Participant Information Sheet

Study title: ***COMFORT-PSYKI STUDY***

The Christchurch IBS cohort to investigate mechanisms for gut relief and improved transit – Psyllium and Kiwifruit translation study

Locality: Christchurch Hospital
Gastroenterology and Endoscopy Specialists
University of Otago, Christchurch

Ethics committee ref. TBA

You are invited to take part in a study on the difference in gut function and digestive health with food related interventions. 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 14 pages long, including the consent form. Please make sure you have read and understood all the pages.

WHAT IS THE PURPOSE OF THE STUDY?

We are performing this study to understand more about two common medical conditions called Functional Constipation and Constipation-Predominant Irritable Bowel Syndrome (IBS/C). Functional constipation affects 1/10 individuals, and IBS 1/6 women and 1/9 men. People with IBS have not only a change in bowel habits (e.g. diarrhoea or constipation) which can vary from day to day, but also abdominal pain. The causes for both conditions are not well understood. Current theories suggest that diet, stress, the types of bacteria in the bowel may all play a role. People with these conditions see their doctor more and have more time away from usual activities. Since dietary factors seem to play such a large role, and because both psyllium and kiwifruit have been used to treat constipation and digestive discomfort in New Zealand for several decades, we decided to test these two natural, food related treatments in this study.

Psyllium is a medical plant from the family of plantains, and the husks of its seeds are a type of dietary fibre called mucilage. Mucilage absorbs water and makes stools bulkier, softer, and easier to pass.
SunGold® kiwifruit is a fruit with a high content of vitamin C and soluble fibre similar to mucilage. Studies in New Zealand and overseas have shown that kiwifruit (both green and gold varieties) are able to improve stool bulk, softness, and passage.

In this study, we aim to find differences between individuals with functional constipation or C-IBS and those without, as well differences between people ingesting two SunGold® kiwifruit daily or Psyllium. This may allow us to gain a deeper understanding of how different dietary fibres affect bowel function, and to develop better ways of diagnosing and treating Functional Constipation and IBS.

For a deeper and more holistic understanding of the effects of the conditions and the dietary fibre treatments on them, we would like to collect information by questionnaire and biological samples in the form of breath, blood, urine, and faeces. We will then analyse the samples and compare the results between participants with constipation or IBS/C and without, and between participants eating kiwifruit and drinking psyllium preparations.

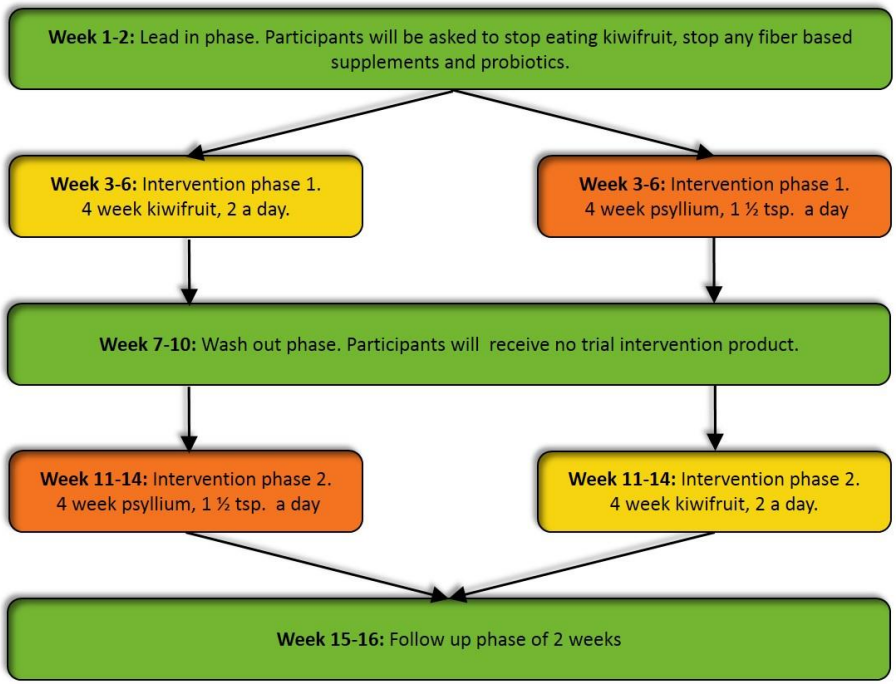
The study is being performed by researchers from the University of Otago. It is funded by the Ministry of Business Innovation and Enterprise, and Zespri international Ltd. Laboratory studies will be performed by researchers at University of Otago, AgResearch, Plant & Food and the Malaghan Institute.

The study protocol will be reviewed by the Southern Health and Disability Ethics committee.

WHAT DOES THE STUDY INVOLVE?

The study is a randomized, controlled, single-blind, crossover study. This means that if you choose to take part in the study, you will be randomly allocated to the treatment order by a researcher and you will take the kiwifruit and psyllium preparation in a random order. Each participant will take both treatments. You will know what treatment you are on as it will be obvious, but the analysts will not know what the order of treatment is. This is to ensure that there is no influence from the researchers as to the effect of the treatments.

The trial will be a maximum of up to 16 weeks in total. A diagram of the study is shown below:



Participants: All participants will be recruited to two populations: a group with constipation or constipation-predominant Irritable Bowel Syndrome (FC/IBS-C), or healthy controls. The age range for both groups is 18 to 65 years and the BMI range is 18 to 35 kg/m^2 (BMI is the abbreviated term of body mass index which is used to estimate a healthy weight range for individuals based on weight and height. BMI is determined by your weight in kilograms divided by your height (in metres squared)).

All participants will need to be:

- Able to give informed consent, and understand what is required of them during the course of this study.
- Free of chronic disease (cardiovascular disease, cancer, renal failure, previous gastrointestinal surgery ((not including appendectomy or cholecystectomy)), neurological conditions (e.g. multiple sclerosis, spinal cord injury, stroke).

- Free of any alarm features associated with bowel habit (recent changes in bowel habit < 3 months, rectal bleeding, sudden weight loss, occult blood in stools, anal fissures, bleeding, and haemorrhoids), and no family history of gastrointestinal cancers
- Free of any known significant gastrointestinal disorder other than IBS-C, such as IBD, diverticulitis, coeliac disease, or previous bowel resection
- Women who are pregnant, breastfeeding or planning a pregnancy in the trial period will be excluded.
- Individuals with known kiwifruit or latex allergy will be excluded
- Individuals who use laxatives and are unwilling to stop using these for the study will be excluded
- Participants should also have a fasting blood glucose ≤ 6.0 mmol/L which will be included in the baseline screening process.

The study groups will be defined as:

Group with constipation or constipation-predominant Irritable Bowel Syndrome. Participants will fit into this group if their bowel habits are similar to the following (assessed using a questionnaire):

A) Presence of functional constipation according to ROME IV Diagnostic Criteria[α]:

1) Must include two or more of the following:

    a. Straining during more than 25% of defecations
    b. Lumpy or hard stools during more than 25% of defecations
    c. Sensation of incomplete evacuation for more than 25% of defecations
    d. Sensation of anorectal obstructions/blockage for more than 25% of defecations
    e. Manual manoeuvres to facilitate more than 25% of defecations (e.g. digital evacuation, support of the pelvic floor)
    f. Fewer than three spontaneous bowel movements per week

2) Loose stools are rarely present without the use of laxatives

3) Insufficient criteria for irritable bowel syndrome

B) Presence of mild IBS-C according to Rome IV Diagnostic Criteria[α]:

1) Recurrent abdominal pain, on average, at least one day per week in the last three months, associated with two or more of the following:

    a. Related to defecation
    b. Associated with a change in frequency of stool
    c. Associated with a change in form (appearance) of stool

2) More than 25% of bowel movements with Bristol Stool form types 1 or 1 and less than 25% of Bowel movements of types 6 or 7.

[α] Criteria fulfilled for the last three months with symptom onset at least six months prior to diagnosis.

Healthy Control Group: Participants will be selected to this group if they do not fit into the previous group.

You have been invited to join the study as part of the…….. group.

The research in this project will be undertaken in a culturally sensitive manner with all aspects of the trial explained in full to you in a manner most suitable to you. We will be available to answer questions throughout the study and will seek advice from appropriate advisory groups should it be necessary. You will be given access to interpreters at any time in the study should you require them. The opportunity for Whanau support is available at all times.

WHAT WILL MY PARTICIPATION IN THE STUDY INVOLVE?

You have responded to the advertising of this study because you have been previously diagnosed with functional constipation or IBS-C, or because you are interested in supporting our research. Otherwise you are a healthy individual with no gastrointestinal issues.

You are invited to this study because you have been participating in the COMFORT study in the past and have indicated that you are interested in supporting our research.

If you choose to take part in the study, we will expect the following from you:

Screening Visit

We will make an initial appointment for you to come either into 40 Steward Street in central Christchurch or to The Nicolls Research Centre in the Christchurch Public Hospital (Saturdays only), depending on your preference.

At this appointment we will measure your height and weight and ask you some questions about your general health and bowel habits. This is so we can assess if you are eligible to participate in the study.

You will also be asked to give a fasting blood sample. This means that you must have nothing to eat or drink except water from 10 pm the night before until you attend the clinic and have your blood taken. The blood sample will be done first thing in the morning so we won't be asking you to go without food for long. We will also provide you with a light snack and a beverage after your blood sample has been collected.

When you attend the clinic, a researcher trained in phlebotomy will take a blood sample (total amount 6 mL, approximately one teaspoon) from a vein in your arm. Due to the nature of the analysis we will not be able to return this blood sample to you once it has been collected. The following tests will be performed on your blood sample which will give us information about your body's metabolic system. Canterbury Health Laboratories will perform the analysis. You will be given access to the results of these blood tests as soon as we have them.

Should any of your blood test results fall outside the normal range, we recommend that you make an appointment with your own medical practitioner.

If you fit all the eligibility criteria you will be offered a place in the study.

TEST	REASON	NORMAL RANGE
Albumin	Liver function	35-50 g/L
Alkaline Phosphatase	Liver function	30-150 u/L
Alanine aminotransferase (ALT)	Liver function	0-40 u/L (males) 0-30 u/L (female)
Aspartate aminotransferase (AST)	Liver function	10-50 u/L
Blood Urea Nitrogen (BUN)	Kidney function	3.2-7.7 mmol/L
Calcium	Heart, Nerve, Kidney function	2.2-2.6 mmol/L
Chloride	Acid/base balance	95-110 mmol/L
Carbon dioxide	Acid/base balance	22-28 mmol/L
Creatinine	Kidney function	50-110 µmol/L (males) 45-90 µmol/L (female)
Glucose	Glucose metabolism	3.5-6.0 mmol/L (fasting) 3.5-7.7 mmol/L (random)
Potassium	Acid/base balance	3.5-5.2 mmol/L
Sodium	Acid/base balance	135-145 mmol/L
Total bilirubin	Liver function	2-20 µmol/L
Total protein	Liver function	64-83 g/L
C-reactive protein	Immune response	< 1.0 mg/ml

During the study

The study will require you to make 6 visits to the clinic, either at 40 Steward Street, or at the Nicolls Centre. It is estimated that the visits will take a maximum of 30 minutes each time.

Due to the nature of the study and the outputs we are measuring, we would prefer that you stop taking any fibre supplements and probiotics you are currently taking for the duration of the study, and not take any laxative in the week before your appointments. Should you become constipated during this time and feel that you require medication, a “rescue” treatment (bisacodyl suppositories) will be available from the research team.

Faecal sample collection: at the baseline visit, you will be asked to provide us with a faecal sample. We ask you to collect the faecal sample the day before you come in and to bring this sample in with you. We will provide you with the appropriate gear to collect a sample hygienically. These samples will be frozen at -80^{o}C and then shipped to our laboratories in Palmerston North for analysis.

The faeces will be used for a number of analyses. We will measure the concentration of proteins that reflect inflammation in your bowel. We will also measure the

concentration of a range of bacteria and other microbes that live in the gut, and what they make with the fibre you are eating.

During the course of the study you will be asked to provide further faecal samples at the following time points: end of treatment 1 (week 6); end of washout period (week 10); end of treatment 2 (week 14). That is a total of 4 faecal samples.

Breath sample collection: at the baseline visit, you will be asked to give us a breath sample. It will be collected into two clear bags that you will have to blow up like a balloon. We will measure trace elements of volatile gases that may reflect aspects of health or disease, and how they change throughout the study. You will be asked to provide us with further breath samples at the end of each treatment (week 6 and week 14).

Urine sample collection: at the baseline visit, you will be asked to provide us with a urine sample. We ask you to collect the urine sample on the morning of the day you come in and to bring this sample in with you. We will provide you with the appropriate gear to collect a sample hygienically. These samples will be frozen at -80^{o}C and then shipped to our laboratories in Palmerston North for analysis. We will measure proteins and metabolites in your urine that may reflect aspects of health or disease, and how they change during the study. During the course of the study, you will be asked to provide further urine samples at the following time points: end of treatment 1 (week 6), end of washout period (week 10), end of treatment 2 (week 14) and end of final washout (week 16). That is a total of 5 urine samples.

Blood sample collection: At the beginning of the study (baseline/end of week 2), you will be asked to provide us with a blood sample. We will collect a total of 24 ml (approximately five teaspoons). The blood will be split into different components and stored. Experiments will include measuring proteins involved in inflammation, hormones that change with gut function, and metabolites of normal body processes. We will also measure your level of vitamin C in your blood. This will change according to the amount of food you have eaten that contains vitamin C and so will help us to know that you have eaten the kiwifruit during the study. The baseline measurement tells us the level before you start the trial so we have a comparison.

During the course of the study, you will be asked to provide further blood samples at the following time points: end of treatment 1 (week 6), end of washout period (week 10), end of treatment 2 (week 14) and end of final washout (week 16). That is a total of 5 blood samples.

If you wish, we can arrange for the remainder of your blood and faecal samples to be returned to you on completion of the analysis, or to dispose of it with appropriate karakia.

Questionnaires: Over the course of the study we will provide you with paper copies or online versions of the following questionnaires to complete. These questionnaires relate to your bowel habits, your health, your socio-economic status, and how you are

feeling, both mentally and physically. While many of the questions of these questionnaires are very similar, they do cover different aspects and details, and are rated differently.

- **Daily Bowel Habit Diary:** The primary measure for this study is the number of complete and spontaneous bowel movements/week for each participant. In order for us to assess this we need to ask you to fill out a record of the number of bowel movements you have during a day and the consistency of that stool sample (using the Bristol Stool Scale). This is done using a short questionnaire. The diary must be completed **EVERY DAY OF THE STUDY**. There are 7 questions in all which require you to tick a box for an answer so it will not take very long but it will mean a total of 112 questionnaires.

- **Weekly Gastrointestinal Symptoms Rating Score:** In addition to bowel habit this study is especially interested in your levels of gastrointestinal comfort. This weekly questionnaire asks you to mark on a scale of seven points how you are feeling. The questionnaire contains 11 questions and will take you about 5 minutes. There will be a total of 16 of these weekly questionnaires over the duration of the study.

- **Weekly Structured Assessment of Gastrointestinal Symptoms**: Assesses detailed information on gastrointestinal symptoms. It has 25 questions, and asks you to tick boxes. It will take you about 10 minutes, and there will be 16 of these weekly questionnaires during the study.

- **Weekly Modified Patient Reported Outcomes Measurement Information System:** we also want to know what other gastrointestinal symptoms you may experience, like reflux or nausea. We also want to know how your bowel habits affect your mental health and vice versa. This questionnaire contains 82 questions, but should not take longer than 10 minutes to fill out. There will be a total of 16 of these weekly questionnaires over the duration of the study

- **Diet Records:** During the course of the study, we would like to get an idea of your usual dietary intake. There will be four diet records to fill out. We ask you to record the type and amount of all the food and beverages you have consumed over a three day period. The time points for these will be at the beginning of the study, the end of week 6, the end of week 10 and the end of week 14. We will give you some photographs to help you estimate the amount of food you have eaten and ask you not to change your diet radically over the course of the study.

- **Modified Hunter New England Health Survey:** At the beginning of the study, you will be asked to fill out this questionnaire, which covers not only your bowel movements again, but also specific health, lifestyle and mental health questions, as well as some personal data. We want to get an overall view of you, and to catch any issues that may affect the data. This questionnaire contains 62 questions, but you only have to fill it out once.

- **Baseline Economic Living Standard Index short form**: This questionnaire, which you only have to fill out once, allows us to understand your standard of living and your socioeconomic class. It allows us to find out if symptoms or results are tied to specific issues in your life that have no obvious link to your bowels. It contains 25 questions and asks you to rate each by ticking a box. It should take you no more than 10 minutes to complete.

WHAT ARE THE POSSIBLE BENEFITS AND RISKS OF THIS STUDY?

You may or may not benefit from taking part in this study. There is no guarantee that you will experience any changes in stool frequency or satisfaction from taking any of the trial products. You will however gain knowledge regarding bowel health and be issued with enough kiwifruit for yourself and your immediate family/whanau/fellow living companions for the kiwifruit part of the study.

Additionally, if we are successful in our aim to understand constipation and its treatment with food, we may develop improved ways of diagnosing and treating constipation and constipation-predominant IBS in the future.

Kiwifruit is firmly established as a safe, effective product for the treatment of digestive discomfort in young and old New Zealanders. However, even though kiwifruit is generally recognized as safe, a small percentage of the population is known to have fruit and kiwifruit allergies. It is recommended those suffering from kiwifruit allergies and other fruit allergies do not do this trial.

Psyllium, which is also an established and generally safe treatment of digestive discomfort, can interfere with prescribed drug absorption, so we recommend that you take psyllium at least two hours before or two hours after any prescribed medications.

As with all blood tests, there may be some slight discomfort when the needle is inserted. You may also receive a bruise from the blood sampling. Should any adverse event related to the blood sampling procedure occur during the study period you will be immediately withdrawn and given access to medical treatment.

If you require it, we will return the rest of your faecal and blood samples to you after analysis. Otherwise it will be disposed of hygienically (in accordance with NZS 4304:2002 ‘Healthcare Waste Management”, or with the appropriate karakia, if you wish.

WHAT IF SOMETHING GOES WRONG?

In the unlikely event that you were injured as a result of treatment given as part of this study you **won’t** be eligible for compensation from ACC. However, compensation would be available from University of Otago in line with industry guidelines. We can give you a copy of these guidelines if you wish. You would be able to take action through the courts if you disagreed with the amount of compensation provided.

This trial is being conducted on behalf of the Ministry of Business Innovation by Otago University. If participants suffer physical harm from the products being tested (kiwifruit or psyllium), liability for compensation is borne by Zespri or ACC. If participants suffer any harm from any other aspects of the trial, for example from blood sampling by the researchers, liability is borne by Otago University, in both instances subject to appropriate application or legal processes. 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.

If you wish to see the Researched Medicines Industry Association guidelines, please do not hesitate to ask the research staff for a copy. You may obtain further information concerning medical treatment for injuries by contacting the Principal Investigator.

WHO PAYS FOR THIS STUDY?

The study is funded by the Ministry of Business Innovation and Enterprise, and fruit is provided by Zespri international Ltd. If discoveries are made from the information and samples that leads to the creation of intellectual property (where the discoveries may have commercial benefits), these will belong to the researchers and their associated institutions.

YOUR PARTICIPATION AND REIMBURSEMENT

Your participation in this study is completely voluntary. We are happy for you to bring along a support person to each of the clinic appointments if you would like.

We will give you a $20 supermarket voucher for the initial screening visit, and if you are accepted onto the study, you will receive a further $50 each time you come in to reimburse you for your travel and time. This will make a total of $320.

If you decide to take part, but later change your mind, you are free to withdraw at any time without having to give a reason. Your participation in the study will be stopped if it appears harmful to you in any way.

WHAT ARE MY RIGHTS?

Your participation in this study is voluntary and you are free to decline participation or withdraw from the study at any time without compromising your medical care.

You have the right to access information about yourself that is collected part of the study. If new information becomes available during the study that may have an impact on your health, you will be informed immediately

At all times your privacy will be maintained. No material that could personally identify you will be used in any reports on this study. A code that identifies you to the research team will be used on all study documentation, and is held on a database that is separate to the databased being used to store your information. Both databases are securely housed in the University of Otago server and are password protected. This

means we can link any important results from the research to your identity so we can communicate these results to you.

During the study your physical file will be held in a locked cupboard or filing cabinet when not in use. At the end of the study, your files will be kept for 10 years in secure document storage, and then destroyed by shredding.

If you have any queries or concerns about your rights as a participant in this research study you can contact an independent health and disability advocate. This is a free service provided under the Health and Disability Commissioner Act.

Telephone (NZ wide): 0800 555 050

Free Fax (NZ wide): 0800 2787 7678 (0800 2 SUPPORT)

Email (NZ wide): advocacy@hdc.org.nz

If you have any questions about the study at any time please do not hesitate to call.

This study will apply for approval by the Southern Health and Disability Ethics Committee.

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

Once the information and samples are collected there are no further requirements with regard to participation in the study and your care will continue with your Gastroenterologist and General Practitioner. All information and biological samples will be stored in the University of Otago on password-protected servers and in research freezers that are locked. No identifying data is kept in the same place that could link results to you as an individual. Secure storage is the responsibility of the University of Otago and the other institutions where the research will be undertaken. The information and samples will be stored securely and be used for ongoing research into the diagnosis and treatment of constipation and IBS. The samples will be destroyed 15 years after the commencement of the study.

If you withdraw from the study after the samples and data have been collected, we will remove any data relevant to you or the samples that you have given from the study database. However, if the samples have already been processed and the data has been used for research purposes then the data cannot be removed from scientific reports. If you were to die, your family will not be able to withdraw the data and samples from the study. Findings from the study will be communicated to participants who wish this by newsletter.

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

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

Researchers:

Simone Bayer and Phoebe Heenan

comfortcohort@gmail.com

☎ 021 279 1519 and (03) 364-1788

Principal Investigator:

Prof. Richard Gearry (Gastroenterologist)

☎ (03) 378 6236

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@hdc.org.nz

For Maori health support please contact:

Nga Ratonga Hauora

Christchurch Hospital

Tel 3640 640 (Ext 86160)

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

Phone: 0800 4 ETHICS

Email: HDECS@moh.govt.nz

Consent Form

If you need an interpreter, please tell us

I have read, or have had read to me in my first language, and I understand the Participant Information Sheet.
I have been given sufficient time to consider whether or not to participate in this study.
I have had the opportunity to use a legal representative, whanau/ family support or a friend to help me ask questions and understand the study.
I am satisfied with the answers I have been given regarding the study and I have a copy of this consent form and information sheet.
I understand that taking part in this study is voluntary (my choice) and that I may withdraw from the study at any time without this affecting my medical care
I consent to the research staff collecting and processing my information, including information about my health.
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 provider being informed about my participation in the study and of any significant abnormal results obtained during the study.
I understand that this study involves 6 visits to 40 Stewart Street, central Christchurch.
I agree to my faecal, urine and blood samples being sent to Palmerston North and I am aware that these samples will be disposed of using established guidelines for discarding biohazard waste.
I understand that during the week before sample collection I must refrain from taking any laxative medication other than that offered as a rescue treatment from the research staff

I understand that during the course of the study, I must refrain from eating extra servings of kiwifruit, other than that provided by the study investigators
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 wish to receive a summary of the results from the study.
I consent to be contacted by the researchers if there are other studies that I may be eligible to participate in.
I would like any remaining samples to be disposed of at the end of the study (please tick one):
Using standard disposal methods ☐ Disposed with appropriate karakia ☐

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: