Anti-inflammatories and Physiotherapy for people with Knee Osteoarthritis: The AP-KO Randomised Controlled Trial

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Ethics committee ref:	2023 EXP 18561

You are invited to take part in a study about anti-inflammatory medication and physiotherapy for people with knee osteoarthritis. 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 can go through this information with you and answer any questions you may have. You do not have to decide today whether to take part 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. You can do this at your first appointment.

This document is 13 pages long, including the Consent Form. Please make sure you have read and understood all the pages.

VOLUNTARY PARTICIPATION AND WITHDRAWAL FROM THIS STUDY

Taking part in this study is voluntary (your choice). You may withdraw from the study at any time without any disadvantage to yourself, or any impact on your healthcare.

WHAT IS THE PURPOSE OF THE STUDY?

People with knee osteoarthritis (OA) often experience pain and stiffness that impact everyday activities and quality of life. Non-steroidal anti-inflammatory medication (NSAIDs) and physiotherapy can both be effective treatments for knee OA. NSAIDs are widely used and can help relieve pain caused by inflammation. Common names for NSAIDs are Voltaren (diclofenac); Nurofen, Advil, and Brufen (ibuprofen); Naprosyn (naproxen); and Celebrex (celecoxib). Sometimes NSAIDs are combined with paracetamol e.g. Nuromol and Maxigesic. However, there can be risks associated with taking NSAIDs, and they are not recommended as a treatment on their own. The risks associated with using NSAIDs increase when they are taken over a long period of time, and include gastrointestinal (stomach) problems, kidney, heart, and circulatory system damage.
Research has shown that physiotherapy such as exercise, physical activity, and education should be the mainstay of care for people with knee OA and has few potential side effects.

We don't know whether NSAIDs and physiotherapy used together are any better than physiotherapy on its own. This study will compare two groups of people who will both receive evidence-based physiotherapy care for their knee OA. In addition, one of the groups will also take NSAIDs with a second medication to protect the stomach (PPI). We will evaluate clinical and cost-effectiveness.

We also want to look at inflammatory markers in the blood and explore how these markers relate to participants OA symptoms. We want to see whether these markers change when participants have physiotherapy or take NSAIDs.

As this is a feasibility (small-scale) trial, we want to see how many people will be interested in taking part, what participants and physiotherapists think about being in the trial and how much it costs to run. We will use this information to plan a full-scale trial in the future.

The results of the study will help guide future healthcare delivery and outcomes for people with knee OA.

HOW IS THE STUDY DESIGNED?

This is a randomised, controlled feasibility trial, with 30 people allocated to either an NSAID group or a placebo group. Both groups will receive best evidence physiotherapy care for knee OA. This will include one-on-one exercise, strengthening, manual therapy (hands-on treatment) and education for an initial four weeks, followed by eight weeks of supervised weekly group exercise, designed for people with knee OA. Physiotherapy will be provided at the School of Physiotherapy Clinics, 325 Great King St., Dunedin and will take 30-60 mins.

In addition to physiotherapy care, one group will take NSAIDs plus a stomach protector pill (PPI) daily for four weeks, while the other group will take inactive placebo pills daily for four weeks. From five to twelve weeks, participants can take their NSAID/placebo if they need it.

There is always risk and benefit associated with taking medicines, and this study has been designed to maximize participants' safety. The research team involves medical doctors, physiotherapists, pharmacists, and microbiologists.

WHO CAN TAKE PART IN THE STUDY?

We are looking for participants aged 45 years and older, who have knee osteoarthritis (OA) with frequent pain and stiffness. You do not need to have an Xray or a specific diagnosis. We can help you work out if you have knee OA.

WHAT WILL MY PARTICIPATION IN THE STUDY INVOLVE?

Interested participants will have a short telephone screen with the Trial Coordinator who will explain the trial and ask a few questions to make sure it is safe for you to exercise and to be prescribed NSAIDs. Alternatively, you can go to the study website to find out about the research and whether you are likely to be eligible.

Following the telephone/website screening, you will be asked to attend an appointment with our study GP, Dr. Sharon Leitch at the Urgent Dr's, Filleul St., Dunedin. We will ask you not to take any NSAIDs for one week before coming. Dr Leitch will explain the study, ask you to sign a consent form, and ask about your knee and other health conditions and medications. She will check your blood pressure, pulse, calculate your BMI (weight and height), check your heart health and whether it's safe for you to exercise. You will be asked to supply a urine sample to check for kidney damage or high blood pressure (hypertension). Dr. Leitch may consult your medical records (with your consent) or talk to your usual GP to ensure she has the correct information about your health. The appointment will take up to 30 minutes.

You then need to go to Awanui Labs (formerly Southern Community Labs) to provide two blood samples. One sample will be tested for liver and kidney function and red blood cells (haemoglobin) to check for safe participation in the study. The other blood sample will be taken to a microbiology lab at the University of Otago to investigate biomarkers for inflammation.

Once Dr Leitch has all your health information and the results of the urine and blood tests, she will decide whether it is safe for you to participate in the study. You will then be randomly allocated to either the NSAID group or the placebo group. You will not know which group you are in, and you have an equal chance of being allocated to the real NSAID medication or to the placebo medication.

Your participation in the study involves four visits to the School of Physiotherapy for research assessments. One visit takes place *before* you start treatment, and the other three at 5 weeks, 13 weeks and 6 months *after* you start treatment. They will take about 20-30 mins each. At each visit you will answer some questionnaires about your knee and how it affects you, some details of your income and costs associated with your knee pain and perform some timed functional tests such as walking and climbing stairs. At the first visit you will be dispensed your trial medications by a NZ registered pharmacist located in the Pharmacy Clinic on the ground floor of the School of Physiotherapy building.

At the three follow-up visits you will also supply a urine sample to monitor your kidney function and will go back to Awanui Labs to provide the blood samples as before. All these lab tests

are designed to monitor your ongoing safety for being in the trial, and to detect any adverse reaction to the NSAIDs. The second blood test will monitor your inflammatory biomarkers and how they respond to the study interventions.

People allocated to the NSAID group will be taking Naproxen 1000mg (a non-steroidal anti-inflammatory) and Omeprazole 20mg (a stomach protector pill, used to reduce the amount of acid produced in your stomach and prevent ulcers) once every day for four weeks. People in the placebo group will take two inactive placebo pills once every day for four weeks. From five to twelve weeks, you may take your medication/placebo when needed as long as you do not exceed the daily dose. You should start your medications the same day you start your physiotherapy treatment.

We will ask you to keep a medicine diary to record when you take the study medicines and will ask you to return any unused medication at the end of the trial. If you need additional pain relief during the trial, you may take paracetamol. If you need stronger pain relief, you should go to your GP for a prescription, and let them know you are in a clinical trial. Please do not take any additional anti-inflammatory or stomach protection medication without medical advice. You may need to check flu or cold remedies as they often include NSAIDs. Record all additional medications in your medicine diary.

If you are prescribed another medication for a different condition, be sure to tell your doctor or pharmacist you are in this trial so they can check for drug interactions. You should avoid pregnancy during the trial as NSAID use is not recommended.

Let one of our research team or your physiotherapist know if you are in a lot of pain, or if you have any adverse reactions to the study interventions. We will help you decide what to do and make a record of what is happening to you. Adverse events are reported to our trial safety team, and they may recommend that you withdraw from the trial if they are concerned about your health.

Physiotherapy treatment will involve four to six individual appointments over a four-week period. These sessions will last up to 45 minutes each and will be held at the School of Physiotherapy Clinics, 325 Great King St., Dunedin. The sessions will include exercise, hands-on treatment, and education. From five to twelve weeks, you will have a weekly group exercise session at the School of Physiotherapy, led by a physiotherapist. Your physiotherapist will also give you a personalised home exercise programme. You will be encouraged to do the exercise programme twice a week and record this in a diary.

WHAT WILL HAPPEN TO MY BLOOD AND URINE SAMPLES?

The urine samples will be disposed of immediately following testing.
The Awanui Labs and the Microbiology Lab at the University have strict procedures they follow for the storing and disposal of samples. The Awanui Labs will analyse one blood sample, very soon after it is drawn from you. The second blood sample will be stored carefully until the research assistant collects it and takes it to the Microbiology lab at the University. It may be frozen and stored there until a number of samples are available to be tested at the same time. This may take several weeks.

Only small amounts of material may remain after testing and these will be disposed of in line with standardized laboratory procedures. Both Awanui Labs and the Microbiology lab can arrange for disposal of blood in a manner respecting tikanga, including saying a karakia if requested. They also have procedures for return of any blood sample material that may remain after testing.

You may hold beliefs about a sacred and shared value of all or any tissue samples removed. The cultural issues associated with storing your tissue (blood sample) should be discussed with your family/ whānau as appropriate. There are a range of views held by Māori around these issues; some iwi disagree with storage of samples citing whakapapa and advise their people to consult before participating in research where this occurs. However, it is acknowledged that individuals have the right to choose. Please inform one of the research team about your cultural requirements so we can respect your beliefs.

WHAT ARE THE POSSIBLE RISKS OF THIS STUDY?

For most people, Naproxen 1000mg is safe. The screening procedures in the study mean that only people with a low risk of an adverse reaction to an NSAID will be included in the trial.

Common side effects of Naproxen 1000mg include:

- Heartburn or indigestion
- Stomach discomfort
- Runny poo (diarrhoea)

These side effects are not usually concerning and should settle within a few days. You will be advised to take the Naproxen 1000mg (or the placebo medicine) with food. You will be encouraged to record any side effects in your medication diary, and your physiotherapist will ask you about side effects at each physiotherapy appointment. If you have any concerns, you will be able to call one of the research team.

In rare cases, using Naproxen 1000mg can have serious side effects. These side effects are more likely to be seen in people who have been taking Naproxen 1000mg over a longer period. Stomach bleeding and ulcers occur in approximately 1% of people who take NSAIDs for 3-6 months and 2-4% of people who take NSAIDs for one year.

Omeprazole 20mg reduces the amount of acid produced by your stomach, to prevent ulcers forming. It belongs to a group of medicines called proton pump inhibitors (PPI's). Common side effects of Omeprazole 20mg include:

- Stomach upset, feeling sick
- Feeling bloated in your stomach
- Loose stools (poo)
- Constipation

These are not usually concerning, but please report any side effects to your physiotherapist or the Clinical Trial Administrator.

Other side effects associated with longer use of NSAIDs are heart or kidney problems. The study physiotherapists will monitor your response and blood pressure at each appointment, and the study GP will be monitoring your urine and blood results, so any adverse event will likely be picked up early and managed appropriately by the Doctors on the team. In some cases, they will recommend stopping the medication.

Physiotherapy treatment can cause slight discomfort, pain or muscle stiffness. This should be mild and ease quickly. You will be asked to report any discomfort lasting more than one day to your physiotherapist, who can adjust your treatment if necessary.

During the study, participants will be told of any new information about adverse effects related to the study that becomes available. This information will be shared with your GP.

WHAT ARE THE POSSIBLE BENEFITS OF THIS STUDY?

Direct benefits of taking part are that you will receive best-evidence physiotherapy care for your knee OA, be provided information to understand your knee OA and what you can do and undertake exercises that benefit your knee as well as whole body health. This will be provided at no cost to you. The NSAIDs may confer additional benefit in the form of pain relief.

Indirect benefits relate to positive effects of exercise and physical activity on your health and well-being.

WHAT ARE THE ALTERNATIVES TO TAKING PART?

The alternative of taking part in the study is to arrange your own physiotherapy care or to consult with your GP about the best care for your knee OA.

WILL ANY COSTS BE REIMBURSED?

You will not have to pay for any of your physiotherapy treatment.
Participants will be given a $30 voucher as a token thank you for completing the screening process.
At the end of the 6-months trial we will give you a $100 voucher to acknowledge your participation in the research.

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 researchers will record information about you and your health. This includes the results of any study assessments, blood, and urine tests. If needed, our study GP may check health information with your own GP, but this will be kept separately and not reported in the research. You cannot take part in this study if you do not consent to the collection of this information, or if you do not agree to your GP being informed you are in the study.

Any information that could identify you is kept separately from other trial data. Results of laboratory testing will be sent to the trial GP with your name on. Your own GP will also have a record of the blood test results. This data will be de-identified by the Clinical Trail Administrator before being handed on to the rest of the team for analysis and reporting.

Identifiable Information

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:

- Clinical Trials Administrator, and School of Physiotherapy Clinic staff who need to contact you to make appointments.
- Your GP will be notified of your participation in this study.
- Laboratory staff, to process and report your screening and safety tests
- The study GP to match your test results and clinical information to decide on safe inclusion and ongoing participation in the trial.
- Study safety monitors, should you experience an adverse reaction.
- 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. The study GP will discuss this with you first.

De-identified (Coded) Information

To make sure your personal information is kept confidential, information that identifies you will not be included in any research report or any study information. Instead, you will be identified by a code. The Clinical Trial Administrator 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 identify you.

Security and Storage of Your Information.

All your identifiable and coded information is stored on password protected databases, or in a locked filing cabinet in the lead researcher's office at the School of Physiotherapy. After the study it is transferred to a secure archiving site and stored for at least 10 years, then destroyed. Coded study information may be kept by the University of Otago in secure, cloud-based storage indefinitely. All storage will comply with NZ 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.

Your coded information may be sent overseas in the future, to combine with other similar sets of data. 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 researchers overseas may work with information in a way that is not culturally appropriate for New Zealanders.

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 lead researcher.

Rights to Withdraw Your Information.

You may withdraw your consent for the collection and use of your information at any time, by informing the Clinical Trial Administrator. You may also request the withdrawal of any remaining blood samples held in storage, awaiting analysis.

If you withdraw your consent, your study participation will end, and the study team will stop collecting information from you.

If you agree, information collected up until your withdrawal from the study will continue to be used and included in the study. You may ask for it to be deleted when you withdraw unless you withdraw after the study analyses have been undertaken. Blood test results are included in your clinical record and cannot be deleted.

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 have consulted with the University of Otago Ngāi Tahu Research Committee about the collection, ownership, and use of study data.

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

You may withdraw from the study at any stage by informing the principal researcher, Dr Cathy Chapple, the Clinical Trial Administrator, or your physiotherapist.

In the final session, the physiotherapist will discuss your future management with you and what options you may want to consider. If needed, we may refer you to your GP or for continued physiotherapy treatment.

CAN I FIND OUT THE RESULTS OF THE STUDY?

If you are interested, we will send you a summary of the study results via email or you may access it on the trial website. You may also request any of your individual data from study assessments. Please let us know your preference.
This study is registered with the Australia New Zealand Clinical Trials Registry (Registration number ACTRN12623001344684). You will be able to access that registry here: https://www.anzctr.org.au/ACTRN12623001344684.aspx

WHO IS FUNDING THE STUDY?

A Health Research Council of New Zealand grant and a Jack Thompson Osteoarthritis New Zealand Memorial grant is funding this research.

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.

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. Cathy Chapple, Senior Lecturer, School of Physiotherapy
Phone: 0800 687 489 or 03 479 7460
Email: cathy.chapple@otago.ac.nz

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@advocacy.org.nz
Website: https://www.advocacy.org.nz/

For Māori cultural support please contact:

Ms Katrina Pōtiki Bryant, Associate Dean Māori, Lecturer/Pūkeka
School of Physiotherapy/Te Kura Kōmiri Pai
Phone/Waea: 03 479 5428
Email/Īmera : katrina.bryant@otago.ac.nz

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

Email: hdecs@health.govt.nz
Phone: 0800 400 569 (Ministry of Health general enquiries)

Consent Form

Please tick to indicate you consent to the following

I have read the Participant Information Sheet, or have had it read to me in a language I understand, and I fully comprehend what it says.		
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.		
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.	Yes ☐	No ☐
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.		
I understand that there may be risks associated with the treatment in the event of myself becoming pregnant. I undertake to take responsibility for the prevention of pregnancy for the duration of the trial.		
I agree to an approved auditor appointed by the New Zealand Health and Disability Ethics 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 wish to receive a summary of the results from the study.	Yes ☐	No ☐
I wish to receive my individual results from the study assessments.	Yes ☐	No ☐

Future related research involvement:

I am willing to be contacted for future similar research	Yes ☐	No ☐
I am willing for my coded (de-identified) data to be sent overseas and shared with international researchers	Yes ☐	No ☐
I consent to my data being used for future unspecified research in NZ, with the understanding that the new research has received ethical approval	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:

NAPROXEN

na-prox-en

What does it do?

Naproxen reduces pain and inflammation.

Before you start

- Tell your doctor if you have heart, kidney, stomach or bowel problems, high blood pressure, asthma, or if you have ever had a stroke or TIA (mini-stroke).
- Tell your doctor if you have had problems with aspirin or anti-inflammatories.
- Tell your doctor if you are pregnant, planning to become pregnant, or breastfeeding.

How should you take it?

Take naproxen with food and a glass of water. Swallow the tablets whole.

What if you forget a dose?

Should an occasional dose be missed it need not be taken later.

Can you take other medicines?

Some medicines available without a prescription may react with naproxen including:

- anti-inflammatories, such as ibuprofen (e.g. Nurofen®), or aspirin (e.g. Disprin®, in doses used for pain relief). These can also be found in some cold and flu medicines (e.g. Nurofen Cold and Flu®), and creams or gels (e.g. Voltaren Emulgel®)
- low-dose aspirin (e.g. Cartia®)

Tell your pharmacist or doctor about allmedicinesortreatments that you may be taking, including vitamins, herbal products or recreational drugs.

What side effects might you notice?

Side Effects	Recommended action
Stomach pain, coughing or vomiting of blood, black bowel motions Swollen lips, tongue, throat or face, trouble breathing Chest pain Symptoms of liver problems including: yellow skin or eyes, itching, dark urine, pale bowel motions, abdominal pain Reduced number of blood cells that help your blood to clot - symptoms include: easy or unusual bruising or bleeding	Tell your doctor immediately
Swollen feet or legs, short of breath Bloody or cloudy pee Ringing in the ears	Tell your doctor
Dizziness Indigestion, nausea, constipation or diarrhoea Skin rash	Tell your doctor if troublesome

If you notice any other effects, discuss them with your doctor or pharmacist.

Other information:

- In most cases, paracetamol and/or codeine may be safely used while taking naproxen.

This leaflet contains important, but not all, information about this medicine.
Prepared by the MyMedicines Committee at Christchurch Hospital, Te Whatu Ora - Waitaha, New Zealand. March 2023

OMEPRAZOLE

oh-mep-ra-zole

What does it do?

Omeprazole is used to treat and prevent some stomach and gut problems, such as indigestion, reflux, and ulcers. It reduces the amount of acid made in your stomach.

Before you start

- Tell your health professional if you are pregnant, planning to become pregnant, or breastfeeding.

How should you take it?

Take omeprazole regularly as directed with a glass of water. You can take it with or without food, but it may work better if you take it before food.

Capsules or tablets: If you have trouble swallowing you can open the capsule or break the tablet and mix with a small amount of soft food or liquid. Swallow without chewing. Do not crush the capsule contents or tablets.

Liquid: Shake well before use. Measure each dose carefully with an oral syringe or measuring spoon.

What if you forget a dose?

If it is nearly time for your next dose, skip the missed dose and take your next dose at the usual time. Otherwise, take the missed dose as soon as you remember. Do not take two doses at the same time.

Can you take other medicines?

Some medicines available without a prescription may react with omeprazole including:

- iron supplements (e.g. Ferro-Tab®)

Tell your pharmacist or doctor about allmedicinesortreatments that you may be taking, including vitamins, herbal products (e.g. St John's wort) or recreational drugs.

What side effects might you notice?

Side Effects	Recommended action
Muscle twitching or cramps, tiredness or weakness, tingling or numbness (may be signs of low magnesium)	Tell your doctor
Headache Stomach upset	Tell your health professional if troublesome

If you notice any other effects, discuss them with your doctor or pharmacist.

Other information:

- If your symptoms are well managed, your doctor may recommend stopping omeprazole. When you stop you may get symptoms like reflux and heartburn but these should only last for a few weeks. Talk to your health professional if these are troublesome, or if they do not get better.
- Long-term use of omeprazole may cause side effects such as weak bones and gut infections. Tell your doctor if you develop severe or persistent diarrhoea and abdominal pain.
- Store omeprazole liquid in the fridge. If you have any liquid leftover after the expiry date on the bottle, take it back to your pharmacy.

This leaflet contains important, but not all, information about this medicine.

Prepared by the MyMedicines Committee at Christchurch Hospital, Te Whatu Ora - Waitaha, New Zealand. March 2023