test is a brief loud sound. We have carefully calibrated these so that the duration and level of sound is not harmful to your hearing – perhaps comparable to a car horn sounded next to you in the street. You will notice that the person running the study wears ear protectors during the experiment: this is because they often conduct multiple studies per week, giving them a higher level of exposure than the person volunteering. People especially sensitive to loud sounds might find them unpleasant, and in that case should not participate in the study.

We may also need to test nerve and muscle with electrical stimulation. We will place adhesive electrodes on the skin and pass a weak electric current through them. This is not painful or harmful but can feel a little strange if you haven't experienced this before, and can be akin to 'pins and needles', and might make your muscles twitch. Please let the experimenter know if you find the stimuli unpleasant, and they will stop the study.

We will measure the strength of connections between your brain and spinal cord using magnetic brain stimulation. A coil will be placed over your head, and a rapid magnetic field produced which can stimulate the part of your brain controlling movement. Again, this is painless and harmless (it feels like a tap on the head); it will make your muscles twitch very slightly. Most subjects tolerate this type of brain stimulation without problems, but please let the experimenter know if you find the stimuli unpleasant and want to stop.

Please ensure that your posture is comfortable at the start of testing as small discomforts at the start can become very unpleasant after you have been sitting in the same place for some time. The experiments will be carried out by research staff that are fully trained and competent in the procedures to be used. Most members of the research team are not medical doctors.

We will then set-up and train you in the use of the transcutaneous electrical nerve stimulation (TENS) system and clip electrode used to stimulate the auricular branch of the vagus nerve. You will be instructed as to where to place the electrode and how to turn the TENS device on, so you can administer the treatments on your own at home. We will also demonstrate how to apply and synchronize the wearable home-monitoring technology with the smart phone provided for the study. Once you are comfortable with operating the TENS device and the smart phone, we will provide you with specific instructions for using these systems at home, with contact details for trouble shooting any issues from home.

The aim of the study is to compare how these measurements change with non-invasive vagus nerve stimulation (nVNS; using TENS to the auricular branch of the vagus nerve) compared to placebo/sham stimulation. You will therefore be asked to return to the lab more than once (after 1-2 weeks, at 8 weeks and 16 weeks) so that we can repeat the assessments and measurements described above. You won't be told which stimulation (nVNS or sham) you've been assigned, but after 8 weeks you will definitely receive active stimulation, so everyone will get to use nVNS. You will be asked to apply the treatment three times per day: after waking, after lunch and at bedtime. One stimulation cycle takes about 60 minutes. We will also ask you to fill in a brief online questionnaire once a month regarding your fatigue symptoms. This will be brief and take less than 5 minutes of your time to complete – you will be given a unique number, so as to avoid having to enter any of

your personal information online, but if you prefer a paper questionnaire instead, please let us know and we can offer that to you in printed form, and we can then digitise the answers in the lab.

During the three lab visits (week 1, week 8 & week 16), we will also collect blood samples from you. This is to help us identify biomarkers that might predict COVID fatigue and the effectiveness of VNS. Blood samples will be collected by fully trained staff and will be stored within the Newcastle University Tissue Resource for analysis.

What precautions are being taken to reduce the chances of COVID transmission during my visit?

If prior to your visit you display any of the symptoms related to the disease (coughing, fever, loss of smell or taste, etc.) you will be asked to reschedule your visit for at least 2 weeks in the future. Before (and after) your visit all contact surfaces will be wiped down with disinfectant. In the lab, whenever possible a 2-metre distance will be kept between yourself and the experimenter. However, where this is not possible (such as during placement of electrodes), appropriate PPE will be worn by staff (surgical mask, gloves and apron) and by yourself (face mask). Both you and the experimenter will be expected to wash your hands at the start and end of the session. New PPE will be used for every participant. Even if you have recently recovered from COVID and are hence less likely to be vulnerable to infection, we will still follow exactly the same procedures.

We will be closely following government guidance on routine COVID testing.

What are the possible disadvantages and risks of taking part?

The methods which we will use are straightforward, and safe. Many are routinely used by doctors for diagnosing and treating their patients. None of the methods to be used will cause any harm.

What are the possible benefits of taking part?

TENS stimulation might alleviate your fatigue symptoms. However as this is a basic science study, we cannot guarantee this and results may vary from person to person. There may therefore be no personal benefit to you for taking part. The information which we gain by doing this study could lead to important advances in understanding the neural mechanisms behind post-Covid fatigue and could help guide treatments for this in the future.

You will also receive a £20 pound amazon voucher per completed session.

What if something goes wrong?

If you are harmed by taking part in this research project, you may be entitled to compensation under an insurance policy held by the University of Newcastle. If you are harmed due to someone's negligence, then you may have grounds for a legal action, but you may have to pay for it. Regardless of this, if you wish to complain, or have any concerns about any aspect of the way you have been approached or treated during the course of this study, you should in the first instance contact Prof. A. Blamire, Director of the Translational and Clinical Research Institute, University of Newcastle, The Medical School, Framlington Place, Newcastle, NE2 4HH.

Will my participation in this study be kept confidential?

All information which is collected about you during the course of the research will be kept strictly confidential. Upon your first visit you will be given a unique identifier number that will be used for all of your data storage and management. A paper document (that never leaves the lab) will match the unique identifier to any identifiable information of you, and this document will be destroyed at the conclusion of the study (3 years). Any information about you which leaves the laboratory will have your name and address removed so that you cannot be identified from it. You will be given a copy of this information sheet to take away with you and may wish to show it to your GP if you want to discuss your participation in the study with him/her.

What will happen to my data collected during this study?

Your data will be digital (both the questionnaire answers and electrophysiological recordings) and will contain no identifiable information that can be related back to yourself. Your data will be stored on the Newcastle University's secure servers for no more than 10 years – the first 3 years will be the duration of this study plus an additional 7 years, to allow completion of any outstanding publications, and should the data be of further interest to ourselves or other for related COVID research. After that time, we would aim to upload the data onto

an open access repository (such as https://openneuro.org/) for others to access. If you wish for your research data to be deleted at the conclusion of the 10 years, please let us know at any point prior to that time.

What will happen to the results of the study?

The results of this study will be published in scientific journals. If you would be interested in seeing a copy of the final paper, please let us know and we will send you one when it is published.

Who is organising and funding the research?

This study is funded by the National Institute for Health Research.

Who has reviewed the study?

This study was approved by the Faculty of Medical Sciences Research Ethics Committee, part of Newcastle University's Research Ethics Committee. This committee contains members who are internal to the Faculty. This study was reviewed by members of the committee, who must provide impartial advice and avoid significant conflicts of interests.

Contact for further information

This sheet provides basic information about the experiment. We will explain more as we go along; please feel free to ask questions. The person conducting the study is Maria Germann. The head of the laboratory in which these experiments are carried out is Dr Mark Baker. Please contact Maria Germann (email: maria.germann@newcastle.ac.uk | Tel. 0191 208 6977) if you have any queries about the study after you leave today. If this does not resolve your query, please contact Dr Baker (Tel. 0191 208 6897 | email: mark.baker@ncl.ac.uk | postal address: Henry Wellcome Building, Medical School, Framlington Place, Newcastle upon Tyne, NE1 4HH).

Thank you for giving your time to this study.

Dr Mark Baker

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