**Master Participant Information and Consent Form (Study 2)**

**Study Title:** The effects of a combined exercise intervention on gut microbiomes and systemic inflammatory biomarkers in NAFLD patients

**Principal Investigators:** Mr Christiaan Hattingh, Prof David Jenkins, Dr Mia Schaumberg, Prof James O’Beirne

**Study Sites:** University of the Sunshine Coast (Sippy Downs), Sunshine Coast University Hospital, Sunshine Coast Health Institute, University of Queensland

**1. Introduction**

You are invited to participate in this study because you have been diagnosed with Non-alcoholic fatty liver disease (NAFLD). Currently, there is no proven treatment or cure for NAFLD patients and may require a liver transplant due to progressive liver failure that occurs over time.

This research project aims to determine the effects of exercise on gut microbiomes and inflammatory marker mechanisms related to liver health.

This Participant Information Sheet/Consent Form tells you about the research project. It explains the tests and treatments involved. Knowing what is involved will help you decide if you want to take part in the research.

Please read this information carefully. Ask questions about anything that you don’t understand or want to know more about. Before deciding whether or not to take part, you might want to talk about it with a relative, friend or your local doctor.

Participation in this research is voluntary. If you don’t wish to take part, you don’t have to. You will receive the best possible care whether or not you take part.

If you decide you want to take part in the research project, you will be asked to sign the consent section. By signing it you are telling us that you:

• Understand what you have read

• Consent to take part in the research project

• Consent to have the tests and treatments that are described

• Consent to the use of your personal and health information as described.

You will be given a copy of this Participant Information and Consent Form to keep.

**2. What is the purpose of this research?**

The purpose of this research is to investigate whether gut microbiomes and inflammatory markers are involved in the improvement of liver health after performing an exercise program.

Multiple factors could be related to the severity of NAFLD, although much is still unknown about the mechanisms which contribute to this disease. This research aims to further our understanding of certain health markers (body composition, muscular strength, cardiovascular fitness, blood biochemical markers, gut bacteria, and inflammation) and if any correlation exists with regards to the risk, severity, and disease progression of NAFLD.

Currently, the only means of improving this disease is through exercise and diet, with no pharmacological treatments available to treat NAFLD directly. Throughout this study we will be focusing on exercise to help further our understanding of the best possible program for our patients to improve liver disease and help improve their overall quality of life. We will also be monitoring all relevant health parameters to determine their impact on liver health after exercise has been completed. Special focus will be on gut microbiomes and biochemical markers in the blood (inflammation and liver enzymes).

Gut microbiome abundance and diversity (Alpha diversity) have been shown to be decreased in patients diagnosed with NAFLD. The health our gut has been shown to correlate with overall health and therefore is still a developing research area of interest. Especially the metabolites produced by these bacteria since they may contribute to inflammation and fatty build up within the liver. A link between the severity of NAFLD and the Alpha diversity of gut microbiomes will be investigated within this research project. Additionally, inflammatory markers present in the blood in patients with NAFLD are shown to have greater activity and therefore contribute to liver cell death and fibrosis of the liver.

Previous studies have demonstrated the effectiveness of exercise improving gut microbiomes alpha diversity and lower systemic inflammation. However, no studies have looked at this from a NAFLD patient cohort

**This study is an exercise intervention (12 weeks) to determine the impact exercise has on liver health and clinical markers measured in study 1.**

The research study is conducted by clinicians, microbiologists, and clinical researchers. No members of the research team will obtain any financial benefit from their involvement in this project (other than their ordinary wages).

**3. What does participation in this research involve?**

This research involves examining the influence of exercise training on potential changes to the gut microbiome and markers of systemic inflammation; along with changes in markers of liver health in patients with NAFLD.

Study 2: You will then be asked to participate in a second study (minimum of 36 other participants from Study 1) to participate in a longitudinal exercise intervention. You will undergo a comprehensive assessment of the same outcome measures used in Study 1 at baseline (0 weeks), again at six weeks and on completion of the intervention of (post week 12), as shown in Figure 1. Diet will be assessed at the same three time points (0, 6 and 12 weeks); you will be asked to maintain the same diet across the 12 weeks.

Participants will perform the exercise program at the University of the Sunshine Coast’s (Sippy Downs) gym and exercise testing facillity, located at the Sport’s Tower building.



**Figure 1:** Outline of Study 2 intervention (FibroScan: Controlled Attenuation Parameter and Liver Fibrosis, 1RMax: one repetition maximum, DXA: Dual-energy x-ray absorptiometry, RT: Resistance training, AT: Aerobic training, HRR: Heart rate reserve).

**Study 2:**

Following Study 1, a 12-week exercise intervention will compare potential changes in the gut microbiome, body composition and biological markers of inflammation and liver stiffness following exercise in a cohort of NAFLD patients. Similar periods of training (≥ 12 weeks) have been shown to elicit significant changes in primary and secondary outcome measures. You will undergo a comprehensive assessment of the same outcome measures used in Study 1 at baseline (0 weeks), again at six weeks and on completion of the intervention of (post week 12), as shown in Figure 1. Diet will be assessed at the same three time points (0, 6 and 12 weeks); you will be asked to maintain your normal diet across the 12 weeks.

**4. What do I have to do?**

If you decide to take part in this research project, we will ask you to commit to the following:

* Attend 3 exercise study appointments per week and a total of 5 re-assessment appointments over 12 weeks (as outlined in the figure above). If you have to miss an appointment, you must reschedule with the study doctor or clinical trials staff.
* No new medication should be introduced during the study without consultation with your study doctor.
* You will be asked to provide health information during the study especially any side effects and report all symptoms whether you think they are related or unrelated to your study participation.
* For your own safety, you should reveal to the best of your ability, your entire relevant medical history. Giving false, incomplete or misleading information concerning previous or present medical problems could be dangerous to your health.
* We are more than willing to accommodate preferable exercise and testing times with qualified exercise professionals available from 6am to 6pm five days a week (Monday to Friday).

**5. What will happen to my test samples?**

All samples and data collected will be identifiable and stored on site within the Pathology Queensland service and deidentified in the Sunshine Coast Health Institute.

These samples will be used for the current study. You may also consent for the use of your data and any left-over and/or un-used samples to be stored for future studies, of which ethics approval will be sought prior to use. If you do not consent for your samples to be used for future studies, any unused samples will be destroyed at the conclusion of the research and after publication.

**6. What are the possible benefits?**

1. Gut microbiome and inflammatory marker assessment

You will receive a gut microbiome assessment through faecal samples provided in Study 1. This assessment is not a common test performed in a general health check-up and may provide insight into their current lifestyle's impact on gut health. In addition, inflammation is also a key element of the disease. Additionally, this assessment may clarify the extent of the impact inflammatory markers have on your liver disease.

1. A body composition assessment.

You will receive individual feedback from the body composition assessment, including DXA scans. Access to this assessment in clinical and public health settings is often costly and associated with long waiting periods. You may experience some benefit from accessing these services within this research-based context.

1. Introduction to different types of exercise.

You will receive expert instruction in exercises that they may be interested in but have not had the opportunity to experience. In addition, familiarisation in a gymnasium setting will allow you to feel confident with basic exercises and are more likely to start/adhere to a program.

1. Potential improvement of NAFLD

Research has shown that exercise improves liver steatosis, reduces inflammation related to NAFLD, and improves gut dysbiosis. These combined effects are likely to manifest during the 12-week training intervention. Available evidence suggests that treatment with vancomycin improves disease activity in patients with PSC with or without IBD. This study aims to confirm this with a multi-centre placebo-controlled clinical trial. In addition, the study will provide guidance who will benefit from therapy. In addition, the study will allow us to identify risk factors for treatment failure.

**7. What are the possible risks?**

*Risk of Cardiovascular Event*

The VO2max and predicted 1RM tests used in this protocol are deliberately challenging. The tests may be confronting and intensive to some people, as they are designed to push you to your best level of performance. As a result, some may experience general performance anxiety or distress associated with testing. With qualified clinical sports scientist supervision, you will be encouraged to perform your best throughout the maximal test to minimise the potential for distress and optimise results. The protocol will be explained before and regularly guided throughout each test with increasing difficulty until their best performance is achieved. With years of exercise experience, the researchers will be aware of anxiety, distress or frustration symptoms and provide appropriate assistance if needed.

All forms of exercise pose a small risk of fatal and non-fatal cardiovascular events. A study by Rognmo and colleagues in 2012 have calculated a risk of 0.11 during moderate intensity exercise based on 14,400 hours of training (1). There is a general consensus that the benefits of exercise far outweigh the risks. Although, specific measures outlined below will be in place to manage and decrease any risk to you.

To minimise risk, we will:

* Have you complete a APSS risk questionnaire before acceptance into the study to confirm the level of risk that may restrict their capacity to complete the exercise program.
* Involve the continuous monitoring of heart rate (within moderate intensity range) and perceived exertion throughout exercise and recovery.
* Safety procedures outlined at UniSC gym will be followed in the rare event that complications may arise during the protocol. For example heart rate, blood pressure, or perceived exertion significantly rising or dropping outside of expected individual specific ranges.
* Ensure that all exercise performed in this study is supervised by qualified exercise professionals.
* Exercise supervisors will have CPR accreditation.
* Participants will be monitored for 15 minutes after testing to ensure they have sufficiently recovered before leaving the testing and training facilities.

*Risk of Injury, Muscle Fatigue and Soreness*

There is a small risk of sustaining injuries such as acute muscle strains. However, exercise professionals will significantly reduce these risks through careful supervision and monitoring of participants throughout each protocol. We are committed to helping you reduce any risks and help manage any muscle soreness. Delayed onset muscle soreness (DOMS) is often experienced after exercise testing/training, especially in relatively untrained or sedentary individuals. You will be informed of this possibility and educated about the symptoms and effective methods for preventing and relieving DOMS. Warm-up and cool-down procedures are essential strategies for preventing DOMS and will be incorporated into each testing and training session. This will reduce muscle soreness and assist participant recovery towards a resting state before leaving the session.

Dual X-ray absorptiometry

This research study includes DXA whole body scans (for assessing muscle, fat and bone mass). DXA is a routine measurement for bone density and body composition. The dose associated with DXA (GE Lunar iDXA) will be 3 µSv for the whole body. In comparison, an individual receives between approximately 4-5.5 µSv for daily natural background exposure, 80 µSv for a return trans-Pacific flight, 100 µSv for a chest x-ray, and 2000 µSv for a lumbar spine x-ray. Therefore, although ionising radiation is used in the scan, the amount of radiation is very low (below the dose incurred on a trans-pacific flight), and the corresponding risk from participating in this study is low.

We will follow all protocols and requirements for using Ionising radiation in research studies and further information will be provided at the scan to help you understand the risks of the scan. All operators are licenced and qualified to use the equipment.

### *Fibroscan*

No anticipated risk from these non-invasive procedures.

*Stool sampling*

No anticipated risks.

*Blood sampling*

This may cause some discomfort or bruising. Sometimes the spot from which blood is taken could become inflamed. Rarely, there could be a minor infection or bleeding. If this happens, it can be easily treated. The staff will use proper aseptic technique in order to reduce the risk for these unwanted effects.

Finally, there may be side effects that the researchers do not expect or do not know about and that may be serious. Tell the research team immediately about any new or unusual symptoms that you experience during the study.

*Answer Questions About Your Health*

These questions may include how you feel, your age, race, ethnicity, medical and surgical history, smoking and alcohol habits, menopausal history (females only), physical activity, sexual activity, contraception and previous and current medications, and questions related to your NAFLD. It is very important that you answer these questions truthfully.

If required, the study doctor, with your permission, may contact your GP or specialist to collect additional medical information or past medical history.

We would also request permission to access your electronic medical records to confirm your health information.

**8. What are the alternatives to participation?**

You do not have to take part in this research project to receive treatment at this hospital. Standard of care treatment options are available to you; your study doctor will discuss these options with you before you decide whether or not to take part in this research project. You can also discuss the options with your local doctor.

**9. What if new information arises during this research project?**

During the research project, new information about the risks and benefits of the project may become known to the researchers. If this happens, your study doctor will tell you about it and discuss with you whether you want to continue in the research project.

If you decide to withdraw, your study doctor will make arrangements for your regular health care to continue. If you decide to continue in the research project, you will be asked to sign an updated consent form.

Also, on receiving new information, your study doctor might consider it to be in your best interests to withdraw you from the research project. If this happens, he/ she will explain the reasons and arrange for your regular health care to continue.

**10. Do I have to take part in this research project?**

Participation in any research project is voluntary. If you do not wish to take part, you do not have to. If you decide to take part and later change your mind, you are free to withdraw from the project at any stage.

Your decision whether to take part or not to take part, or to take part and then withdraw, will not affect your routine treatment, your relationship with those treating you or your relationship with Sunshine Coast University Hospital.

**11. What if I withdraw from this research project?**

If you decide to withdraw from the project, please notify a member of the research team before you withdraw.

If you do withdraw your consent during the research project, the study doctor and relevant study staff will not collect additional personal information from you, although personal information already collected will be retained to ensure that the results of the research project can be measured properly. If you do not want them to do this, please let them know.

**12. Could this research project be stopped unexpectedly?**

This research project may be stopped unexpectedly for a variety of reasons. These may include reasons such as:

* Contraindications to exercise
* Illness or injury outside of the research study
* This may be for reasons of your safety or if you are not complying with the study restrictions as outlined.
* Decisions made by local regulatory/health authorities.

**13. What happens when the research project ends?**

When this research project ends you and your doctor will discuss the options available to manage your NAFLD. No specific follow up arising from this research project is necessary.

**14. How will I be informed of the results of this research project?**

At the conclusion of the study, when all patients have been recruited, you

may be given a summary of the results in the mail by request.

**15. What else do I need to know?**

* **What will happen to information about me?**

Of the people treating you, only those named on the front page or necessary others eg. nursing staff involved in your care, will know that you are participating in this study. Any identifiable information that is collected about you in connection with this study will remain confidential and only disclosed with your permission, or except as required by law. Your data and identifying information will be kept in a locked filing cabinet and/or password protected computer file.

Your health records and any information obtained during the study are subject to inspection (for the purpose of verifying the procedures and the data) by the relevant authorities at Sunshine Coast University Hospital or as required by law. By signing the consent section, you authorise release of, or access to, this confidential information to the relevant study personnel and regulatory authorities as noted above. Any information obtained for the purpose of this research project that can identify you will be treated as confidential and securely stored. It will be disclosed only with your permission, or as required by law.

It is anticipated that the results of this research project will be published and/or presented in a variety of forums. In any publication and/or presentation, information will be provided in such a way that you cannot be identified, except with your permission.

* **How can I access my information?**

In accordance with relevant Australian and/or Queensland privacy and other relevant laws, you have the right to access the information collected and stored by the researchers about you. You also have the right to request that any information with

which you disagree be corrected. Please contact one of the researchers named at the end of this document if you would like to access your information.

* **What happens if I am injured as a result of participating in this research project?**

If you suffer any injuries or complications as a result of this study, you should contact the study doctor as soon as possible, who will assist you in arranging appropriate medical treatment.

You may have a right to take legal action to obtain compensation for any injuries or

complications resulting from the study. Compensation may be available if your injury or complication is sufficiently serious and is caused by unsafe drugs or equipment, or by the negligence of one of the parties involved in the study (for example, the researcher, the hospital, or the treating doctor).

If you receive compensation that includes an amount for medical expenses, you will be required to pay for your medical treatment from those compensation monies. You do not give up any legal rights to compensation by participating in this study.

If you are not eligible for compensation for your injury or complication under the law, but are eligible for Medicare, then you can receive any medical treatment required for your injury or complication free of charge as a public patient in any Australian public hospital.

* **Is this research project approved?**

The ethical aspects of this research project have been approved by the Gold Coast Hospital and Health Service Human Research Ethics Committee (HREC) [add in HREC reference number]

This project will be carried out according to the National Statement on Ethical Conduct in Human Research (2007) produced by the National Health and Medical Research Council of Australia. This statement has been developed to protect the interests of people who agree to participate in human research studies.

**16. Who is organising and funding the research?**

Funding for this project will be sourced through the PhD funds of Mr Christiaan Hattingh and consultancy funds of Dr James O’Beirne.

**17. Further information and who to contact?**

**For further information or appointments:**

If you want any further information concerning this project or if you have any medical problems which may be related to your involvement in the project (for example, any side effects) you can contact the researchers directly:

Name: Prof James O’Beirne

Role: Co-supervisor/Clinician

Telephone: 0752021012

Email: james.obeirne@health.qld.gov.au

Name: Mr Christiaan Hattingh

Role: Student Investigator

Telephone: 0432905604

Email: cdh012@student.usc.edu.au

**For complaints:**

For matters relating to research at the site at which you are participating, the details of the local site complaints person are:

Position: Research Governance Officer

Telephone: 07 5202 2991

Email: SC-Research-Governance@health.qld.gov.au

If you have any complaints about any aspect of the project, the way it is being conducted or any questions about being a research participant in general, then you may contact:

Name: Patient Liaison Service

Position: Patient Liaison Coordinator

Telephone: 07-5470 5085

Email: SC-PLO-Inquiry SC-PLO-Inquiry@health.qld.gov.au

**References:**

1. Rognmo Ø, Moholdt T, Bakken H, Hole T, Mølstad P, Myhr NE, et al. Cardiovascular risk of high- versus moderate-intensity aerobic exercise in coronary heart disease patients. Circulation. 2012 Sep 18;126(12):1436–40.

**CONSENT TO PARTICIPATE IN RESEARCH**

**Title of the study:** The effects of a combined exercise intervention on gut microbiomes and systemic inflammatory biomarkers in NAFLD patients.

**Declaration by Participant**

1. I understand that the researcher will conduct this study in a manner conforming to ethical and scientific principles set out by the National Health and Medical Research Council of Australia and the Good Clinical Research Practice Guidelines of the Therapeutic Goods Administration.
2. I understand that I have read or have had read to me the Participant Information Sheet relating to this study. I understand the Participant Information Sheet. I understand that the general purposes, methods, demands and possible risks and inconveniences which may occur to me during the study have been explained to me by \_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_ (“the researcher”) and I, being over the age of 18 understand that I understand the general purposes, methods, demands and possible risks and inconveniences which may occur during the study.
3. I understand that I have been given time to consider the information and to seek other advice.
4. I understand that taking part in this study will not affect the usual treatment of my condition.
5. I understand that I am volunteering to take part in this study, and I may withdraw at any time.
6. I understand that this research has been approved by the Metro South Human Research Ethics Committee*.*
7. I understand that I have received a copy of this form and the Participant Information Sheet, which I have signed.
8. I understand that any regulatory authorities may have access to my medical records to monitor the research in which I am agreeing to participate. However, I understand my identity will not be disclosed to anyone else or in publications or presentations.
9. I give permission for my doctors, other health professionals, hospitals or laboratories outside this hospital to release information to Sunshine Coast Hospital and Health Service concerning my disease and treatment that is needed for this project. I understand that such information will remain confidential.
10. I consent to my data and any unused and/or left-over blood/stool samples taken from myself for this study to be stored in the SCHI research labs for use in future research.

Optional: I consent to the study without consenting to retention of blood/stool samples (please tick if appropriate)

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|  |
|  | Name of Participant (please print) |  |  |  |  |
|  |
|  | Signature |  |  Date |  |  |
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*Under certain circumstances (see* Note for Guidance on Good Clinical Practice CPMP/ICH/135/95 at 4.8.9*) a witness\* to informed consent is required.*

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| --- |
|  Name of Witness\* toParticipant’s Signature (please print): \_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_Signature: \_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_ Date: \_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_  |

\* Witness is not to be the investigator, a member of the study team or their delegate. In the event that an interpreter is used, the interpreter may not act as a witness to the consent process. Witness must be 18 years or older.

**Declaration by Study Doctor/Senior Researcher†**

I have given a verbal explanation of the research project; its procedures and risks and I believe that the participant has understood that explanation.

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|  |
|  | Name of Study Doctor/Senior Researcher† (please print) |  |  |
|  |  |
|  | Signature |  |  Date |  |  |
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† A senior member of the research team must provide the explanation of, and information concerning, the research project.

Note: All parties signing the consent section must date their own signature.

**Form for Withdrawal of Participation**

**Title of the study:** The effects of a combined exercise intervention on gut microbiomes and systemic inflammatory biomarkers in NAFLD patients.

**Declaration by Participant**

I wish to withdraw from participation in the above research project and understand that such withdrawal will not affect my routine treatment, my relationship with those treating me or my relationship with *Sunshine Coast University Hospital*.

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|   |
|   | Name of Participant (please print) |  |   |   |   |
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|   | Signature |   | Date |   |   |
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**Declaration by Study Doctor/Senior Researcher†**

I have given a verbal explanation of the implications of withdrawal from the research project and I believe that the participant has understood that explanation.

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|   |
|   | Name of Study Doctor/Senior Researcher† (please print) |   |   |
|   |   |
|   | Signature |   | Date |   |   |
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† A senior member of the research team must provide the reason for withdrawal from the study if the participant discloses this information and any other information concerning withdrawal from the research project

Note: All parties signing the consent section must date their own signature.