Participant Information Sheet

The LipoCre Study

MASSEY UNIVERSITY
COLLEGE OF HEALTH
TE KURA HAUORA TANGATA

Formal Study title: The pharmacokinetics and dose response to ingestion of liposomal encapsulated creatine monohydrate

Sponsor: Pharmako Biotechnologies, Factory 2 & 3/ 2 Aquatic Drive, Frenchs Forest, NSW, 2086, AUSTRALIA

Lead Researcher: Professor David Rowlands

Study Site: Massey University Albany

Contact phone number: 0272099383

Ethics committee ref.: 18021

This is the first clinical trial of liposomal encapsulated creatine in healthy people. You may not get any health benefit from the study nutritional intervention. While the liposomal encapsulation approach has been used previously to deliver other nutrients commonly ingested by humans and shown to be safe, there are risks of injury or illness with your involvement in the study.

You are invited to take part in a study on the gut response and rate of blood appearance of creatine monohydrate ingested in the form of liposomal vesicles, which are tiny fat-coated particles containing the creatine. 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. If you do want to take part now, but change your mind later, you can pull out of the study at any time without experiencing any disadvantage.

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 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 14 pages long, including the Consent Form. Please make sure you have read and understood all the pages.

Voluntary Participation and Withdrawal From This Study

Participation in the study is voluntary and you are free to decline to participate, or to withdraw from the research at any time, without experiencing any disadvantage.

What is the purpose of the study?

The purpose of the LipoCre study is to investigate the digestibility and bioavailability of liposomal creatine. Creatine is used as a sports supplement and in some other applications. Creatine is a naturally occurring compound found in foods like fish and meat that provides energy for rapid, powerful short burst maximal efforts in sports. The most common form of creatine used in supplements is creatine monohydrate (CrM), which can enhance high-intensity performance and training adaptations in various sports. CrM supplementation may also have potential benefits for brain health and function in tasks requiring memory and performing challenging tasks, diabetes, immunity, vascular and heart health, cancer, post-viral fatigue, and exercise capacity in children with muscular dystrophy.

However, one of the reported side-effects of 5 g doses of CrM is gut discomfort for an hour or two after ingestion. To address this issue, a recent innovation has been to wrap up CrM into liposomal vesicles, which are small lipid packages, to increase and speed absorption by the gut (Figure 1). The LipoCre study aims to investigate whether liposomal creatine provides greater benefits to delivery of creatine into the body, compared to creatine monohydrate, which may lead to further research into possible benefits for sports performance and some aspects of health.

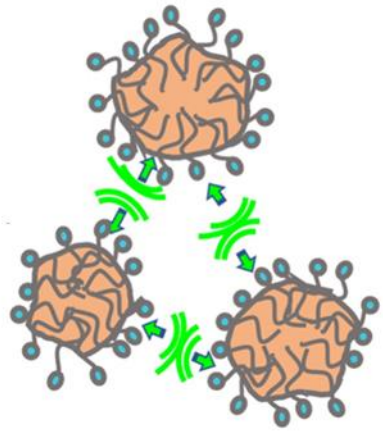

Figure 1. CrM embedded within liposomes in water. Repulsive forces between the particles prevent clumping, allowing lipid-coated CrM lumps to spread out more fully and evenly across the gut wall for more complete nutrient absorption (Briskey et al., 2019).

How is the study designed?

The design is a 6-arm randomized crossover conducted in 12 men and women aged 18 to 45 y.

In each arm of the study, the absorption kinetics of 3 doses of LCr (1, 2.5, and 5 g) will be compared to the same 3 doses of CrM. The identity of each treatment will be hidden to both the participants and researchers, with the code held by a third party.

In total, you will come to the lab 7 times: 1 for introduction and 6 times for each arm of the study, representing the test day (Figure 2). In addition, we will ask you to collect all your urine at home and work collection for the day prior to the test day, overnight, during, and again overnight up to the morning upon waking the day following.

Administration and sampling will occur in an air-conditioned clinic room after an overnight fast starting at an agreed time between 600 and 900am. You will ingest the LCr and CrM artificially flavoured and sweetened water.

Blood will be collected from a hand-vein at regular intervals for 5.5 hours after ingestion. Additionally, gut comfort will be measured at regular intervals on a linear scale. Participants will remain rested either fully or semi reclined on a research bed or chair during sampling and may do (1-handed) computer work, watch TV or relax.

There will be a minimum 1-week washout between trials.

Blood plasma be stored and later analyzed for Cr concentration using mass spectrometry at Massey University. Data will be analyzed to determine how much of and how fast the Cr has been absorbed. Results will be used to inform upon the dose strategy to be applied to studies on muscle and performance and possibly brain and cognitive function with the LCr product.

WHO CAN TAKE PART IN THE STUDY?

Healthy men and women aged 18 to 45 years, with a body mass index (BMI) of 18-30, who pass a general health questionnaire and provide written consent may volunteer for the study. Important *exclusion* include:

- Failure to meet health requirements defined in the Health Questionnaire
- Known bleeding disorder or blood borne disease
- Gastrointestinal (e.g., cancer, celiac, irritable bowel) or metabolic (e.g., diabetes, hyperthyroid) disease
- Taking medications thought to interfere with the study outcomes
- Currently participating or having participated in another clinical study during the last four weeks prior to the beginning of this study that may affect results
- Habitual creatine user or planning on starting supplementation during course of the study
- Recent change in high dietary creatine-containing food (meat, fish) intake or plan to change dietary pattern during participation in the study
- Unable to meet study requirements Oligomenorrhea (irregular periods) or amenorrhea (no periods) in women. Where eumenorrhea (regular periods) are periods occurring every 21-40 days with the average of 28 days
- Currently on hormonal contraceptives including hormonal oral contraceptive pills, hormonal injection (such as Depo Provera), or hormonal implant (such as rods). However, intrauterine devices (Mirena and Jayes) are permitted

Women will be asked to book testing sessions between days 3-11 of their cycle.

WHAT WILL MY PARTICIPATION IN THE STUDY INVOLVE?

The timeline for your participation in the experiment is shown in Figure 2.

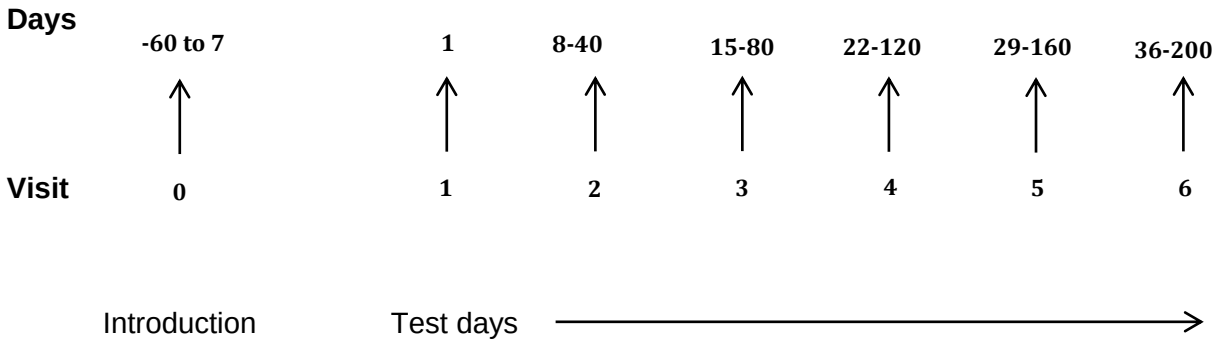

Figure 2. Study plan showing the 7 visits to the lab. The days 8 through 36 assume weekly testing.

Flow Chart Timeline of the Study Procedures (see also Figure 1).
Visit 0. Introduction • Following initial contact, a meeting at Massey University to review the study information and procedures, and to ask and answer any questions you may have. • If you agree to participant in the study (and you can go home again and think about it, if you don't feel ready), we will conduct the Health screening via questionnaire. If all in order, you will be invited to sign the Consent form. • Following this, baseline parameters (age, height, body weight and fat and lean mass) will be recorded. Mass and lean mass will be measured by bioelectrical impedance scales. • Instructions and a container for the first 24h urine collection will be provided, which will occur the day prior to Visit 1.
The Day prior to Visit 1 (Day -1) • After waking up, you will go to toilet as normal. • 24-h total urine collection: <u>all urine</u> will need to be collected into the container provided, during the day, and overnight. • Women will be contacted to confirm between days 3-11 of cycle.
Visit 1. Main trial day. Total duration about 6 h. Will comprise: • Upon waking, complete the 24-h urine collection by urinating into the container provided. Bring this container with you into the lab/clinic and we will measure the volume and take a sample. • After the waking urine collection, please <u>drink 1-2 glasses of water</u>. <u>Eat no food</u> and have <u>no tea or coffee</u> or any other drinks before coming into the lab. • You then travel to the lab to arrive between 0600-0900 h at a consistent time across the study. • You will go to the toilet to urinate prior to beginning the experiment. [After which, a second 24-h urine collection will start on the onset of the supplement protocol.

You will end this second urine collection with the collection of the first morning urine the day following the lab day.]

- You will then be asked to be seated or semi-reclined in a comfortable chair or clinic bed.
- Your non-dominant or hand of choice will be placed into a heated-hand box to warm up the hand. A line will then be placed into a hand vein for blood sampling by a trained person (Ayla Blaxell, David Rowlands, Cameron Haswell) to allow repeated blood sample collection over the next 5.5 h. These lines are the same as would be placed in a hospital and shouldn't be painful or sore after they have been placed.
- Following completion of the test, the line will be removed, and the access site covered with a band-aid.
- During the test you may work (one hand only available) or watch movies, read, relax.
- At baseline and every 30 min you will mark a simple line on a scale to assess your gut-comfort level.
- At time=0 you will ingest the test supplement.

The morning after Visit 1. Day +1.

- Upon waking, pass all urine into the container provided; this completes the second 24 h urine collection.
- A measuring flask and sample collection container will be provided, and you will need to store the sample in the freezer at home and bring it into the lab/clinic on next visit. Or alternatively if you prefer, the research team will come and collect the full urine container.

Time between next test (washout period)

- There will be a minimum of one week before the next test. For women, time between visits will be one month (one cycle) to ensure they are at a similar stage of their cycle.

Visits 2-6 (Study arms 2 through 6).

- These visits will occur on a weekly (or monthly) basis but can be longer if required to meet personal or lab schedules. Please discuss with the researchers the most suitable testing dates.
- In the next 5 study arms, you will repeat all of the procedures from day -1, Visit 1, and day +1 as listed above, but with the ingestion of a different test supplement.

WHAT WILL HAPPEN TO MY *BLOOD, URINE* SAMPLES?

Blood samples

Blood will be collected from a dorsal hand vein using the heated-hand method in a Perspex box; this is to improve sample quality. Samples will be collected at time=0 (prior to Cr supplement ingestion), and at the following time periods after: 0, 10, 20, 30, 40, 50, 60, 90, 120, 180, 240, 300 min. 12 samples. Sample volume will be 10 ml each.

Urine samples

Total 24-h urine will be collected into specific containers containing some preservative. Volume will be measured, then the sample mixed thoroughly, and a 30-ml sample saved for analysis.

Both blood and urine samples will be measured at Massey University. Samples will be stored for 10 years. You may not withdraw your samples after you have *completed* the study, and if already measured, the data will be retained for use in the analysis. You have the right to have the *used*, or *unused* portion prior to analysis, sample returned (see below). If you wish to enact this right, please inform the researchers at the start of the study.

You may hold beliefs about a sacred and shared value of all or any tissue samples removed. The cultural issues associated with sending your samples overseas and/or storing your tissue 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.

WHAT ARE THE POSSIBLE RISKS OF THIS STUDY?

The two primary risks associated with the study are those associated with blood sampling and gut comfort response. With respect to blood sampling, you may experience a pin prick sensation on placement of the catheter and there is a small chance of bruising and a remote chance of hematoma (bruising), thrombosis (clotting), or site-infection risk. The catheter is placed by a trained nurse (Ayla Blaxell) or phlebotomist (David Rowlands, Cameron Haswell) and full sterile procedures are followed according to standard operational procedures.

Nil or perhaps mild gastrointestinal discomfort might be experienced for a time after ingesting one or more of the supplement doses.

You may feel uncomfortable will the urine collection and handling procedures.

You may get hungry during the procedures. We will provide a light snack and drink upon completion of each test.

You will be told of any new information about adverse effects related to the study if such information becomes available during the study.

WHAT ARE THE POSSIBLE BENEFITS OF THIS STUDY?

You will not gain any benefits from being in this study but you may enjoy learning about a prototype new creatine product that may be more effective in boosting blood (and presumed muscle) creatine levels, than regular creatine monohydrate. You may enjoy being involved in sport nutrition and health research for altruistic or other reasons.

WILL ANY COSTS BE REIMBURSED?

Participation will not incur any direct costs except perhaps travel costs (e.g., petrol or bus). To in part compensate for costs and as koha you will be reimbursed gift vouchers of your choice (usually MTA or supermarket) $40 per day involved in the study (total 3 days or $120/study arm), which will sum to a total of $760, which will be provided upon completion of all 6 arms of the study.

WHAT IF SOMETHING GOES WRONG?

As this research study is for the principal benefit of its commercial sponsor Pharmako, if you are injured because of taking part in this study you won't be eligible for compensation from ACC.

However, Pharmako has satisfied the Northern Health and Disability Ethics Committee that approved this study that it has up-to-date insurance for providing participants with full no-fault clinical trial compensation of up to $AUD20,000,000 if they are injured as a result of taking part in this study. Massey University also has public liability insurance that covers any accident or harm caused by participation in the research trial. Confirmation of the insurance policy is available from the insurer of the study sponsors; contact researchers if you wish to view a copy of relevant sections of the policy.

New Zealand ethical standards require compensation for injury to be at least ACC equivalent. Compensation should be appropriate to the nature, severity and persistence of your injury and should be no less than would be awarded for similar injuries by New Zealand's ACC scheme.

Some sponsors voluntarily commit to providing compensation in accordance with guidelines that they have agreed between themselves, called the Medicines New Zealand Guidelines (Industry Guidelines). These are often referred to for information on compensation for commercial clinical trials. There are some important points to know about the Industry Guidelines:

- On their own they are not legally enforceable and may not provide ACC equivalent compensation.
- There are limitations on when compensation is available, for example compensation may be available for more serious, enduring injuries, and not for temporary pain or discomfort or less serious or curable complaints.
- Unlike ACC, the guidelines do not provide compensation on a no-fault basis:
- The Sponsor may not accept the compensation claim if:
  - Your injury was caused by the investigators, or;
  - There was a deviation from the proposed research plan, or;
  - Your injury was caused solely by you.

An initial decision whether to compensate you would be made the by the sponsor and/or its insurers.

If they decide not to compensate you, you may be able to take action through the Courts for compensation, but it could be expensive and lengthy, and you might require legal representation. You would need to be able to show that your injury was caused by participation in the trial.

You are strongly advised to read the Industry Guidelines and ask questions if you are unsure about what they mean for you.

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, nurses and other site staff will record information about you and your study participation. This includes the results of any study assessments. You cannot take part in this study if you do not consent to the collection of this information.

Identifiable Information

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

- Pharmako study monitors, to make sure the study is being run properly and that the data collected is accurate.

- The sponsor and its representatives, if you make a compensation claim for study-related injury. Identifiable information is required in order to assess your claim.
- The sponsor, ethics committees, or government agencies from New Zealand or overseas, 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 (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.
- Rarely, it may be necessary for the principal investigator 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.

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 researcher and any study information sent to the sponsor. Instead, you will be identified by a code. The researchers 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 (Australian based), for the purposes of this study.
- People and companies working with or for the sponsor, for the purposes of this study (this may include 2-20 people and companies).
- Regulatory or other governmental agencies worldwide.

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

Future Research Using Your Information.

If you agree, your coded information may be used for future research related to creatine or other nutrients packaged within liposomes.

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 Massey University during the study. After the study it is transferred to a secure archiving site and stored for 10 years, then destroyed. Your

coded information will be entered into electronic case report forms and sent through a secure server to the sponsor. Coded study information will be kept by the sponsor in secure, cloud-based storage indefinitely. 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.

Your coded information is being sent overseas. 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.

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.

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

Rights to Withdraw Your Information.

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

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 Pharmako. 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.

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 Dr. Bevan Erueti (Taranaki, Ngāti Tūwharetoa, Te Atihaunui-a-Pāpārangi), Associate Dean Māori, School of Health Sciences, Massey University about the collection, ownership, and use of study data.

- While the study focusses on the general population of Aotearoa NZ, it will collect health data which may be relevant to Māori and may add to the growing body of research required to inform government and policymakers.
- Consideration is given to the term *taonga,* which refers to both tangible and intangible possessions/assets hence bodily fluid as a tangible *taonga* needs to be regarded and valued in scientific research as a gift/prized possession. Accordingly, the blood and urine samples will be treated with respect and you have the right to have the *used*, or *unused* portion prior to analysis, sample returned. If you wish to enact this right, please inform the researchers at the start of the study.
- The signing of consent also comprises reciprocal *whakaute* - a responsibility of the individual to make informed choices, which may require consultation with whanau and iwi prior to consent to be involved in the study – the *whakaute* relates to the considerable financial (~$8500/participant) and time investment made to collect the samples by all involved in the research process from the sponsors, ethics committee, other participants, the Universities. A request for return of the *unused* blood and/or urine samples would result in withdrawal from the study. Accordingly, *kōtua* – if in doubt about storage and use of the blood and urine samples, you should in the first instance, not participate in the study; in the second instance you should consult as above or with the researchers for resolution. If you exercise your right to change your mind during the study, any request should be made as soon as possible, so an replace participant may be found, if resources permit.
- A karakia is available if requested up to end of the creatine analysis point of the study. Please inform the researchers if you would like this.
- A karakia will not be available at the time of final tissue destruction due to the complexity of finding individual samples in deep freezer boxes.
- If you have any questions, please discuss with the researchers, your whanau or iwi, Dr Erueti (see below), or other contacts (see below).

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

If you wish to withdraw from the study, you should contact the researcher in team who you are most in contact with your email or call Professor David Rowlands. Unless you request return of your unused samples, the sample may be processed, and the data used in the study analysis. No study intervention material will be available to any participants, irrespective of completion status, after the study completion. You will not be told what order of treatment you received, where completed the study or not.

CAN I FIND OUT THE RESULTS OF THE STUDY?

Participants will be provided with a plain English summary of study results, if requested, within 1 year of study completion. The study will be registered in the Australian New Zealand Clinical Trials Registry, which is publicly accessible.

WHO IS FUNDING THE STUDY?

The study is funded by Pharmako Biotechnologies, Sydney, Australia. They make nutritional and health supplements. See for details: https://www.pharmako.com.au/

The research team includes:

Massey University
Professor David Rowlands, lead investigator, School of Sport, Exercise and Nutrition
Ms Ayla Blaxall, registered nurse, School of Nursing,
Ms Hannah Tiedt, research assistant, School of Sport, Exercise and Nutrition
Ms Kyria Bacinski, research assistant, School of Sport, Exercise and Nutrition

AUT University
Dr Ed Maunder, co-investigator, School of Sport and Recreation
Dr Eric Helms, co-investigator, School of Sport and Recreation

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 Central Committee has approved this study.

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:

Miss Hannah Tiedt, lead research coordinator and assistant
P 021 0869 7932
E hannahtiedt@gmail.com

Professor David Rowlands, principal investigator
P 027 2099 383
E d.s.rowlands@massey.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
Fax:	0800 2 SUPPORT (0800 2787 7678)
Email:	advocacy@advocacy.org.nz
Website:	https://www.advocacy.org.nz/

For Māori cultural support please contact:

Dr. Bevan Erueti, Associate Dean Māori, College of Health, Massey University
P + 64 6 356 9099 ext. 83087
E B.Erueti@massey.ac.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

The LipoCre Study

MASSEY UNIVERSITY
COLLEGE OF HEALTH
TE KURA HAUORA TANGATA

An interpreter for Te Reo, most Pacific languages, and Chinese is available on request.

Please tick in the optional box to indicate your consent for the listed item; all other items, signing the consent entails agreement with the study procedures

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.		
I consent to my information being sent overseas.		
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.	Yes ☐	No ☐
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 agree to my de-identified data being deposited in an online database associated with publication of the results in a scientific journal.	
I understand my responsibilities as a study participant.	
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: