Participant Information Sheet

Study title:	***Pregabalin for the Treatment of CANVAS-associated Chronic Cough***		
Locality:	**Centre for Brain Research Neurogenetics Research Clinic. University of Auckland.**	Ethics committee ref:	**TBC**
Lead investigator:	**A/Prof Richard Roxburgh**	Contact phone number:	**09 376-0000**

You are invited to take part in a research study because you are known to have a condition called CANVAS syndrome – a form of inherited progressive clumsiness. Whether or not you take part is your choice. If you do not want to take part, you do not have to give a reason, and it will not affect the care you receive. If you do want to take part now, but change your mind later, you can pull out of the study at any time.

This Participant Information Sheet will help you decide if you would like to take part. It sets out why we are doing the study, what your participation would involve, what the benefits and risks to you might be, and what would happen after the study ends. We will go through this information with you and answer any questions you may have. 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, whānau, friends, or healthcare providers. Feel free to do this.

One of the research team members will contact you by phone to go through this information with you and answer any questions you might have. If your condition makes it difficult for you to speak on the phone, the researcher may email or text you. You may take as long as you need to decide if you would like to consent or not. If you agree to take part in this study, you will be asked to complete the online Consent Form. You can do this by filling in your details and electronically signing the form. The researcher who contacted you will also sign an online form confirming that they have contacted you and answered any questions you might have. You will be emailed a copy of both the Participant Information Sheet and the Consent Form to keep.

This document is 14 pages long. Please make sure you have read and understood all the pages.

Voluntary participation and withdrawal from this study

Participation in this study is voluntary. You are free to decline participation and it will not affect the care you receive outside of the study or your relationship with the study investigators.

WHAT IS THE PURPOSE OF THE STUDY?

This study has three main aims:

- Firstly, we will be trying to understand how CANVAS syndrome affects you, with particular attention to cough.
- Secondly we aim to determine whether a common medication, pregabalin, is effective in the treatment of your cough
- Thirdly we want to know how well tolerated pregabalin is

We are aiming to recruit 18 people to the study. Everyone who participates will be seen at the University of Auckland's Clinical Research Centre in Grafton, Auckland.

INVESTIGATORS

The Principal Investigator of the study is Richard Roxburgh who holds positions as Associate Professor in the Medicine Dept of the University of Auckland and as a Consultant Neurologist and Clinical Lead for Research and Neurogenetics within the Neurology Dept of Auckland City Hospital. He is responsible for the overall running of the study.

The Co-Investigator is Juno Barnett Collins who is a study coordinator at the Centre for Brain Research Neurogenetics Clinic at the University of Auckland. She will help administer the study including contacting you about appointments.

The Student Researcher is Rory Burnell who is completing a Bachelor of Medical Science (Honours) degree. He has currently completed five of six years of his medical degree and this study will contribute to him completing an Honours degree. He will be doing most of the hands-on work in the study.

Associate Professor Jacqui Allen is an ENT surgeon in the Department of Surgery at the University of Auckland with a particular interest in neurodegenerative disorders. She treats chronic cough as part of her usual work and is advising us on the protocol for this study.

Carol Chelimo is a statistician and is giving us advice on how to plan our study and to analyse the data that the study generates.

WHO HAS APPROVED THE STUDY?

This study has been approved by an independent group of people called a Health and Disability Ethics Committee (HDEC), who check that studies meet established ethical standards. The [insert Committee name] has approved this study.

This study has also been registered with the Australian and New Zealand Clinical Trials Registry. This Registry lists the protocol and Investigators running the study. Registration with ANZCTR or similar accredited bodies is a requirement for the publishing of any results that emerge from clinical trials. Registration number [to be completed upon successful registration]

WHO CAN TAKE PART IN THIS STUDY?

Only participants with genetically or clinically confirmed CANVAS can participate in this study. You may take part if you meet the inclusion criteria but do not meet the exclusion criteria.

Inclusion	Exclusion
• Participants with symptoms of CANVAS syndrome • Positive *RFC1* genetic test • Have had chronic cough for more than a year • Over 18 years old. • Can give informed consent. • Have access to a smart phone and prepared to download and use the cough app. • If able to become pregnant or the partner of someone able to become pregnant, - willing and able to use highly effective contraception methods.	• History of cancer (other than certain localised skin cancers). • Severe kidney disease • Previous bad reaction to pregabalin • Pregnancy/breastfeeding or planning to be pregnant • Active respiratory disease. • Current smoker or given up in the last six months. • On medications like inhibace or other “ACE inhibitors”. • Cough regularly bringing up sputum • Use of prebabalin or gabapentin within 3 months of baseline visit • Having anther medical condition that the Dr Roxburgh thinks may interferer with our ability to assess whether pregabalin is effective or which might make it dangerous to take pregabilin. • Blood tests at the screening exam which indicate severe kidney or liver disease.

Note – while the only medications that you’re not allowed to be taking are gabapentin and pregabalin, if you are on medications that make you drowsy like sleeping tablets or medication that can cause fluid accumulation, we will be particularly careful to watch out for these symptoms.

The inclusion and exclusion criteria will be discussed with you further at the screening visit.

HOW IS THIS STUDY DESIGNED?

This is a cross-over study design, split into two twelve-week treatment phases. You will be randomly assigned to one of two arms: either A or B. Participants in arm A will receive pregabalin during the first treatment period and placebo during the second whereas arm B, will have placebo in the first treatment period and pregabalin in the second. There will be equal numbers of participants in both arms.

This study is “double-blinded”; this means that neither you nor the study team will know whether you are in arm A or arm B so we won’t know when you’re on active drug. This is to reduce the risk of bias from you (or us) believing strongly in the drug.

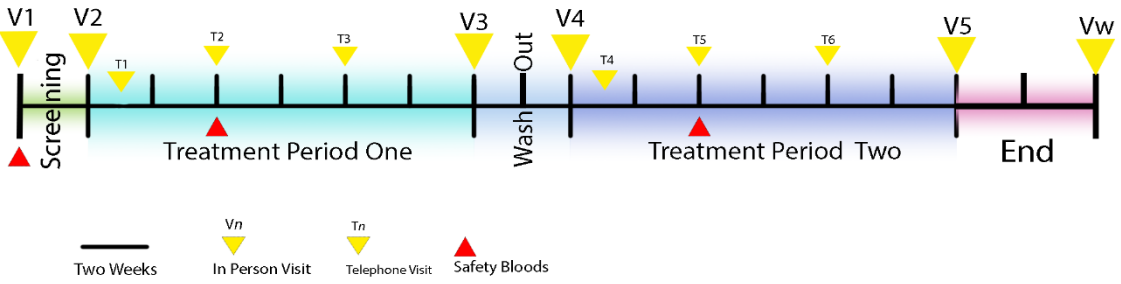

Figure 1. schematic diagram showing the treatment periods, in person and phone visits.

The active pregabalin tablets have 75 mg of pregabalin in them. In each treatment period you will start taking one tablet, twice-a-day. If you have bad side effects we would like you to contact us, and then we will reduce the dose to one tablet a day. If you still can’t tolerate the dose and you’ve completed less than four weeks of treatment, we will withdraw you from the study. If you have completed four weeks of treatment, then we will go straight to the four week washout period and then start you on the other phase of the treatment study.

If you tolerate the medication but you feel you have ongoing significant cough then at four weeks you can increase the dose to two tablets twice-a-day. Similarly, if after eight weeks you still have significant cough you can increase to three tablets twice-a-day.

If, after increasing the dose, you get side effects you can go back to the lower dose.

If you tolerate the medication and you fell that your cough is adequately treated, you will stay on that dose.

These dose changes are aimed at getting you on to the dose most likely to treat your cough. From two weeks before the first treatment phase until the end of the study your cough frequency will be monitored by an app on your phone. We will also assess you in-person six times throughout the study to assess whether you are responding to the medication and to see if it is having any other effect on your health.

We will also be having regular phone calls (1 week, 4 weeks, and 8 weeks into each treatment period) to assess your side effects – at these times we will advise you on dosage adjustments.

We will do safety blood tests at the beginning and four weeks into each treatment phase.

If you have any severe reactions, we will arrange extra visits and safety tests.

When all the data from all the study participants has been collected you will be able to find out which arm you were in.

WHAT WILL MY PARTICIPATION IN THE STUDY INVOLVE?

You will need to agree to download the cough assessment app to your phone and be happy to use the app throughout the study.

At the first (screening) visit we will check whether you meet the criteria for the study. If you are eligible, approximately two weeks (and no more than a month) after screening you will commence treatment period one. During the two twelve-week treatment blocks you will need to take medication reliably and report back to us if you have side effects. You will need to attend the six face-to –face visits and engage with the telephone visits and have your blood tests (see Figure 1).

We will measure the frequency of cough using a smartphone application called Cough Pro, which is an application specifically designed to record cough frequency and severity. This software records 0.5 second snippets of explosive noise and uses a secure, cloud-based server based in the USA to determine if these sounds are coughs. This process does not involve any human beings listening to this data, it is all done by a computer. The Cough Pro software does not record anything else, such as conversations, and can be turned on and off by the user. This application does not collect any other data or information about you and only requires an internet function and permission to access your phone's microphone to function. Personal, identifying information that this company may have access to is limited to your name and email address which are required for registration. The company may only use this data according to the terms of use in their privacy agreement.

Cough Pro works by subscription. The study will cover the cost of the app. We will contact the company once you have been enrolled and organise the subscription for you. You will not be asked for your credit card or to make any payments. Cough Pro, and their parent company Hyfe AI, have a full list of privacy information available on their website: coughpro.com

If you want to take part in the study, we will talk you through how to install and use the application and will be able to be provide ongoing support to help you through any unforeseen difficulties. We will ask you to share the application data to a secure online data storage, and this may need to be done every week throughout the duration of the study.

As part of your consent (which can be completed on-line), we will ask you to give us access to your medical notes for the specific purpose of looking at any related test results, such as blood tests, neurological test results, genetic test results and relevant respiratory or cardiological tests.

At each of you in-person visits and at each phone clinic you will need to fill in questionnaires about the frequency and severity of your cough and will also ask about the impact of cough on your quality of life.

During your clinic visits, you will be seen by a doctor and the other members of the research team, who will ask you about your medical history and perform a standard general and

neurological examination and assessments. These assessments will take 1 hour 20 minutes on the first visit and 1 hour on subsequent visits.

The research team may:

- Ask about your medical history and any surgery or major medical issues that you have had in the past. They will also ask if you are currently taking any medications. Some participants find it helpful to make a list of these prior to attending the clinic.
- Ask about whether other people in your family have had the same condition as you, or any similar neurological conditions.
- Perform a physical exam. This may include your height, weight, blood pressure measurements.
- Perform a neurological exam. This may include assessments of your muscle strength, reflexes, coordination, whether you have any muscle wasting, tremor or uncontrolled movements, your ability to feel touch and vibration, your eye movements, and the clarity of your speech.
- Perform some basic breathing tests to check your lung health. This will be during the first visit.
- Take blood tests during the first visit and organise subsequent blood tests during the treatment phase if required. A pregnancy test may also be administered.
- Conduct an ECG to check your heart rhythm.

As part of this research, health information about you will be collected. This will include information from your medical records including results of scans, blood tests, and genetic tests if you have had these, and from the assessments described above.

During remote visits, you will be contacted by one of the Investigators for a telehealth appointment by phone or video conference. This will take around 30 to 45 minutes.

The research team may:

- Ask about your recent medical history and any surgery or major medical issues that you have had in the past. They will also ask if you have started taking any new medications.
- Ask you about any side effects of taking the study drug, or if you have had any medical emergencies not related to the study drug.
- Ask you about your cough, how frequently you cough and how severe it is. The researchers will use a variety of surveys to measure this.
- Ask you about how the cough recording software is working and provide support for helping you send the data to the study team.

WHAT WILL HAPPEN TO MY BLOOD?

Your blood samples will be sent to Auckland City Hospital or Awanui Labs for testing. These samples will have identifying features such as your name, date of birth, and NHI. The results of this testing will be listed in your medical records just like any other blood test. The pathology service providers will not be made aware that you are in this study unless necessary, as determined by the Investigators. We will NOT be doing any genetic testing as part of this study. Your samples will not be sent overseas and will not be stored for any future research

and will be destroyed once the testing is completed. Your samples may be returned to you; however, this is at the discretion of the pathology service provider.

You may hold beliefs about a sacred and shared value of all or any tissue samples removed.

What will happen to my information?

During this study the Investigators will record information about you and your study participation. This includes the results of any study assessments. If needed, information from your hospital records and your GP may also be collected. You cannot take part in this study if you do not consent to the collection of this information.

Your data will be kept in a password protected Internet based *REDCap* database, hosted at the Faculty of Medical and Health Sciences. The investigators will have access to this data but will be required to treat it with the same degree of confidentiality as they would if they were seeing you in private or public hospital practice.

Identifiable Information

Identifiable information is any data that could identify you (e.g. your name, date of birth, or address). They will need this information to conduct the research, to assure the quality of the data, or to analyse the data. The following groups may have access to your identifiable information:

- Named Investigators listed on this document and authorised members of the Neurogenetic Research Group.
- Your GP will be notified of your participation in this study
- Your usual doctor (your GP or specialist), if a study test gives an unexpected result that could be important for your health or well-being. This allows appropriate follow-up to be arranged.
- Laboratory staff to process and report your screening and safety tests
- People from agencies and organisations that perform independent accreditation and / or oversight of research. This may include ethics committees or government agencies.
- The Cough Pro software providing company (Hyfe AI) who will know your name, cough frequency, and email address.

De-identified (Coded) Information

To make sure your personal information is kept confidential, information that identifies you will not be included in any report generated by the Investigators. Investigators will keep a list linking your code with your name, so that you can be identified by your coded data if needed.

The results of the study may be published or presented, but not in a form that would reasonably be expected to identify you.

Examples of how the information collected on you could be used might include

- Demonstrating whether the medication improves cough frequency or severity for patients with CANVAS.

Security and Storage of Your Information.

Your identifiable information is held at University of Auckland during the study. After the study it is transferred to a secure archiving site and stored for at least 10 years, then destroyed. Coded study information will be kept in secure, cloud-based storage database called REDCap indefinitely. All storage will comply with local and/or international data security guidelines The REDCap database is hosted and manged by the Faculty of Medical and Health Sciences of the University of Auckland.

Rights to Access Your Information.

You have the right to request access to your information held by the research team. You also have the right to request that any information you disagree with is corrected.

Please ask if you would like to access the results of your screening and safety tests during the study. You may access other study-specific information before the study is over, but this could result in you being withdrawn from the study to protect the study's scientific integrity.

If you have any questions about the collection and use of information about you, you should ask the Investigators.

Rights to Withdraw Your Information.

You may withdraw your consent for the collection and use of your information at any time, by informing one of the Investigators.

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.

Māori Data Sovereignty

Māori data sovereignty is about protecting information or knowledge that is about (or comes from) Māori people. We recognise the taonga of the data collected for this study. To help protect this taonga we are adhering to the following principles:

- Whakapapa – Whilst we are not specifically analysing how this condition affects Māori compared to any other group, if such information arises, other researchers interested in reducing health inequities suffered by Māori

- Whanaungatanga – The data kept in Aotearoa will be stored securely in the research unit and accessed only by research staff members who maintain confidentiality, it is collected only from those patients who have consented to the collection after consultation with whānau, some data maybe be analysed overseas by the software company so once it leaves the shores of Aotearoa we are unable to confirm that the obligations will be met. The dissemination of results from the data will be done through clinics where Māori are encouraged to bring whānau and community support.

- Kotahitanga – we are committed to supporting Māori patients through their treatment and trying to reduce inequities. Although the trial does not specifically target Māori populations, the Investigators will ensure that if a Māori patient was considered for the trial, they would be supported through the process.

- Manaakitanga – Free and prior informed consent will be asked for, time to discuss with whānau and the wider community will be given and it will be clearly explained that if the patient decides not to participate in the trial this will not affect their treatment at any other health provider or study. There will be no data analysis to stigmatise Māori in any way

- Kaitiakitanga – The data in Aotearoa will be stored in a way that Māori data will be accessible if required however the data sent overseas will not be, as it will not identify whether someone is Māori in anyway.

WHAT ARE THE POSSIBLE BENEFITS AND RISKS OF THIS STUDY?

There are some risks associated with taking part in the study. As you will be taking a medicine, there is a chance that you may experience some side effects. Although pregabalin is generally well tolerated, we will ensure that you are fully informed of these potential side effects before you start the study. You will be able to withdraw from the study if you do not want to continue taking the medication.

Pregabalin is unlikely to harm a developing foetus, however this risk cannot be ruled out. All individuals of childbearing potential will be required to use highly effective methods of contraception for the course of this study. Examples will be presented by the research team during your screening visit. Please note that if you are taking hormone based contraception you will also need to use barrier based methods. For those participants that are fertile but cannot bear children, you must use barrier protection during sex for the duration of the study.

There is some discomfort associated with having your blood taken. The risks for this are the same as for any regular blood test or donation. Brusing or bleeding may occur, but this is easily treated. Your blood will be taken only by qualified health professionals.

The routine assessments performed are similar to what a neurologist would perform. This includes testing your reflexes, coordination and senses. Likewise, ECG, blood pressure monitoring, and measuring your lung capacity are minimally invasive and should not cause any discomfort.

There is a possibility that someone who is not involved with the study could get access to your information, however this is unlikely, and every precaution will be taken to secure participants' personal information to ensure confidentiality. Release of medical information could result in loss of privacy. Discrimination for health insurance or employment sometimes occurs for those with genetic disorders.

The study team cannot guarantee any direct benefit but possible benefits include experiencing an improvement in cough frequency and severity.

WHO PAYS FOR THE STUDY?

This study is paid for by a small project grant from the Neurological Foundation of New Zealand. Additional funding may be provided by the Centre for Brain Research Neurogenetic Research Group where required. I have no idea at this stage

We can offer you a once time koha of $50 in vouchers to cover any incidental costs you might incur by travelling to and from the study site.

WHAT IF SOMETHING GOES WRONG?

If you were injured in this study, you would be eligible **to apply** for compensation from ACC just as you would be if you were injured in an accident at work or at home. This does not mean that your claim will automatically be accepted. You will have to lodge a claim with ACC, which may take some time to assess. If your claim is accepted, you will receive funding to assist in your recovery.

If you have private health or life insurance, you may wish to check with your insurer that taking part in this study won't affect your cover.

WHAT ARE MY RIGHTS?

Your participation in this study is voluntary and you are free to decline to participate or to withdraw from the research at any time.

You have the right to access the information we collect about you in the course of the study with the exception of any information that may unblind you or the Investigators.

WHAT HAPPENS AFTER THE STUDY OR IF I CHANGE MY MIND?

You can pull out of the study at any time, during or after the study finishes. You just have to contact any one of the Investigators to say you don't want to be involved any more.

If you choose to withdraw, any blood that already been collected will be processed. No further samples will be collected.

Formal publication in the literature of our study findings will be provided in a way that does not identify individuals' personal information. Your data will be included in any publications, unless you pull out before publication.

To preserve the integrity of the study, you will not be able to find out whether you were on pregabalin or placebo until all participants have finished the study. Once all participants have finished and the study team have been 'unblinded' to who was on what treatment, we will inform you if you wish.

If pregabalin made your symptoms better, you may continue to take it after the study finishes. It is an approved medication and your GP can prescribe it for you.

Can I find out the Results of the Study?

If the results of this study are publishable you will be notified (if that is what you selected on the consent form). An Investigator will contact you and let you know the results of the study. You may also access the final publication when and if it is published.

In the even the study cannot be published, you will be informed of this in the same way.

WHO DO I CONTACT FOR MORE INFORMATION OR IF I HAVE CONCERNS?

If you have any questions, concerns or complaints about the study at any stage, you can contact:

A/Prof Richard Roxburgh, Neurologist, Auckland City Hospital, Phone 09 367-0000

If you want to talk to someone who isn't involved with the study, you can contact an independent health and disability advocate on:

Phone: 0800 555 050
Email: advocacy@hdc.org.nz

For Maori health support please contact:

He Kamaka Waiora, Maori Health
Auckland City Hospital
Phone: (09) 484 6114
Email: hkw@adhb.govt.nz

You can also contact the health and disability ethics committee (HDEC) that approved this study on:

Phone: 0800 4 ETHICS
Email: hdecs@moh.govt.nz

Pregabalin for the Treatment of CANVAS Associated Chronic Cough: Consent Form

An Interpreter is available upon request.

Please read the following and if you agree with these statements sign and ate the form at the bottom. Where there are options please circle 'YES' or 'NO' to show your preference.

I have read or have had read to me in my first language, and I understand the Participant Information Sheet.

I have been given sufficient time to consider whether or not to participate in this study. I have had the opportunity to use a legal representative, whanau/ family support or a friend to help me ask questions and understand the study.

I am satisfied with the answers I have been given regarding the study and I have a copy of this consent form and information sheet.

I understand that taking part in this study is voluntary (my choice) and that I may withdraw from the study at any time without this affecting my medical care.

I consent to the research staff collecting and processing my information, including information about my health and the sharing of this information in the manner described in this information sheet.

I agree to an approved auditor appointed by the New Zealand Health and Disability Ethic Committees, or any relevant regulatory authority or their approved representative reviewing my relevant medical records for the sole purpose of checking the accuracy of the information recorded for the study.

I understand that my participation in this study is confidential and that no material, which could identify me personally, will be used in any reports on this study.

I understand the compensation provisions in case of injury during the study.

I know who to contact if I have any questions about the study in general. I understand my responsibilities as a study participant.

I understand that if I decide to withdraw from this study the information collected about me, up to the point when I withdraw, will continue to be processed and used in research unless I ask for it to be removed or deleted.

I understand that that some of my data will be sent overseas as part of the cough frequency monitoring and reporting.

I understand that blood samples must be collected at specific dates to ensure my safety during this study but that samples will not be sent overseas nor will any genetic testing be performed.

I understand that to participate in this study I will need to download and operate software on my own mobile device.

I consent to my GP or current provider being informed about my participation in the study and of any significant abnormal results obtained during the study

YES NO

I am a member of Punaha Io: The New Zealand Neuro-Genetic Disease Registry and consent to my data being shared with the Registry

YES NO

I wish to receive a summary of the results from the study.

YES NO

Declaration by Participant:

I hereby consent to take part in this study.

Participant's Name:

_____

Signature:

_____Date:_____

Declaration by member of research team:

I have given a verbal explanation of the research project to the participant and have answered the participant's questions about it.

I believe that the participant understands the study and has given informed consent to participate.

Researcher's Name:

_____

Signature: _____Date:_____