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**Participant Information Sheet**

Study title:Kiwifruit Ingestion to Normalise Gastrointestinal Symptoms (KINGS)

Locality: University of Otago, Christchurch

Ethics committee ref. TBA

You are invited to take part in a study on the effect of kiwifruit on gut function. 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 (FC) and Constipation-Predominant Irritable Bowel Syndrome (IBS/C). FC affects 1/10 individuals, and IBS affects 1/6 women and 1/9 men. People with IBS not only have 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, and the types of bacteria in the bowel may all play a role. On average, people with these conditions see their doctor more often and have more time away from usual activities. Since dietary factors seem to play such a large role, and because kiwifruit have been used to treat constipation and digestive discomfort in New Zealand for several decades, we decided to test the effect of green kiwifruit on gut health in people with FC and IBS/C.

In this study, we aim to find differences in abdominal comfort between individuals with FC or IBS-C, ingesting either two Green Kiwifruit daily or Maltodextrin for four weeks. The findings may allow us to better understand how kiwifruit affects bowel function and to develop better ways of diagnosing and treating FC and IBS-C.

Green kiwifruit is a fruit with a high content of soluble fibre. Studies in New Zealand and overseas have shown that kiwifruit (both green and gold varieties) can improve stool bulk, softness, and passage. Maltodextrin is a type of sugar that is commonly used in processed food.

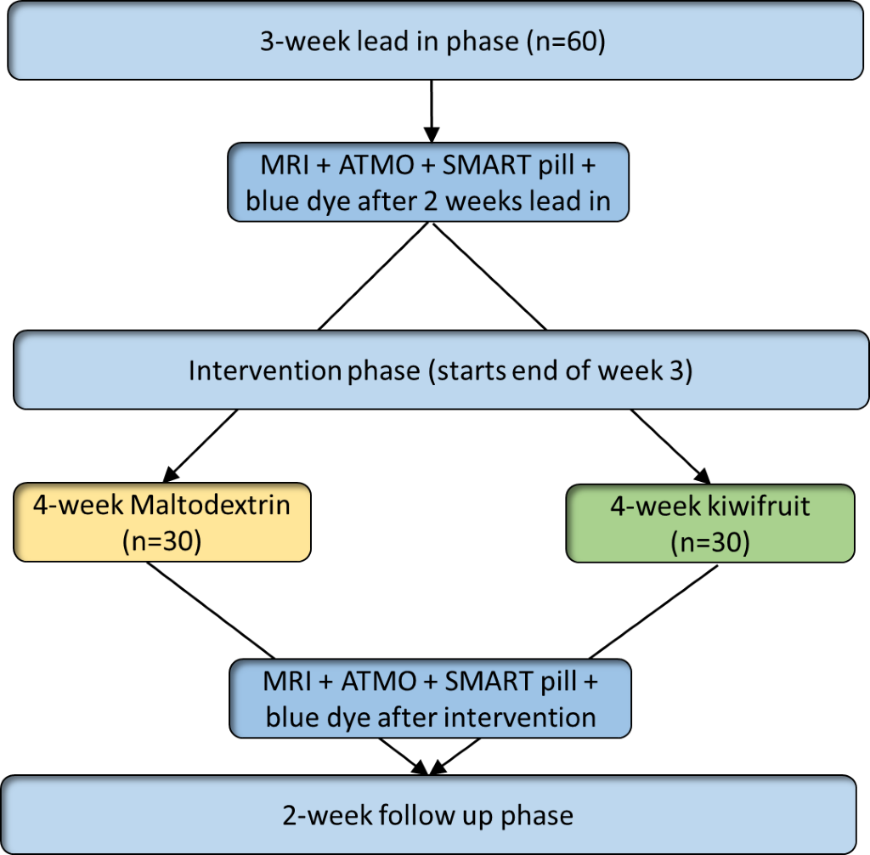
For a deeper and more holistic understanding of the effects of kiwifruit treatment on these conditions, we would like to collect information from you by questionnaire, undergo Magnetic Resonance Imaging (MRI) to assess lower bowel function, and blue food dye to measure whole gut transit as well as biological samples in the form of blood and stool. You may also be randomly asked to ingest a diagnostic device in the form of two capsules (SmartPill®, Atmo gas-sensing capsule). We will then analyse the samples and compare the results between participants who have ingested Green Kiwifruit or Maltodextrin during the study period.

The study is being performed by researchers from the University of Otago, Department of Medicine, Gastrointestinal Unit for Translational Studies in Christchurch. The study is funded by the High-Value Nutrition National Science Challenge. Zespri International Ltd. is providing the Green Kiwifruit. Laboratory studies will be performed by the Canterbury District Health Laboratories, Pacific Radiology, Christchurch (MRI), AgResearch, Riddet Institute, Plant & Food Research, Malaghan Institute of Medical Research and The University of Auckland, and the National Institute of Health Research (NIHR) Nottingham Biomedical Research Centre in the United Kingdom.

The study protocol has been reviewed by the Southern Health and Disability Ethics committee.

# What does the study involve?

The study is a single-blinded, negative controlled, randomised, parallel design study. This means that you will be randomly assigned to receive either two Green Kiwifruit (*Actinidia deliciosa* ‘Hayward’) or Maltodextrin (matching the energy content of the fruit) per day for four weeks. You will know what group you are on as it will be obvious, but the researchers will not know which group you will belong to. 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 nine weeks in total. A diagram of the study is shown below:

**Participants:** Study participants will be recruited through the general population with symptoms of FC or IBS-C.

The age range of all participants is 18 to 65 years, and the BMI range is 18 to 35 kg/m2 (BMI is the abbreviated term of body mass index, 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 alarm features associated with bowel habit, such as recent changes in bowel habits (onset less than three months), rectal bleeding, sudden weight loss, occult blood in stool, anaemia, anal fissures, bleeding haemorrhoids, and family history of gastrointestinal cancer at a young age or Inflammatory Bowel Disease (IBD)
* Free of systemic disease that could influence the gut directly or through medication use (e.g. diabetes, opiates or regular NSAID use)
* Free of severe chronic disease or neurological conditions.
* Free of any known significant gut disorder other than IBS-C or functional constipation. This includes diverticulitis, coeliac disease, mixed IBS, diarrhoea-predominant IBS or previous bowel resection.
* Female participants who are **NOT** pregnant, breastfeeding or planning a pregnancy in the three months post-selection (study time frame).
* Free of known Kiwifruit, latex, food dye or Maltodextrin allergy
* Willing to stop laxative use for the seven days before each study meeting
* Able to swallow pills
* Able to access MRI machines (e.g., absence of pacemakers, cochlear implants)
* Able to comply with the study procedures

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. The research team 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 are invited to this study because you have indicated that you are interested in supporting our research.

If you choose to take part in the study, you will be expected to do the following:

**Screening Visit**

We will make an initial appointment for you to come either into 40 Stewart Street in central Christchurch or to the Nicholls’ Centre of Christchurch Public Hospital during the week, in the morning, before work.

At this appointment, you will have the time to ask questions, and we will give further explanation of the study. If you are eligible and have provided written informed consent, we will measure your height and weight and ask you some questions about your general health and bowel habits.

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 (9 hours fast) and have your blood taken. The blood sample will be done first thing in the morning, so we will not be asking you to go without food for long. We will also provide you with a light snack after your blood sample has been collected.

A researcher will take a blood sample (total amount of 12 mL, approximately two teaspoons) 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 health. Canterbury Health Laboratories will perform the analysis. You will be given access to the results of these blood tests if you wish.

It is common that a test result falls just outside the normal range and is usually not concerning. Should any of your blood test results be clinically significant, we will inform you and recommend that you make an appointment with your medical practitioner.

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

|  |  |
| --- | --- |
| **TEST** | **REASON** |
| Albumin | Liver function |
| Alkaline Phosphatase | Liver function |
| Alanine aminotransferase (ALT) | Liver function |
| Aspartate aminotransferase (AST) | Liver function |
| Blood Urea Nitrogen (BUN) | Kidney function |
| Calcium | Heart, Nerve, Kidney function |
| Chloride | Acid/base balance |
| Carbon dioxide | Acid/base balance |
| Creatinine | Kidney function |
| Glucose | Glucose metabolism |
| Potassium | Acid/base balance |
| Sodium | Acid/base balance |
| Total bilirubin | Liver function |
| Total protein | Liver function |
| C-reactive protein | Immune response |
| Blood count | Immune response, overall health |

**During the study**

The study will require you to make three visits with the research team, either at St. Georges Hospital or Pacific Radiology on Bealey Ave for the MRI or 40 Stewart Street for the last meeting. It is estimated that the visits will take about 60 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) is permitted during the week before sample collections, which we can provide.

**Intervention:** We will provide you with either Green Kiwifruit or Maltodextrin powder during the study. The research staff will organise pick up with you, and instruct you on how the interventions are to be taken. Please let the research staff know when you run out, so we can provide more, if necessary.

**Stool sample collection:** At the baseline visit, you will be asked to provide us with a stool sample. We ask you to collect the stool 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 -80oC and shipped to our New Zealand collaborators for analysis. Faecal DNA or RNA extracted will also be shipped to a commercial service provider lab in Ireland for sequencing before these data is analysed by our research team.

The stool will be used for several analyses. We will measure the concentration of proteins and metabolites 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 stool samples at the following time points: post-intervention (day 28) and follow up (day 42). This is a total of three stool samples (including baseline visit).

**Blood sample collection:** At the baseline visit, you will be asked to provide us with a fasting blood sample. We will collect a total of 40 mL (approximately three tablespoons). The blood will be split into different components and stored. Experiments will include measuring proteins and metabolites involved in inflammation, and metabolites of normal body processes. 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 fasting blood samples at the following time points: 40 mL at post-intervention (day 28) and 22 mL at follow up (day 42). That is a total of four blood samples (including screening and baseline visit).

You may hold beliefs about a sacred and shared value of all or any samples removed. The cultural issues associated with sending your samples overseas and/or storing your samples should be discussed with your family/whanau as appropriate. There are a range of views held by Māori around these issues; some iwi disagree with the storage of samples citing whakapapa and advise their people to consult prior to participation in research where this occurs. However, it is acknowledged that individuals have the right to choose.

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 them with appropriate karakia.

**MRI:** at the baseline visit and post-intervention (day 28), a fasting MRI will be conducted. You will be required to lie on your back in the scanner for 15-20 minutes to administer MRI. The images will be sent to collaborators in the UK who have developed a method to measure gas and water in the lower gut. We will also provide you with a standardised meal that you have to eat the night before the MRI.

**Gut Motility Measures:** Over the course of the study, we will use various methods to measure gut function and motility.

* **Blue food dye:** at baseline visit and post-intervention (day 28), following MRI, you will be asked to ingest Royal Blue Liqua-gel® food colouring in 200 mL water to measure how long it takes for food to travel through your body. You will be asked to record the passing of the dye in stool via the daily bowel movement app.
* **SmartPill® and ATMO gas-sensing capsule:** Selected participants will be required to ingest SMARTPill® and Atmo gas-sensing capsules at baseline and post-intervention (day 28) to measure transit time, pressure, temperature and various gases in the gut. We will also give you standardised food bars before swallowing the capsules. This also means that you are asked to carry recorders on your body until all capsules have passed, to fill in additional details such as food, drink, and bowel movements into the recorders, and to drop the recorders off at our clinic at 40 Stewart street once all capsules have passed.

**Questionnaires:** Over the course of the study, we will provide you with the following online questionnaires to complete. These questionnaires relate to your bowel habits, health, 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.

* **ROME IV:** Assesses your gastrointestinal symptoms. This questionnaire helps us to determine if you show symptoms of IBS-C or FC, if your symptoms have shifted during the study, and to assess if there are any changes to upper gut symptoms. You will need to fill out this questionnaire four times: at enrolment, one day before baseline, one day before the after intervention visit, and at follow up. There are 60 short questions in total, but it will not take you more than 15 minutes to complete each time.
* **Gastrointestinal Symptoms Rating Score:** The primary interest of the study is your level of gut comfort. This questionnaire asks you to mark on a scale of seven points how you are feeling. The questionnaire contains 15 questions and will take you about five minutes. There will be a total of three of these questionnaires over the duration of the study.
* **Daily Bowel Habit Diary (accessible via smartphone app):** We like to know the number of complete and spontaneous bowel movements per week for each participant. In order for us to assess this, we need to ask you to fill out a record for each bowel movement you have in 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 AFTER ENROLMENT OF THE STUDY**. There are 11 questions in total which require you to tick for an answer, so it will not take very long, but it will mean a total of 62 questionnaires. If the daily bowel habit diary is not completed regularly, you may have to be withdrawn from the study. If you have problems with the online version or cannot go online for a while, we can provide you with paper versions to cover that time if you wish.
* **Structured Assessment of Gastrointestinal Symptoms**: Assesses detailed information on gut symptoms. It has 25 questions and asks you to tick boxes. It will take you about 10 minutes, and there will be 3 of these questionnaires over the duration of the study.
* **Patient-Reported Outcomes Measurement Information System:** We also would like to know what other gut symptoms you may experience, like pain or reflux. We also want to know how your bowel habits affect your mental health and vice versa. This questionnaire contains 50 questions but should not take longer than 10 minutes to fill out. There will be a total of three questionnaires over the duration of the study.
* **Irritable Bowel Syndrome** – **Quality of Life (IBS-QOL):** This questionnaire reports on the quality of life measure that is specific to IBS. It can help us to assess how IBS has impacted you and its treatment. You only have to fill up this short questionnaire three times that contains 34 questions and will not take you more than 10 minutes to complete each time.
* **World Health Organisation - Five Question Well-Being Index (WHO-5):** This questionnaire only contains five questions assessing how you have felt in the past week. You only have to fill it out three times over the duration of the study, and will not take you more than five minutes to complete.
* **Warwick-Edinburgh Mental Wellbeing Scale:** Alongside with other questionnaires that assess mental wellbeing, this questionnaire contains 14 questions that are all worded positively and cover both your feelings and functioning aspects of mental wellbeing. Similar to other questionnaires, you will only require to complete this three times over the duration of the study, which will take you no more than five minutes to complete.
* **Multidimensional Fatigue Inventory:** This questionnaire contains 20 questions designed to measure fatigue. It contains a seven point-scale to indicate to what extent the particular statement applies to you. You will be required to fill up this questionnaire three times 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 two food diaries 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 one week before the baseline of the study and post-intervention. 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.
* **Fibre-specific Food Frequency:** In addition to the diet records, we would also like you to fill out a fibre-specific questionnaire to assess your habitual fibre intake. Your total servings of consumed fibre-specific foods will be determined, and your fibre intake will be ranked into either low, medium or high. You will fill up this simple questionnaire only twice, one day prior to your baseline and post-intervention visit.
* **Modified Hunter New England Health Survey:** At the beginning of the study, you will be asked to fill out this questionnaire, which covers specific health, lifestyle and mental health questions, as well as some personal data. We want to get an overall view of you and to raise any issues that may affect the data. This questionnaire contains 11 questions, and you only have to fill it out once.
* **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.

If you cannot complete the questionnaires during the study, you will have to be withdrawn from the study.

If you would like to switch from online to paper or from paper to fill out the questionnaires online at any time of the study, just tell us. We are happy to provide you with the necessary paperwork or send you the links via email.

# 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 study products. You will, however, gain knowledge regarding bowel health and be issued with Green Kiwifruit for yourself and your immediate family/whanau/fellow living companions following the completion of the study.

Additionally, if we are successful in understanding constipation and its treatment with food, we may be able to develop improved ways of diagnosing and treating FC and IBS-C in the future.

Green Kiwifruit is firmly established as a safe, effective food for the treatment of digestive discomfort. However, even though Green Kiwifruit is generally recognised as safe, a small percentage of the population is known to have kiwifruit allergies. It is recommended those suffering from kiwifruit allergies and other fruit allergies do not participate in this study.

Although Maltodextrin is a commonly used food additive, it can cause spikes in blood sugar levels, allergies or intolerance for some people. Individuals with diabetes will be informed of this risk and possible symptoms. However, it is recommended that those with diabetes or known Maltodextrin allergies/ intolerance do not participate in this study.

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 asked to seek medical treatment.

There are minimal but possible risks associated with the use of both Smartpill and Atmo gas-sensing capsules. There is a risk of the capsule becoming stuck on the way through the gut, but this has not yet been reported in healthy adults. For the majority of people, the capsule is passed within five days of ingestion (In clinical trials for SmartPill®, 99.6% had spontaneously passed when assessed at 21 days. Bowel obstruction is another possible serious risk but has not been reported with SmartPill® or Atmo gas-sensing capsules.

Brilliant Blue food colouring (blue 1) is primarily used as a food colouring, and the ingested dye is found in the stool. It is considered non-toxic and commonly used in medical settings. However, similar to Maltodextrin, it can induce allergic reactions. Should any adverse event related to the procedure occur, you will be immediately withdrawn and asked to access medical treatment.

If you require it, we will return the rest of your stool 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?

Maltodextrin and blue food dye are commonly used in processed food, and Green Kiwifruit is a natural food. Therefore, they are safe for consumption. If you are injured in this study, which is unlikely, you will be eligible for compensation from ACC just as you would be if you were injured in an accident at work or home. 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 will not affect your cover.

# What else do I need to tell you?

It is really important that you keep us informed on any health issues that may come up suddenly during the study, especially if they are related to your digestion. This includes a stomach bug or food poisoning, but also if you get ill and need to take antibiotics.

We need to know this to make sure the health issue is not related to the intervention we gave you but also to make sure it does not change the data we collect. Depending on the severity, we may need to withdraw you from the study in those cases.

# Your participation and reimbursement

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

We will give you a $20 MTA voucher for the initial screening visit, and if you are accepted onto the study, you will receive a further $66 each time you come in to reimburse you for your travel and time, which will be given at the completion of the trial in the form of New World Vouchers. This will make a total of $220. Additionally, all participants will receive a set of green kiwifruit following the completion of the study.

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 withdrawn 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 as 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 or closely related projects in the future. If the results of the trial are published, anonymity will be maintained. A code that identifies you to the research team will be used on all study documentation. The code will also be used for the faecal DNA or RNA that has to be sent to a commercial service provider lab in Ireland. The code is held on a database that is separate from the database being used to store your information. Both databases are securely housed on a University of Otago server and are password protected. This means only the Christchurch research team can link important results from the research to your identity so we can communicate these results to you, but other researchers analysing data cannot. Other countries may have lower levels of data protection than New Zealand. There may be no New Zealand representation in overseas organisations that make decisions about the use of your information.

During the study, your physical file will be held in a locked 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 secure research freezers. 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 hard copy data will be destroyed 10 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 a 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:

**Research team:**

Dr Simone Bayer, Jasjot Maggo, and Hwei Min Ng

[HVN.GIstudies@gmail.com](mailto:HVN.GIstudies@gmail.com)  021 279 1519

If you want to talk to someone who is not 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 **Māori 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