INFORMED CONSENT FORM

1. Study Information

Protocol Title:

Study on the Effect of Atorvastatin Co-administered with Omeprazole on statin Lactone (SEACOL)

Principal Investigator & Contact Details:

Principal Investigator:
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2. Purpose of the Research Study

You are invited to participate in a research study. It is important to us that you first take time to read through and understand the information provided in this sheet. Nevertheless, before you take part in this research study, the study will be explained to you and you will be given the chance to ask questions. After you are properly satisfied that you understand this study, and that you wish to take part in the study, you must sign this informed consent form. You will be given a copy of this consent form to take home with you.

You are invited because you are a male between 21 and 75 years old or a female betweem 50 and 75 years old who have not taken a statin (e.g. Atorvastatin) or proton pump inhibitor (e.g. Omeprazole) within the past 30 days.

This study is carried out to find out if co-administration of Atorvastatin with Omeprazole results in a higher level of the Atorvastatin lactone metabolite.

This study will recruit 78 subjects from National University of Singapore (NUS) over a period

of 12 months. About 78 subjects will be involved in this study.

3. What procedures will be followed in this study

If you take part in this study, you will be randomized to receive Atorvastatin + Omeprazole or Atorvastatin only for 30 days. Randomization means assigning you to one of two groups by chance, like tossing a coin.

If you take part in this study, you will be asked to provide your signed informed consent and you will receive your assigned treatment medications. You will be required to complete study assessments at each study visit (T1 and T2 below). This includes two blood sampling, with 18mL of blood drawn on each study visit, a demographics + medical + medication history survey on visit T1, as well as a self-reported compliance questionnaire on visit T2. The blood sampling (B) performed is a study activity and not routine medical care.

Your medical and medication history will be collected from you when the demographics + medical + medication history survey is administered, and your medical records will not be accessed. In addition, your demographics, medical and medication history, compliance information, as well as blood samples will be collected in a de-identified manner. De-identified means that your personal data will be masked with a code so that your identity will remain confidential. Only a subject ID will be used to identify you throughout the study.

There will be no difference to your follow-up care and management plans. You are encouraged to continue follow-up with your existing healthcare provider for any pre-existing medical conditions.

Your participation in the study will last 31 days. You will have to take your assigned medications once a day, in the morning before meal, for 30 days and be followed up after the 30 days of treatment.

If you agree to take part in this study, the following will happen to you:

<u>Study Visits and Procedures</u>

The total study duration is 31 days and consists of 2 study visits (Fig. 1). Blood samples will be collected at each timepoint (T1 and T2) for metabolic panel and biomarker measurements. This means that we will analyze the compounds that the drug is broken down into in your body. We will also look into possible compounds that may reflect the health status of your body. All blood sampling (B) are study activities and not routine medical care.

Study Visit T1 (Day 0)

This will be the screening and enrolment visit. Estimated duration is 90 mins. The following procedures will be performed during this visit:

i) Confirming eligibility and completion of demographic + medical + medication history survey (10 minutes)

ii) Informed consent taking (30 minutes)

iii) Blood sample collection (10 minutes)

iv) Post-collection health monitoring (20 minutes)

v) Randomization, distribution of drugs and explain how to take the assigned medications (20 minutes)

Study Visit T2 (Day 30)

T2 will be follow-up visit 30 days after intervention. Estimated duration is 60 mins. The following procedures will be performed during this visit:

i) Self-reported compliance questionnaire and return of unused drugs if any (20 minutes)

ii) Blood sample collection (10 minutes)

iii) Post-collection health monitoring (20 minutes)

iv) Reimbursement (10 minutes)

Study assessments:

Blood sample (B) will be performed by a medically qualified study member (i.e phlebotomist) whereas demographics + medical + medication history survey (D) and self-reported compliance questionnaire (Q) will be administered by a study team member.

18mL of blood will be collected on each study visit. In total, 36mL of blood will be collected as part of this study.

When your participation in the study ends, you will no longer have access to Atorvastatin or Omeprazole, unless special additional arrangements are made by the Principal Investigator.

Consent for future research use for general research purpose.

Any blood samples obtained during the course of this study will be stored and analysed only for the purposes of this study. Your leftover blood samples and individually identifiable information obtained during the course of the study will be stored for future research (up to 6 years) beyond the completion of the study. Future research will be related to metabolomics, cardiovascular diseases, Atorvastatin or Omeprazole. The blood samples will not be used for future restricted human biomedical research involving human-animal combinations. You must explicitly agree to this storage and future use in the signed Consent Form. To ensure privacy and confidentiality, your blood samples and personal data will be used in an individually de-identifiable form.

This study only recruits participants who can personally give consent to the study and the donation of the leftover samples. The samples will not be used for any purpose other than for future research. Please note that we will not contact you for further consent each time your information is used in future general research.

Your personal data may be shared in a de-identified manner with other collaborating researchers and institutions outside of the study team.

Incidental Findings

During the course of the study, there is a possibility that we might unintentionally come to know of new information about your health condition from metabolic panel and blood biomarker testing that is/are conducted as part of the study. These are called “incidental findings”.

“Incidental findings” are findings that have potential health or reproductive importance to research participants like you and are discovered in the course of conducting the study, but are unrelated to the purposes, objectives or variables of the study. These findings may affect your current or future life and/or health insurance coverage. Examples of potential incidental findings that may be discovered during the course of this study may include but are not limited to cardiovascular risk and metabolic diseases.

You will be asked to indicate whether you wish to be re-identified and notified in the case of a clinically significant incidental finding that is related to you.

If you agree to be re-identified and notified, your study doctor/a qualified healthcare professional will explain the incidental finding to you/your child and discuss and advise you on the next steps to follow. For this purpose, please inform the Principal Investigator or any of the study contact persons listed in this document whenever there are changes in your contact details. You may wish to do more tests and seek advice to confirm this incidental finding.

The costs for any care that will be needed to diagnose or treat an incidental finding would not be paid for by this research study. These costs would be your responsibility.

4. Your Responsibilities in This Study

If you agree to participate in this study, you should follow the advice given to you by the study team. You should be prepared to visit the National University Health System (NUHS) Investigational Medicine Unit (IMU) located at NUS MD6, level 7, two times and undergo all the procedures that are outlined above.

5. What Is Not Standard Care or is Experimental in This Study

The study is being conducted because there is limited evidence of the effect of co-administration of Atorvastatin and Omeprazole on the Atorvastatin lactone metabolite and this lactone metabolite has been associated with an increased risk of Major Adverse Cardiovascular Events (MACE). Hence, we hope that your participation will help us to determine whether the combination of Atorvastatin and Omeprazole results in an equivalent or higher level of the Atorvastatin lactone metabolite than Atorvastatin alone.

Randomization (study drug selection by chance) is done only for research studies. Study procedures include collection of blood samples, a demographics + medical + medication history survey, and a self-reported compliance questionnaire.

Although blood sampling may be part of standard medical care, in this study this procedure is only being performed for the purpose of the research, and is not part of your routine care.

6. Possible Risks and Side Effects

Atorvastatin is a synthetic lipid-lowering drug which is commonly prescribed for patients with high cholesterol or as a heart protection agent in patients at risk of heart diseases while Omeprazole is a gastric protection drug that suppresses acid secretion in your stomach. It is indicated for patients with reflex, heartburn, excessive acid secretion, gastric ulcers and helicobacter pylori (a type of bacteria infection) eradication.

Although both drugs are approved by regulatory authorities such as Singapore Health Sciences Authority (HSA) as well as the United States (US) Food and Drug Administration (FDA) and are also widely prescribed, there is still a possibility that you may experience an allergic reaction to Atorvastatin and / or Omeprazole or even suffer from the side effects of Atorvastatin. Allergic reactions can occur with any drug. Common symptoms may include: rash, itching etc. Rarely, a severe and possibly life-threatening allergic reaction can occur. Symptoms of a severe reaction include swelling of the face, difficulty breathing, or a sudden drop in blood pressure that may cause dizziness. If you have any of these symptoms, call your doctor at once. There is a possibility that Atorvastatin may result in liver injury or muscle-related side-effects. The risk of getting a severe form of muscle injury is about 0.5 – 1.0% over 5 years. If you experience yellowing of your skin or eye whites, dark brown colour urine or unexplained muscle aches (not due to exercise or exertion), inform your doctor or the Principal Investigator immediately.

You may also experience other side effects that have not yet been reported. However, you will be kept informed of any significant new findings that may relate to your willingness to continue to take part in this study. If you experience any new symptoms, you should contact your doctor or the Principal Investigator as soon as possible.

This study involves collecting blood samples. Obtaining blood can cause pain, bleeding, bruising, or swelling at the site of the needle stick. Fainting sometimes occurs and infection rarely occurs. You will be monitored for 20 minutes after the blood collection to ensure that you are well. Biscuits and water will also be provided to you if required during the monitoring period.

There might be a risk of breach of confidential details from the data collected from subjects. Potential risks include invasion of privacy and impermissible access to electronic protected health information by unauthorized users, or information about medical history being revealed to others. Extensive efforts are made to protect all research subjects from prejudice, discrimination, or uses of this information that will negatively affect them. When results from this study are reported in medical journals or at meetings, the identification of research subjects will be withheld. Study records that identify subjects will be kept confidential as required by law.

7. Possible Benefits from Participating in the Study

There is no direct individual benefits from participating in this study. However, the knowledge gained from this study may contribute to the medical field regarding the possible negative implications of co-prescription of drugs.

8. Important Information for Women Subjects

Atorvastatin is contraindicated in pregnancy due to the risk of fetal harm. Therefore, pregnant women may not take part in this study. If you become pregnant during this study, you must stop taking Atorvastatin and call your doctor or the Principal Investigator immediately.

9. Alternatives to Participation

If you choose not to take part in this study, you will receive standard care for your condition.

10. Costs & Payments if Participating in the Study

You will be reimbursed $50 for your participation in the study. If you withdraw from the study mid-way, your reimbursement will be pro-rated. For example, if you completed study visit T1 but withdraw before study visit T2, you will receive $25 reimbursement. You are not expected to incur any additional expenses from participating in this study.

11. Voluntary Participation

Your participation in this study is voluntary. You may stop participating in this study at any time. Your decision not to take part in this study or to stop your participation will not affect your medical care or any benefits to which you are entitled. If you decide to stop taking part in this study, you should tell the Principal Investigator.

If you withdraw from the study, you will be required to return remaining treatment medications and inform the Principal Investigator.

However, the sample and data that have been collected until the time of your withdrawal will be kept and analyzed. The reason is to enable a complete and comprehensive evaluation of the study.
The biological samples collected for the study will be deemed to be gifted to National University of Singapore Yong Loo Lin School of Medicine (NUS YLLSoM) and will not be returned to you. You will also not have any right or claim to any share in the commercial gain derived from the research (if any). However, you retain your right to ask the Principal Investigator to discard or destroy any remaining samples if the biological sample(s) is individually identifiable and has not been used for the research/future research or it has been used for research but it is practicable to discontinue further use of the biological sample(s) for the research/future research.

Your doctor, the Investigator and/or the Sponsor of this study may stop your participation in the study at any time if they decide that it is in your best interests. They may also do this if you do not follow instructions required to complete the study adequately. If you have other medical problems or side effects, the doctor and/or nurse will decide if you may continue in the research study.

In the event of any new information becoming available that may be relevant to your willingness to continue in this study, you *(or your legally acceptable representative, if relevant*) will be informed in a timely manner by the Principal Investigator or his/her representative.

12. Compensation for Injury

If you follow the directions of the doctors in charge of this study and you are physically injured due to the trial substance or procedure given under the plan for this study, NUS will pay the medical expenses for the treatment of that injury.

Payment for management of the normally expected consequences of your treatment will not be provided by NUS

NUS without legal commitment will compensate you for the injuries arising from your participation in the study without you having to prove NUS is at fault. There are however conditions and limitations to the extent of compensation provided. You may wish to discuss this with your Principal Investigator.

By signing this consent form, you will not waive any of your legal rights or release the parties involved in this study from liability for negligence.

13. Confidentiality of Study and Medical Records

Your participation in this study will involve the collection of "Personal Data". "Personal Data" means data about you which makes you identifiable (i) from such data or (ii) from that data and other information which an organisation has or likely to have access. This includes medical conditions, medications, investigations and treatment history. This study uses health information that may affect your privacy. To protect your confidentiality, only a unique code number will be used to identify data and/or biological material that we collected from you.

Information and "Personal Data" collected for this study will be kept confidential. Your records, to the extent of the applicable laws and regulations, will not be made publicly available.

However, the Sponsors National University Health System (NUHS), NUS YLLSoM, Regulatory Agencies Health Sciences Authority (HSA) and NHG Domain Specific Review Board and Ministry of Health will be granted direct access to your original medical records to check study procedures and data, without making any of your information public. By signing the Informed Consent Form attached, you (*or your legally acceptable representative, if relevant*) are authorising (i) the collection, access to, use and storage of your "Personal Data", and (ii) the disclosure to authorised service providers and relevant third parties.

Data collected and entered into the Case Report Forms are the property of NUS. In the event of any publication regarding this study, your identity will remain confidential.

Research arising in the future, based on your "Personal Data", will be subject to review by the relevant institutional review board.

Any biological samples and/or information containing your "Personal Data" that is collected for the purposes described in this Informed Consent Form will not be transferred out of Singapore.

By participating in this research study, you are confirming that you have read, understood and consent to the Personal Data Protection Notification available at https://www.nuh.com.sg/Pages/Personal-Data-Protection-Act.aspx

14. Who To Contact if You Have Questions

If you have questions about this research study, or in case of any injuries during the course of this study, you may contact the Principal Investigator,

Dr Chester Lee Drum,
Senior Consultant, Department of Cardiology,
National University Heart Centre,
Singapore (NUHCS),
5 Lower Kent Ridge Rd, Singapore 119074

Assistant Professor, Department of Medicine,
National University of Singapore,

MD6, 14 Medical Drive Level 8,
Singapore 117599

Phone: +65 6601 5010
Mobile: +65 8318 3106
Primary email: mdccld@nus.edu.sg
Secondary email: chester_lee_drum@nuhs.edu.sg

The study has been reviewed by the NHG Domain Specific Review Board (the central ethics committee) for ethics approval.

If you want an independent opinion to discuss problems and questions, obtain information and offer inputs on your rights as a research subject, you may contact the NHG Domain Specific Review Board Secretariat at 6471-3266. You can also find more information about participating in clinical research, the NHG Domain Specific Review Board and its review processes at www.research.nhg.com.sg.

If you have any complaints or feedback about this research study, you may contact the Principal Investigator or the NHG Domain Specific Review Board Secretariat.

15. Consent to be Contacted for Future Research (Optional)

You are being asked for permission to be contacted in the future for participation in research studies that you may be suitable for. If you agree to be contacted, your information and contact details will be entered and stored in a secured database in National University Hospital (NUH). Your information, contact details and samples will not be released to any parties outside NUH without your permission. When investigators from NUH identify you to be suitable for a particular research study, the investigators or authorised personnel from NUH will contact you to inform you about the research study. Your decision to be contacted for future research studies is completely voluntary and separate from your decision to participate in this study. Your decision will not affect your medical care or any benefits to which you are entitled. You may change your mind at any time by contacting the study PI:

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Singapore (NUHCS),
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Principal Investigator:
Dr Chester Lee Drum,
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Co-investigator:
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NUS Department of Medicine
Address: National University of Singapore,
MD6, 14 Medical Drive Level 8,
Singapore 117599

I voluntarily consent to take part in this research study. I have fully discussed and understood the purpose and procedures of this study. This study has been explained to me in a language that I understand. I have been given enough time to ask any questions that I have about the study, and all my questions have been answered to my satisfaction. I have also been informed and understood the alternative treatments or procedures available and their possible benefits and risks.

By participating in this research study, I confirm that I have read, understood and consent to the Sponsors National University Hospital (NUH) / National University Health System (NUHS) and National University of Singapore Yong Loo Lin School of Medicine (NUS YllSoM) Personal Data Protection Notification.

Consent for the Use of Biological Specimen and/or Data for Future Research

☐ Yes, I agree to donate my <blood samples and/or research data> for future research as long as the research is related to <metabolomics, cardiovascular diseases, Atorvastatin or Omeprazole>.

☐ No, I do not agree to donate my <blood samples and/or research data> for future research.

Consent to be Re-Identified and Notified in the Case of an Incidental Finding

☐ Yes, I agree to be re-identified and notified in the case of an incidental finding from this research.

In the event that I cannot be reached, please contact my next of kin

Name of next of kin:
Contact:

☐ No, I do not agree to be re-identified and notified in the case of an incidental finding from this research.

Consent to be Contacted for Future Research

☐ Yes, I agree to be for contacted for future research that I may be eligible for.
I agree to be contacted via:

☐ Phone _____

☐ Mail _____

_____

☐ Email _____

☐ Others _____

☐ No, I do not agree to be contacted for future research.

_____	_____	_____
Name of Participant	Signature	Date

Translator Information
The study has been explained to the participant / legally acceptable representative in

_____*<insert language>*_____ by _____*<insert name of translator >*_____

Witness Statement
I, the undersigned, certify that:

- I am 21 years of age or older.
- To the best of my knowledge, the participant/ the participant's legally acceptable representative signing this informed consent form has the study fully explained in a language understood by him/ her and clearly understands the nature, risks and benefits of his/ her participation in the study.
- I have taken reasonable steps to ascertain the identity of the participant/ the participant's legally acceptable representative giving the consent.
- I have taken steps to ascertain that the consent has been given voluntarily without any coercion or intimidation.

_____	_____	_____
Name of Witness	Signature	Date

1. In accordance with Section 6(d) of the Human Biomedical Research Act and Regulation 25 of the Human Biomedical Research Regulations 2017, appropriate consent must be obtained in the presence of a prescribed witness who is 21 years of age or older, and has mental capacity. The witness must be present during the entire informed consent discussion, and must not be the same person taking the appropriate consent. The witness may be a member of the team carrying out the research.
2. However, if the participant/ the participant's legally acceptable representative is unable to read, and/ or sign and date on the consent form, an impartial witness should be present instead. The impartial witness should not be a member of the study team.

Investigator Statement

I, the undersigned, certify that I explained the study to the participant and to the best of my knowledge the participant signing this informed consent form clearly understands the nature, risks and benefits of his / her participation in the study.

_____	_____	_____
Name of Investigator / Person administering consent	Signature	Date

The Parties (Investigator, Participant / Legally Authorised Representative & Witness) may execute this Informed Consent Form requiring a party's signature by using electronic signature process (e.g. by DocuSign, E-signature by Adobe Sign etc) and agree that signatures obtained or transmitted through electronic means, including the abovementioned signature process, shall be binding and effective for all purposes as if the signatures were executed in-person.