# Participant Information Sheet

## Low-dose Naltrexone as an adjunctive Treatment in Major Depressive Disorder

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Ethics committee ref.: 2022 FULL 12781

**This is the second clinical trial of low dose naltrexone in people with major depressive disorder.**

**You may not get any health benefit from the study drug; but there are risks of you having a drug reaction, injury or illness.**

You are invited to take part in a study involving the use of low dose naltrexone (LDN) as an adjunctive (add-on) treatment for major depressive disorder (MDD). Whether or not you take part is your choice. If you don't want to take part, you don't have to give a reason, and it won't 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'd 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.

If you agree to take part in this study, you will be asked to sign the Consent Form on the last page of this document. You will be given a copy of both the Participant Information Sheet and the Consent Form to keep.

This document is 19 pages long, including the Consent Form. Please make sure you have read and understood all the pages.

## VOLUNTARY PARTICIPATION AND WITHDRAWAL FROM THIS STUDY

It is up to you if you take part in this study or not. 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 don't want to take part, you don't have to give a reason. If you decide to take part, you are still free to withdraw at any time and without giving a reason. A decision to withdraw at any time, or a decision not to take part, will not affect the standard of care you receive from us or your participation in future studies.

## WHAT IS THE PURPOSE OF THE STUDY?

This study will be investigating the role chronic inflammation has in depression. Inflammation is a short-term response to injury (e.g., cuts, burns, sprains, allergic reaction etc.) and normally only lasts a few days. In comparison, chronic inflammation can last from weeks to years and is commonly a response to disease (e.g., heart disease, rheumatoid arthritis, auto-immune diseases, chronic fatigue syndrome etc.). Approximately one third of people with depression show signs of chronic inflammation, those that do are more likely to have recurring episodes of depression and are more likely to be resistant to treatment. Low-dose naltrexone (LDN) is a drug that is thought to have unique anti-inflammatory properties and, in a pilot trial by another research group, was shown to reduce symptoms of depression. In that trial, 12 participants already taking certain antidepressants were randomly assigned to take 1 mg of LDN twice daily or a placebo (an identical but inactive pill) for 3 weeks. At the end of the trial, the depression symptoms in the 6 participants taking LDN had improved significantly more than in 6 participants taking the placebo. Insomnia (trouble sleeping) was the most commonly reported side-effect of LDN.

The purpose of this study is to determine whether LDN equally helps people with both high and low levels of inflammation and depression.

This study will help with the understanding of the underlying cause of depression as well as potentially provide a new treatment option for those suffering with depression.

## HOW IS THE STUDY DESIGNED?

This study aims to recruit 48 individuals with depression and 24 healthy individuals. **You are reading this information sheet because you have indicated that you are currently being treated for depression and would be part of the treatment group.**

To participate you will have to undergo a psychological evaluation to ensure you meet the inclusion and exclusion criteria (listed below under "Who can take part in this study?"). You will also have to do two blood tests (at least one week apart) to determine your consistent levels of high sensitivity C-reactive protein (hs-CRP), a protein in the blood that is associated with inflammation, and so we can check your blood cell counts and liver function.

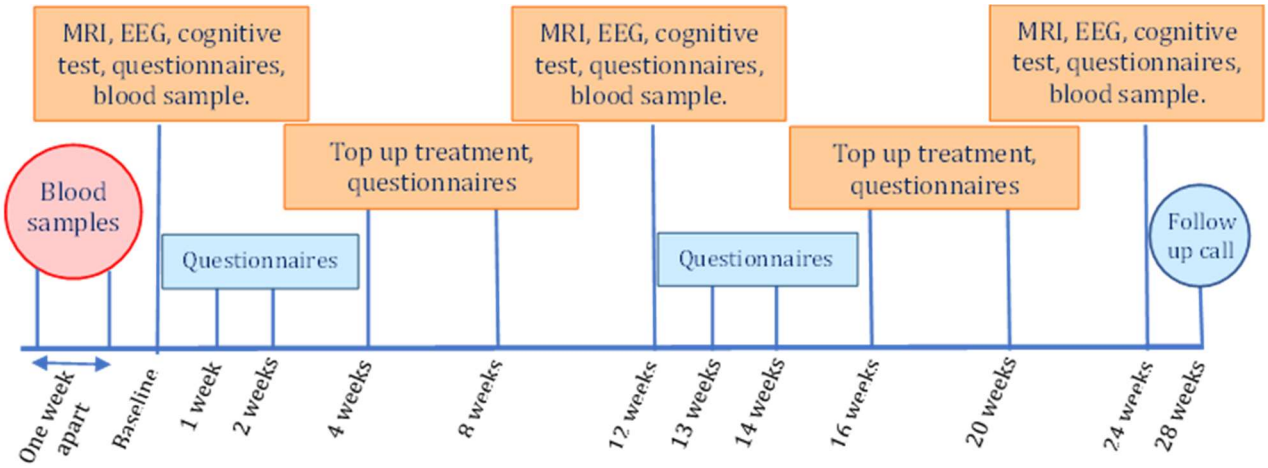
If you meet either the low or high inflammatory group criteria, you will be invited to the Grafton campus for half a day to complete baseline measurements. You will not be informed which inflammatory group you are part of until after you complete the study. The measurements at baseline include magnetic resonance imaging (MRI), electroencephalography (EEG), electrocardiography (ECG), cognitive tests, questionnaires, and a further blood sample. More information on these procedures is provided in a later section. Repeat measurements of the

MRI, EEG, ECG, cognitive tests, and questionnaires will be done after 12 weeks and 24 weeks where you will be invited back to campus for another half day to complete these measures.

You will randomly be assigned to either placebo (24 participants) or LDN (24 participants) for the first 12 weeks of the trial, after which, all participants will take LDN for a further 12 weeks. A placebo is a substance that appears identical to the study drug but is inactive and has no beneficial effect. Using a placebo and randomising participants in a clinical trial helps improve the accuracy of the trials results. This trial will use 8 randomisation blocks, with six participants in each block. In this trial, the placebo is microcrystalline cellulose, a food additive that is also used in the LDN capsule as an additive.

Researchers working on the trial will not know what treatment you are receiving. You can be informed which treatment you received for the first 12 weeks only after the final participant has completed the study. This may be more than a year after you complete the study if you were one of the first participants. This type of design, where researchers and participants are unaware of who is receiving the active drug is called “double-blinding” and increases the accuracy of the trials results. However, in the event of an emergency, the blind can be broken (see section “What are the possible risks of this study?” for more information). At the baseline appointment, you will be given a four-week supply of your assigned treatment. You will be started on 1.5mg of LDN or placebo (one capsule), increasing to 3mg LDN or placebo (two capsules) after the first week, then increasing again to 4.5mg LDN or placebo (three capsules) after the second week. Your capsules are to be taken before bed each night. You will then need to come in once every four weeks to receive the next four weeks’ supply of your assigned treatment.

There will be extra questionnaires (including a questionnaire on side effects) at the 1-, 2-, 4-, 8-, 13-, 14-, 16- and 20-week marks that can either be done over the phone, online, or when you come in to receive your next supply of treatment. We will also give you a follow up call after you have completed the study.




## WHO CAN TAKE PART IN THE STUDY?

You have been chosen to take part in this study because you have indicated that you are currently being treated for depression. You must be aged between 18 and 55 years. Our study medical team will help determine if you meet the criteria for inclusion in this study.

You will not be eligible to participate in this study if you:

- Currently use certain prescription medicines other than your antidepressant. For example, pain relief medicines
- Currently use recreational opioid-based drugs
- Have or have had certain medical or mental health conditions other than depression. For example: bipolar disorder, kidney, liver or heart conditions or a history of cancer
- Are feeling suicidal. See "What are the possible risks of this study?" below for more information
- Have an infection or another condition that might cause inflammation in your body. For example, autoimmune disease
- Have chronic pain
- Have recently had a substance use disorder
- Have a condition or circumstance that means you are unsuitable for MRI or blood tests. This includes refusing to be informed of an incidental finding. See section "What are the possible risks of this study?" for more information
- Are pregnant or breastfeeding, or of child-bearing age and not on an effective method of contraception. See section "What are the possible risks of this study?" for more information.

During the study we ask that you please:

- Abstain from alcohol and drugs for the 24 hours before each MRI session.
- Have a plan with your doctor to stay on the same anti-depressant for at least 6 months.

## WHAT WILL MY PARTICIPATION IN THE STUDY INVOLVE?

### ***Screening***

Initial interview: At the beginning of the study, you will receive a call from a researcher to inform you further about the study content and to check if you are eligible for study participation. You also have the option for this screening to be done via zoom or in person. If you meet all eligibility criteria for this study, we will arrange for you to have your first blood sample taken, and for you to fill in a brief form about your medical history.

Blood samples: After your initial interview you will need to go into a Labtests site to have your blood sample taken. This sample will be used to check your blood cell count, liver function, and the level of hs-CRP in your blood, and to ensure you are not pregnant if you are a person of child bearing potential. Then at least one week later you will need to get another blood sample taken from Labtests so we can measure hs-CRP again. This is to help us confirm if you have the right levels for inclusion in this study, and if so, the study group you will be in (high inflammation if hs-CRP is greater than or equal to 3 mg/L or low inflammation if hs-CRP is less than or equal to 1mg/L). You will not be informed which study group you are part of until after you finish the study. You can find your nearest Labtests site at: https://www.labtests.co.nz/collection-centres/. There is about a 30% chance your blood test will not be within the required range for inclusion in the study. See the section "What are the possible risks of this study?" below for information about handling abnormal results that may arise.

Medical interview: If your first blood test is in the required range for participation in the study, while you are waiting to have your second blood test, we will arrange a video call for you with one of our medical professionals to ask more detailed questions of your medical history and any medications you are taking. Your level of depression will be assessed using the Montgomery Asberg Depression Rating Scale (MADRS). We will also ask you questions about drug use using the NIDA-Modified Alcohol, Smoking, and Substance Involvement Screening Test (NM-ASSIST), and about your mental state using the Mini International Neuropsychiatric Interview (MINI). You also have the option for this to be done in person.

We invite you to bring whānau along to attend screening appointments with you.

***Baseline, 12 Weeks, and 24 Weeks***

You will be required to attend the University of Auckland, Faculty of Medical and Health Sciences, Grafton Campus for three assessment sessions that will take approximately 5 to 6 hours each. Refreshments will be provided. You will also collect your next four weeks' supply of treatment. We invite you to bring whānau along to attend these sessions with you.

MRI: MRI is a medical imaging technique that uses a magnetic field to produce detailed images of the brain. We are using MRI to measure levels of inflammation in the brain. Scans will be compared to those of people without depression to help us understand the role of brain inflammation in depression, how it relates to inflammation in the body and how LDN works. Scans will include magnetisation transfer imaging, diffusion weighted imaging and echo planar spectroscopic imaging and will take approximately one hour. Whilst this is not a clinical MRI (i.e., cannot be used to diagnose illnesses) anything of significance will be reported to your GP. See the section "What are the possible risks of this study?" below for more information.

EEG: An EEG is a test that measures electrical activity in the brain. We are using EEG to measure the varying brain signals that often coincide with depression. This will help us determine what symptoms of depression are associated with high levels of inflammation, and how LDN effects this. The EEG test will involve doing several tasks while an EEG is measuring brain activity and will take approximately one hour and a half. EEG recordings are not able to detect clinical abnormalities and are recordings are for scientific purposes only.

ECG: ECG is used to measure the electrical activity of the heart. This is done simultaneously with the EEG.

Cognitive test battery: The cognitive test battery is a series of tasks that are used to test cognitive abilities (brain-based skills) including memory, executive function (mental processes that enable us to plan, focus attention, remember, and juggle multiple tasks), attention, and response time, and will take approximately 40 minutes. The cognitive test battery results will help us determine which characteristics and symptoms of depression are associated with high levels of inflammation, and how LDN effects this.

Blood sample: A blood test measures the quantities of different components in your blood. A blood sample of 50 ml (less than 3 tablespoons) will be taken to measure 14 markers of inflammation. The level of these markers in the blood will help us determine the relationship between inflammation in the body and the brain in depression, and how these markers are affected by LDN. See "What will happen to my blood samples?" below for more details about

how we handle your blood samples. See the section “What are the possible risks of this study?” below for information about handling abnormal results that may arise

Questionnaires: You will be asked to complete a series of five questionnaires on your depressive symptoms, your mood and your quality of life which will take 30-45 minutes. You will also be assessed by a member of the team on your level of depression using the MADRS scale. You will also be asked to complete a short questionnaire on your expectancy for the trial at baseline and week 12. You will be asked to complete a lifetime stress and adversity inventory (STRAIN), which will take approximately 20 minutes and assesses your exposure to different types of stress throughout your life. This questionnaire only needs to be completed once at the baseline appointment. Overall, these questionnaires help us identify the differences in the nature and severity of depressive symptoms between people with depression who have high or low levels of inflammation, and the effect of LDN.

Semi-structured interview: At your last appointment at 24 weeks, we will conduct a semi-structured interview talking about your overall experience participating in this trial, and whether you think the medication has helped you. Audio from this interview will be recorded and transcribed. This will take approximately 30 minutes and will be done in person at the University of Auckland Clinical Research Centre.

Drug test: It is important that we know if you may be taking any recreational drugs before you start taking your treatment. You will be asked to complete a drug test at the baseline visit. This is a simple test that uses a small sample of urine, gives a quick result, and you will do it in private. If you fail the drug test, the study team may decide to reschedule your baseline appointment, or you may not be eligible for continuation in the study.

Pregnancy test: If you are a person of childbearing potential, it is important that we know if you may be pregnant. You will be asked to complete a pregnancy test at the 12-week visit. This is a simple test that uses a small sample of urine, gives a quick result and you will do it in private.

***Weeks 1 and 13***

Questionnaires: A member of the study team will give you a call to check if you are having any side effects and that you are adhering to the dosing protocol. These will take approximately 10 minutes.

***Weeks 2 and 14***

Questionnaires: A member of the study team will give you a call to assess your level of depression, check if you are having any side effects and that you are adhering to the dosing protocol. You will be asked to complete two questionnaires online about your symptoms of depression. These will take approximately half an hour.

***Weeks 4, 8, 16, and 20***

You will be required to come into the University to collect your next 4 weeks’ supply of treatment.

Questionnaires: You will have the same questionnaires as weeks 2 and 14, however you can choose to either complete them when you come into the University or do them at another time over the phone/online

## WHAT DOES BRAIN IMAGING (MRI AND EEG) INVOLVE?

**For MRI scans:**

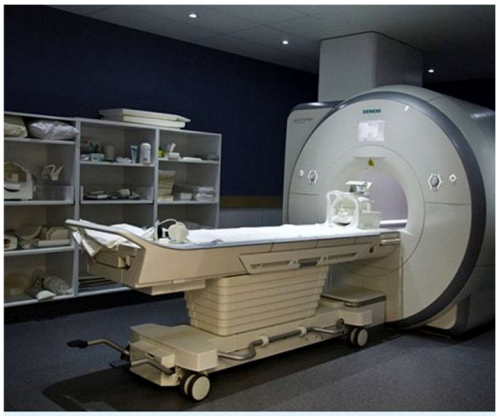


Figure 1: Siemens Skyra 3T system

You will change into clothes we will provide for you. We will check that you have no metal on your body before you enter.

The scan will take up to an hour. We will ask you to lie as still as possible during the scan.

The MRI scanner is very loud and for some people can feel very enclosed. As such, it can be a little scary if you have not been in one before. We will give you headphones to protect your hearing. Let us know if you feel uncomfortable or apprehensive in any way. You will be given an emergency buzzer that you can press so that you can leave the scanner at any time during the procedure.

Whilst this is not a clinical MRI (i.e., cannot be used to diagnose illnesses) anything of significance will be reported to your GP. See the section "What are the possible risks of this study?" below for more information.

**EEG and ECG:**

An EEG recording involves putting on a soft cap that has 64 electrodes (black plugs in the above image). The electrodes sit near your scalp and record electrical activity from your brain while you complete simple tasks on a computer. A good electrical signal is reached by using an electrolyte gel to ensure good contact with your skin. After the recording session, the electrolyte gel needs to be removed from the hair, which is easily done by a hair wash. We have facilities for you to wash your hair and will provide you with a towel and shampoo. You will also have ECG electrodes placed on your left and right chest/shoulder area.

The EEG takes around 15 minutes to setup, and the simple tasks will take up to an hour and a half (total 90 minutes). To make the set-up easier please come to the study days with clean, dry hair with no hair-care products in your hair.

## WHAT WILL HAPPEN TO MY BLOOD SAMPLES?

Our study requires participants to provide blood samples to look at 14 markers of inflammation in the body, so we can understand how it relates to inflammation in the brain. We will not

conduct any genetic testing on these samples that could lead to you being identified. All samples will be labelled with a study identifier, not your name.

We acknowledge that personal and health information is a tāonga (treasure) and will be treated accordingly. We will not retain any samples and will ensure culturally appropriate processes regarding data management including maintaining privacy, and communication with Whānau when appropriate. No blood samples will leave Aotearoa. The cultural issues associated with storing or disposing of your tissue should be discussed with your family/whānau as appropriate. Options for karakia and returning tissue samples can be discussed during the informed consent process.

## WHAT ARE THE POSSIBLE RISKS OF THIS STUDY?

Naltrexone is a safe and approved medicine at a 50 mg dose but not at the 1.5 mg, 3 mg, or 4.5 mg doses, which can currently only be prescribed off-label. “Off-label” means that Medsafe, New Zealand’s medicine regulation body, has not reviewed and cannot guarantee the safety and effectiveness of naltrexone at this dose.

While the risk of side effects is very low at the 4.5 mg dose you may experience: vivid dreams, nausea, epigastric pain (pain or discomfort right below your ribs in the area of your upper abdomen), diarrhoea, mood changes, mild irritability, headache, joint pain, fatigue and insomnia (trouble falling and/or staying awake). In the pilot trial of LDN in depression, the 6 participants receiving LDN for depression most reported insomnia as a side-effect. However, starting at the 1.5 mg dose and working your way up to 4.5 mg helps prevent possible side effects.

You will be informed of any new information about side effects related to LDN that becomes available during the study that may have an impact on your health.

Most of these side effects are reported to begin after the first dose then decrease over time. If the side effects are intolerable, we can discuss decreasing the dose to 3 mg, or splitting the dose so you take 1.5 mg in the morning and 1.5 mg at night, decreasing the dose in these ways has been reported to cease the unwanted side effects. If you are experiencing stress from receiving the medication you should contact us immediately. We can then arrange appropriate care for you.

If your depressive symptoms become severe then we will encourage you to call the Auckland crisis team on 0800 800 717. Occasionally, the symptoms of depression may include thoughts of self-harm or suicide. It is important that you tell the crisis team or your doctor immediately or go to the nearest hospital for treatment if you have any thoughts about suicide or self-harm. If you are in immediate danger, call 111. If we are concerned for your wellbeing and believe you may be at risk of suicide, we may contact emergency services such as the police.

Naltrexone should not be taken in conjunction with opioids or by individuals with acute hepatitis (liver disease) or liver failure. Opioids are a class of medications commonly used to treat severe pain; naltrexone blocks opioid medicines from working effectively and the dose used in this study may make you more or less sensitive to opioids. Individuals with opioids in their system who start taking naltrexone may experience severe withdrawal symptoms. During the screening visit our medical staff will check to make sure it is safe for you to participate in the study. If at any point in the study you need to take opioids then cease taking your

medication immediately and contact the study team so we can make appropriate arrangements for you to continue the study or not. You will be provided with a card to present to health care providers stating you may be on naltrexone. It is important you always keep this card with you, in case you ever need emergency pain-relief treatment. This card will contain the contact information of a study team member available 24 hours to advise treating health care professionals about dose adjustment or to identify the treatment you are receiving in the event of an emergency. You can also find this contact information below under “Who do I contact for more information or if I have concerns?”.

Your MRI scan is for research and is not a diagnostic exam. The scans are not the same as those that a doctor might order. Research scans are not routinely reviewed; however, in the event that a condition that is assessed to be a clinical abnormality is detected through performing an MRI scan on you, you will be informed of this and a general practitioner or other health professional of your choice must be notified. Because images are not routinely reviewed by a radiologist, we are unable to perform diagnostic scans for medical purposes. You should be aware that once you have been informed a clinical abnormality has been detected, this could affect your ability to obtain insurance, whether or not you take the matter further. If you do not wish to be informed of an incidental finding, you will not be eligible to take part in this study.

EEG and ECG recordings are not able to detect clinical abnormalities. Recordings will not be routinely reviewed by a clinician. The recordings are for scientific purposes only and are not able to provide diagnostic information. Sometimes there may be some minor skin redness or itchiness from the ECG electrode.

There is a slight risk of bruising from the blood tests. hs-CRP and erythrocyte sedimentation rate (ESR; a type of blood test that measures how quickly erythrocytes (red blood cells) settle at the bottom of a test tube that contains a blood sample) indicate levels of inflammation in the blood and on their own do not provide a diagnosis, but a high result can indicate infection or inflammatory diseases. Given it is expected that 30% of people with depression have an elevated hs-CRP and ESR, a study doctor will assess any abnormal results in the context of your other test results, and will consult with you and provide information on follow-up care if needed, for example, referring you to your general practitioner. In the case of the screening blood test, abnormal hs-CRP results will be identified within 24 hours of receiving the result. On the study day, abnormal ESR results will be known within 24 hours of collection, however, your hs-CRP result will not be measured and therefore cannot be assessed until some time after collection.

Other abnormal blood test results that arise from screening will be identified within 24 hours of receiving the result and will be assessed by a study doctor. Our doctor will consult with you to assess the significance of the result and provide information on follow-up care if needed, for example, referring you to your general practitioner.

**Reproductive risks for sexually active participants of child-bearing potential**

The effects of naltrexone in pregnancy and breastfeeding are unknown, but there is a risk it may cause birth defects or foetal deaths, and/or be passed on in breast milk. If you are pregnant or breastfeeding, you cannot take part in this study.

If you are sexually active and of child-bearing potential (able to become pregnant), it is very important that you do not become pregnant during this study. You must use one of the

methods of contraception listed below, from at least 10 days before your first dose of study drug until at least 72 hours after your last dose:

A highly effective method (less than 1 pregnancy per 100 women using the method for one year) e.g.:

- Implant contraceptive (e.g., Jadelle®)
- Intra-uterine device (IUD) containing either copper or levonorgestrel (e.g., Mirena®)
- Male sterilization (vasectomy)
- Female sterilisation (e.g., bilateral tubal ligation ('clipping or tying tubes') or hysterectomy)

OR an effective method (5 - 10 pregnancies per 100 women using the method for one year) e.g.:

- Injectable contraceptive (e.g., Depo Provera)
- Oral Contraceptive Pill (combined hormonal contraceptive pill or progestogen-only 'mini-pill')
- Vaginal contraceptive ring (e.g., NuvaRing®)

You must also agree not to donate eggs, from dosing until at least 3 months after your last dose of study drug.

**If you do become pregnant during the study, you must tell a member of the study team as soon as possible**. If you are pregnant, this will result in the cessation of the study for you and we will ask to collect information about the pregnancy and outcomes, including that of the infant.

**Reproductive risks for sexually active participants able to father a child**

The effects of naltrexone if passed on through semen are unknown, but there is a risk it may cause birth defects or foetal deaths. **You are responsible for informing your sexual partner** of these possible risks.

If you are sexually active and have any partner who is of child-bearing potential (meaning a partner who may become pregnant) it is very important that you use contraception during this study. You and your partner must use one of the contraception options listed above for participants of child-bearing potential, from at least 10 days before your first dose of study drug through until at least 72 hours after your last dose.

**If a pregnancy occurs, you must report this to a member of the study team as soon as possible**. Your partner will be asked to give consent for her information and her infant's information to be collected for monitoring purposes.

You must also agree not to donate sperm, from dosing until at least 3 months after your last dose of the study drug.

## WHAT ARE THE POSSIBLE BENEFITS OF THIS STUDY?

You may experience a reduction in symptoms.

You will be informed of any new information about beneficial effects related to LDN or depression that becomes available during the study that may have an impact on your health.

The results from this study may help advance knowledge on the causes of depression and open new avenues of treatment to help people with depression in the future.

## WHAT ARE THE ALTERNATIVES TO TAKING PART?

You do not have to participate in this study to receive treatment for your depression. There are other treatments for depression such as medications and therapies that are known to be effective. These can be discussed with your doctor.

## WILL ANY COSTS BE REIMBURSED?

We will pay for any costs that you incur by taking part in the study. If you require a taxi to get to and from the study, then we can arrange and pay for this. We recognise that taking part in the study will take **up to 23 hours** of your time and several months of contact with us and we will provide you with a minimum of $320 in vouchers throughout the study in recognition of this generosity. At the baseline, 12- and 24-week appointments, $80 will be gifted, with approximately another $20 gained based on results from one of the EEG tasks, therefore approximately $100 at each appointment. Another $20 will be given at the 4-, 8-, 16- and 20-week marks when you come in to get the next 4 week's supply of treatment. This gives a total of approximately $380 over the six month trial.

## 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 WILL HAPPEN TO MY INFORMATION?

During this study the study doctors/researchers, nurses and other study staff and PhD students 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; access to your records is limited to that required for study purposes. You cannot take part in this study if you do not consent to the collection of this information.

<u>Identifiable Information</u>

Identifiable information is any data that could identify you (e.g., your name, date of birth, or address). The following groups may have access to your identifiable information:

- University of Auckland investigators, staff and PhD students (to complete study assessments)
- Labtests staff, to process and report your screening blood tests

- The University of Auckland (the sponsor) and/or the Health Research Council (the funder) and its representatives, if you make a compensation claim for study-related injury. Identifiable information is required in order to assess your claim.
- The University of Auckland, the funder, ethics committees, or government agencies from New Zealand, if the study or site is audited. Audits are done to make sure that participants are protected, the study is run properly, and the data collected is correct.
- Your usual doctor, if a study test gives an unexpected result that could be important for your health. This allows appropriate follow-up to be arranged.
- Rarely, it may be necessary for a Study Doctor to share your information with other people – for example, if there is a serious threat to public health or safety, or to the life or health of you or another person OR if the information is required in certain legal situations.

Audio recordings will be de-identified by the assignment of the study code, however, there is a risk that they will remain potentially identifiable due to tone and sound of voice or experiences shared in the discussion. Audio recordings will be stored on password protected secure University of Auckland servers for up to approximately ten years after which they will be destroyed. Audio recordings may be accessed by members of the study team or a contracted transcriber who has signed a confidentiality agreement. Audio recordings will be transcribed, and all potentially identifiable information will be deleted from transcripts. Audio recordings and transcripts are unable to be corrected. Direct quotes from the transcripts may be used in publications and presentations with your permission. In the event of withdrawal from the study, audio recordings will be destroyed.

<u>De-identified (Coded) Information</u>

To make sure your personal information is kept confidential, information that identifies you will not be included in any report generated by the study team and any study information sent to the sponsor and/or funder. Instead, you will be identified by a code. The study team will keep a list linking your code with your name, so that you can be identified by your coded data if needed.

The following groups may have access to your coded information:

- The sponsor and/or the funder, for the purposes of this study.
- People and companies working with or for the sponsor and/or the funder, for the purposes of this study.
- Ethics committees, health, regulatory or other governmental agencies.

De-identified data from one of the stress tests (STRAIN) will be sent overseas to the Laboratory for Stress Assessment and Research, University of California Los Angeles. Only two staff members at this overseas laboratory will have access to the data. Data can be accessed and changed upon request.

A de-identified blood sample will be given to LabPlus to assess one of the inflammatory markers.

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

<u>Anonymised Information</u>

The sponsor may remove the code from your de-identified information – this is called 'anonymisation'. This makes it very difficult (but not impossible) to identify the information that belongs to you. The sponsor may use this information for future research (see below).

Future Research Using Your Information

Your coded information may be used for future research related to low-dose naltrexone or this study. Your coded information may also be used for other medical and/or scientific research that is unrelated to the current study. This does not include your tissue samples, which will be disposed after they are analysed.

This future research may be conducted overseas. You will not be told when future research is undertaken using your information. Your information may be shared widely with other researchers or companies. Your information may also be added to information from other studies, to form much larger sets of data.

You will not get reports or other information about any research that is done using your information.

Your information may be used indefinitely for future research unless you withdraw your consent. However, it may be extremely difficult or impossible to access your information, or withdraw consent for its use, once your information has been shared for future research.

Security and Storage of Your Information

Your identifiable information is held at the 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. Your coded information will be entered into electronic case report forms and remain on secure University of Auckland servers for up to approximately ten years. Coded information held by the overseas laboratory will remain on a secure server where results are produced after processing the data offline, and transferred back to us using secure end-to-end encryption. Data stored at the overseas laboratory will be destroyed at the end of the study. All storage will comply with local and/or international data security guidelines.

Risks

Although efforts will be made to protect your privacy, absolute confidentiality of your information cannot be guaranteed. Even with coded and anonymised information, there is no guarantee that you cannot be identified. The risk of people accessing and misusing your information (e.g., making it harder for you to get or keep a job or health insurance) is currently very small, but may increase in the future as people find new ways of tracing information.

Some of your coded information is being sent overseas to the University of California Los Angeles, United States of America. Other countries may have lower levels of data protection than New Zealand. There may be no New Zealand representation on overseas organisations which make decisions about the use of your information. There is a risk that overseas researchers may work with information in a way that is not culturally appropriate for New Zealanders.

This research includes basic information such as your ethnic group, geographic region, age range, gender and handedness. It is possible that this research could one day help people in

the same groups as you. However, it is also possible that research findings could be used inappropriately to support negative stereotypes, stigmatize, or discriminate against members of the same groups as you.

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, however this could result in you being withdrawn from the study to protect the studies scientific integrity.

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

Rights to Withdraw Your Information

You may withdraw your consent for the collection and use of your information at any time, by informing a member of the study team.

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.

Ownership Rights

Information from this study may lead to discoveries and inventions or the development of a commercial product. The rights to these will belong to the sponsor. You and your family will not receive any financial benefits or compensation, nor have any rights in any developments, inventions, or other discoveries that might come from this information.

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

**The medication that you receive during the study will not be available to you after your participation in this study, as it is not approved for the treatment of depression in New Zealand.** However, you may ask your doctor to prescribe it off-label and it is completely at your doctor's discretion whether to do this or not.

You can be informed which treatment you received for the first 12 weeks and the inflammatory group you were allocated to only after the final participant in your randomisation block has completed the study. This may be more than a year after you complete the study if you were one of the first participants.

You may withdraw your consent for the collection and use of your information at any time, by informing a member of the study team. 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.

## CAN I FIND OUT THE RESULTS OF THE STUDY?

It can take quite a long time to analyse data from these kinds of studies. We hope to be able to tell you the final results one to two years after completion of the study. We plan to publish the results in specialised academic journals. If you want us to, we can send you a summary of the results in an easier format to read.

This trial is registered on the Australian New Zealand Clinical Trials Registry (ANZCTR). This can be accessed at anzctr.org.au

## WHO IS FUNDING THE STUDY?

The Health Research Council (HRC) of New Zealand.

## 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 Southern Health and Disability Ethics Committee has approved this study.

The scientific aspects of this study have been approved by the Standing Committee on Therapeutic Trials (SCOTT), which is part of Medsafe.

## 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:

Dr Joanne Lin, Senior Lecturer
Phone: +64 9 923 2255
Email: joanne.lin@auckland.ac.nz

For urgent questions and concerns that arise during the study you can contact:

On-call (24/7) study team member
Phone: 0273107137

If your depression symptoms become severe or you are experiencing suicidal thoughts you can contact:

The Auckland Mental Health Crisis team
Phone: 0800 800 717 (operating 24/7)

If you are in immediate danger, please contact 111 and ask for Police.

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
Fax: 0800 2 SUPPORT (0800 2787 7678)
Email: advocacy@advocacy.org.nz
Website: https://www.advocacy.org.nz/

For Māori health support please contact:
He Kamaka Waiora (Māori Health Team)
Phone: +64 9 486 8324 x 2324
Email: hkw@adhb.govt.nz

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

Phone: 0800 4 ETHIC
Email: hdecs@health.govt.nz

# Consent Form

**Low-dose Naltrexone as an adjunctive Treatment in Major Depressive Disorder**

UNIVERSITY OF AUCKLAND Waipapa Taumata Rau NEW ZEALAND | MEDICAL AND HEALTH SCIENCES

**Please tick to indicate you consent to the following**

| |
|---|
| I have read, or have had read to me in my first language, and 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, whānau/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. |
| If I decide to withdraw from the study, I agree that the information collected about me up to the point when I withdraw may continue to be processed. |
| I consent to my GP or current care provider being informed about my participation in the study and of any significant abnormal results obtained during the study. |
| I understand that there may be risks associated with the treatment if I am taking opioid-based drugs when commencing treatment, or if I take opioid-based drugs during treatment. I undertake to inform the study team in the event I need to take opioids before or during the study. |
| I understand that there may be risks associated with the treatment in the event of myself or my partner becoming pregnant. I undertake to inform my partner of the risks and to take responsibility for the prevention of pregnancy. |
| I wish to be informed of any potential abnormalities found on my scans. |
| I consent to analysis of my blood samples and understand this analysis will be limited to this research project. |
| I agree to my blood samples being disposed of using established guidelines for discarding biohazard waste. |
| I agree to my de-identified data being used for future research studies related to naltrexone and this study, and for other medical and/or scientific research that is unrelated to the current study |
| 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 am aware that at any time during or after the study I may request a full copy of my individual data, however this may result in me being withdrawn from the study to protect the studies scientific integrity |
| Please tick to indicate you consent to all statements above Yes ○ |
| I wish to receive a summary of the results from the study. Yes ○ No ○ |
| If yes provide contact details (email): |

**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:

**Doctor/Primary Care Provider Details:**

Name: _____

Address: _____

_____

_____

Contact number: _____

Email address: _____