PARTICIPANT INFORMATION SHEET

You are invited to participate in a research study. This information sheet provides you with information about the research study. The Principal Investigator (the research doctor or the personin charge of this research) or his/her representative will also describe this research to you and answer all of your questions. Read the information below and ask questions about anything you don't understand before deciding whether or not to take part.

PART I: General Information

NUS-IRB Reference Code: NUS-IRB-2024-806

1. Protocol title

Project SIRT6 activator

2. Principal Investigator and co-investigator(s), if any, with the contact number and address of organization

Principal Investigator:

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Co-Investigators:

1. Vera **Gorbunova,** PhD, Professor of Biology, University of Rochester, Co-Director, Rochester Aging Research Center
2. Christopher **Chen** Li-Hsian, Associate Professor, Department of Pharmacology, Yong Loo Lin School of Medicine, National University of Singapore.
3. Dr Agnes **Slater**, Senior Research Fellow, NUS Academy for Healthy Longevity, Yong Loo Lin School of Medicine, National University of Singapore.
4. Lihuan **Guan**, Research Fellow, NUS Academy for Healthy Longevity, Yong Loo Lin School of Medicine, National University of Singapore.
5. Weilan **Wang**, PhD, is a Research Fellow at the NUS Academy for Healthy Longevity, Yong Loo Lin School of Medicine, National University of Singapore.
6. **Tay** Jian Hua, PhD student, NUS Academy for Healthy Longevity, Yong Loo Lin School of Medicine, National University of Singapore.
7. Atikah **Dahiyah**, Research Assistant, NUS Academy for Healthy Longevity, Yong Loo Lin School of Medicine, National University of Singapore.
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9. Sharon Nadiyah Binte **Shahul Hameed**, Research Assistant, NUS Academy for Healthy Longevity, Yong Loo Lin School of Medicine, National University of Singapore.
10. **Sim** Ming Ann, Associate Consultant, Anesthesia, Clinical Senior Lecturer, Yong Loo Lin School of Medicine, National University of Singapore
11. Ellie **Choi**, Consultant, Division of Dermatology, Department of Medicine, National University Hospital.
12. Christian **Sotelo**, Research Assistant, NUS Academy for Healthy Longevity, Yong Loo Lin School of Medicine, National University of Singapore.
13. Mazzarine Loan Ariella **Dotou** is a Research Fellow at the NUS Academy for Healthy

Longevity, Yong Loo Lin School of Medicine, National University of Singapore.

14. **Zhang** Ding Ding, Clinic Manager, NUS Academy for Healthy Longevity, Yong Loo Lin School of Medicine, National University of Singapore.
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Renee **Chng** Yee Sin, Research Assistant, NUS Academy for Healthy Longevity, Yong Loo Lin School of Medicine, National University of Singapore.

17. Shamita **Venkatesh**, Visiting Student, NUS Academy for Healthy Longevity, Yong Loo Lin School of Medicine, National University of Singapore.
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19. **Wang** Jiaqiu, Visiting Scholar, NUS Academy for Healthy Longevity, Yong Loo Lin School of Medicine, National University of Singapore.
20. Tong **Chen**, Visiting Student, NUS Academy for Healthy Longevity, Yong Loo Lin School of Medicine, National University of Singapore.
21. **Chen** Yong, Visiting Scholar, NUS Academy for Healthy Longevity, Yong Loo Lin School of Medicine, National University of Singapore.

External NUS Co-Investigators:

1. Alan **Graves**, Chief Executive Officer of DoNotAge.org
2. Lai Hock **Tan**, General practitioner, Certis Group

Collaborators:

1. **L'Oréal**

3. Whom should I call if I have any questions or problems?

Please contact the Principal Investigator, **Andrea B. Maier** for all research-related matters and in the event of research-related injuries.
Telephone: (65) 66012839/ 87142730 [Monday to Friday, 8.30 am to 5.30 pm]
Email: a.maier@nus.edu.sg; longevitytrials@nus.edu.sg

This study has undergone an ethics review by the National University of Singapore Institutional Review Board (NUS-IRB). For an independent opinion specifically regarding the rights and welfare of research participants, you may contact a staff member of the National University of Singapore Institutional Review Board at telephone (+65) 6516 1234 [Mondays to Thursdays from 8.30am to 6pm, and Fridays from 8.30am to 5.30pm, except public holidays] or email at irb@nus.edu.sg.

4. Who can participate in the research? What is the expected duration of my participation? What is the duration of this research?

You **can** participate in this study if you:

1) Are a **50-80 years** old man
2) A resident of Singapore (citizenship or permanent residency is not required).
3) Have none or ONE of the following conditions that must be medication-controlled:
    a) Hypertension
    b) Hyperlipidemia
    c) Hyperglycemia
    d) Osteopenia/osteoporosis
    e) Osteoarthritis

f) Type 2 diabetes

4) Have completed the pre-screening requirements and have managed to schedule the screening visit;
5) Agree to shave at least one day prior to each visit if you have dense facial hair on your cheeks that may interfere with skin microbiome sampling, agree to shave at least one day before each visit.
6) Agree to wash your skin the night before the visit and refrain from applying any facial products in the morning before the visit for skin assessments.
7) Met the randomization criteria after the screening visit i.e., **prefrail** according to Fried frailty phenotype score;
8) Are able to **attend all 4 research visits** for screening and research data collection at **MD11, Yong Loo Lin School of Medicine, National University of Singapore**: screening visit, baseline visit, 3-month visit and 6-month end of intervention visit. The screening visit will last about **1 hour,** while the remaining three visits will last around **2 ~ 3 hours;**
9) Willing to download study platform applications onto your mobile phone throughout the study period (if applicable).
10) English-literate who can understand, read and write in English.
11) Without severe cognitive impairment, as determined by PI judgment.

You will **NOT** be able to participate in this study if you fall into the following categories:

1) Pre-existing or history of major cardiovascular disease (e.g., coronary artery disease, heart failure, stroke, abnormal blood clotting or bleeding disorders, peripheral vascular disease), wound healing defects (hypertrophic scars, keloids etc.)
2) You have HIV, HEPATITIS B, HEPATITIS C*
   * If you consent to undergo microbiopsy, we will take your blood sample at the screening visit and again at Visit 3 to test for HIV, Hepatitis B, and Hepatitis C. The cost for the test will be borne by the study team.
3) Pre-existing or history of cancer or chronic obstructive pulmonary disease (COPD)
4) You used within the 3 past weeks for more than 3 consecutive days any antibiotics or related drugs or having planned to use these treatments during the study.
5) You have hypersensitivity or any serious reaction to local anesthesia (lidocaine/prilocaine), local antibiotics, and antiseptics, or any other contra-indication for skin microbiopsies.
6) Use anticoagulant medication.
7) Consume seaweed more than 3 times a week.

The duration of this research will be 6 months.

5. What is the approximate number of research subjects involved?

The study aims to recruit and randomize 60 participants into 2 equal groups (n = 30 per group) in a double-blinded, randomized, placebo-controlled design.

6. What will be done if I take part in this research study?

If you meet the randomization criteria (**prefrail** according to Fried frailty phenotype score); you will be randomized (the computer will randomly assign) into one of the 2 groups: either to receive a Sirtuin 6 (SIRT6) activator or placebo at a dose of total 4 capsules per day, 2 capsules in the morning and 2 capsules in the evening orally (by mouth) for a total of 6 months in a double-blinded fashion (neither you nor the study team member will know if you are given a SIRT6 activator or placebo).

Before you could be randomized into one of the two groups, you need to complete the screening visit today and meet all the eligible criteria. Today, we will be collecting your sociodemographic data, medical history, medication records, assess self-reported exhaustion and activity patterns by a questionnaire, perform anthropometric

measurements (height, weight, waist and hip circumference), physical assessments (blood pressure measurement, handgrip strength, 15 feet-timed walking test) and skin assessments. Additionally, a maximum of 13.5 ml of blood will be collected to analyse your health status. You will also require downloading the study platform called IQVIA. This platform will be used to schedule your next visits, completion of study questionnaire and reporting of any adverse events. The study platform also serves as a direct connection to the study team.

This study will be conducted at MD11, Yong Loo Lin School of Medicine, National University of Singapore. All biological specimens will be obtained at MD11 and will be processed at National University of Singapore (NUS), and all other assessments such as anthropometric analysis, skin analysis, cardiovascular analysis, cognition test and muscular test will be conducted at AHL.

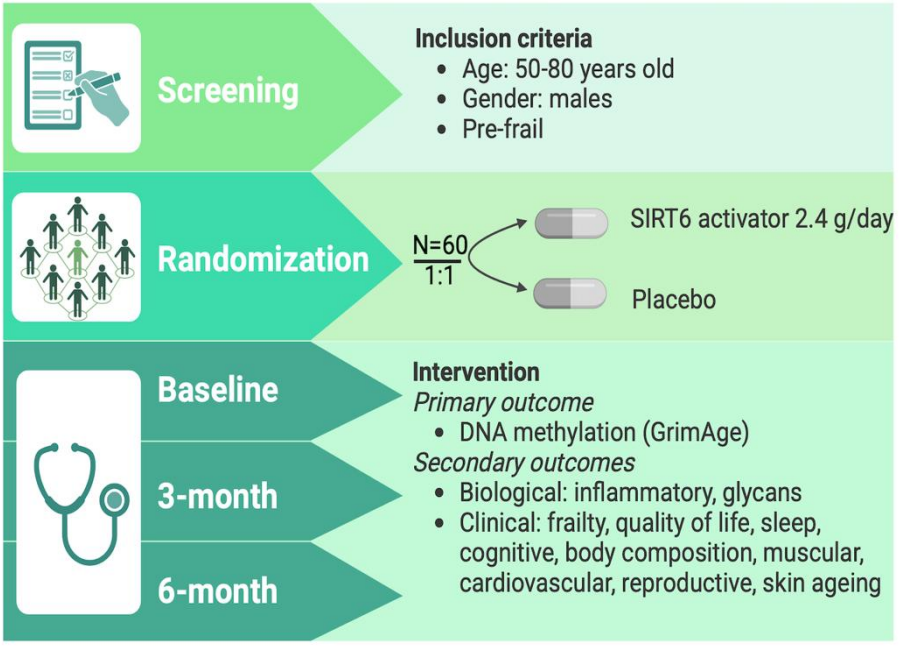

Figure 1. Study flowchart, outlining the study visits, procedures and the timepoints.

Following your visit today, you will be informed if you are eligible to join the study based on your frailty status. Once enrolled in the study, you will perform a series of study procedures which are explained in detail below:

For **the following 3 study visits**, you will come to MD11 **in the morning**. You would need to **fast overnight** for the blood draw as fasting blood collection is required for the study. You have to **refrain from alcohol / caffeine consumption for 24 hours** and abstain from dietary supplements. To assist you, the study team will send notification to you via the study platform on the preparation for your appointment 14 days before your visits. We will check whether you are feeling fine (no fever, cold, etc.) and physically fit to undergo the procedures listed below. If you are feeling unwell, your visit will be rescheduled to another day. You will be requested to self-declare your health status.

You will be required to donate blood samples in the four study visits. You will be in contact with the clinic to arrange your visit schedule for your blood samples donation. You are required to be fasting overnight before donating your blood samples. The following is the procedure involved in the donation process:

Blood samples
Peripheral fasting blood will be drawn by a nurse/ phlebotomist/ trained SAF medic. Other

than 13.5 ml donated during the screening visit, up to 46ml of blood will be taken during each study visits. Hence, 4 venepunctures (blood draws) will be performed within 6 months (total blood donated: 141.5 ml).

Additionally, you will perform the following study procedures:

a) **Height** and **weight**: You will have your height and weight taken using a standard stadiometer and a digital weight scale respectively. Your BMI will be calculated using these values.

b) **Waist/hip ratio**: A staff member will perform this assessment to measure your waist and hip circumference three times with a cloth measuring tape, at the level of the umbilicus (waist) and at the level of the symphysis pubis and the greatest protrusion of the gluteal muscles (hip).

c) **Bioimpedance analysis**: A staff member will measure your estimation of water content; muscle mass and fat percentage will be measured using inBody 77 bioimpedance analyzer.

d) **Skin assessments:** You will rest for 20 minutes under conditions (temperature of 22±2°C – relative humidity between 45% ± 5%). During this period, you are required to fill up a self-assessment questionnaire for skin and hair. It comprises of complete a baseline self-assessment questionnaire for daily exposure, smoking habits, lifestyle, cosmetic care habits, skin history, current conditions and hair quality. The research team will also collect facial photos and measurements using noninvasive devices to assess skin oiliness, hydration, elasticity, proteomics, and microbiome. You will also have the option to take part in a microbiopsy, which involves taking a small, sample of the surface of your skin under local anesthesia (using a numbing cream to make it painless). If you choose not to consent to the microbiopsy, you can still participate in the study and undergo the other assessments including the transparent adhesive discs for stratum corneum proteomics and epigenetic analysis as well as swabs for skin microbiome. Measurements will be done by a trained technician all along the study. All the skin assessments included here are initiated by the collaborator L'Oreal, and the skin analysis results will be used in the presentation to consumer panels solely for the purpose of understanding general trends.

Additional details about the assessments are provided below, and the specific locations on the face for each assessment are shown in Figure 2.

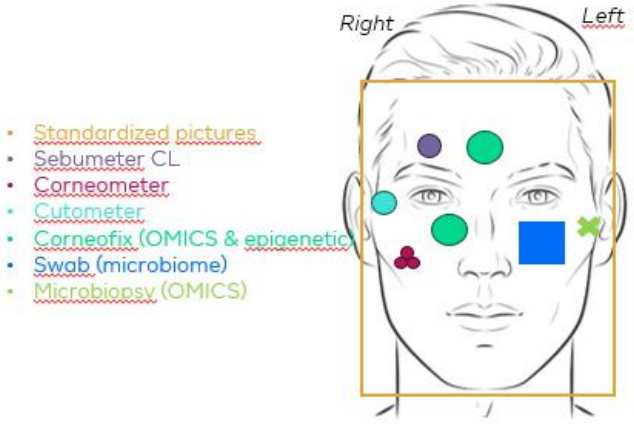

Figure 2. Investigational site identification on face for each assessment

Standardized facial skin imaging will be conducted with ColorFace. The research staff will Photograph half and full faces. The colour, pigmented spots, texture, wrinkles, and apparent age will be assessed after the study by image analysis. You are allowed to close your eyes for the facial imaging. You will be asked whether you consent to using your identifiable facial images for analysis and presentation to consumer panels.

Skin oiliness will be measured by a sebumeter: You will need to lie down on a bed or a reclining chair next to the device, and your hair will be covered by a hair cap or clipped properly. For hygiene reasons, your forehead will be wiped with a paper tissue after each measurement. One measurement will be performed on a vertical line from the middle of the eye and starting just above the eyebrow on each hemi forehead. Please refer to Figure 3 below for the specific location of the sebumeter assessment.

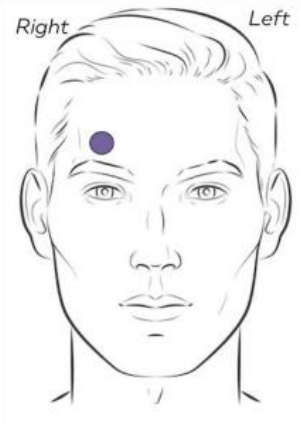

Figure 3. Skin location (purple dot) for sebumeter assessment

Skin hydration will be measured by a corneometer: You will need to lie down on a bed or a reclining chair next to the device, and your hair will be covered by a hair cap or clipped properly. The probe will be placed perpendicularly on the skin surface, and measurements will be taken in less than one second. Three measurements will be taken on each side. Please refer to Figure 4 below for the exact location of the skin corneometer assessment.

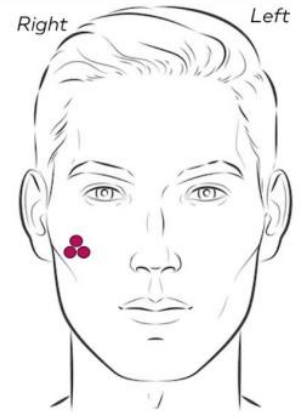

Figure 4. Skin location (3 red dots) for corneometer assessment

Skin elasticity will be measured by a cutometer: You will need to lie down on a bed or a reclining chair next to the device, and your hair will be covered by a hair cap or clipped properly. The instrument applies a vacuum to a small area of skin and measures the elastic response of the skin. The probe will be kept at a 90° angle during the measurements. The measurement will last for 4 seconds, during which there will be 1 cycle of a 2-second on (vacuum) time and a 2-second off (skin release) time. The movement of the skin into and out of the probe will be recorded during the application and release of suction. Please refer to Figure 5 below for the exact location used for cutometer assessment.

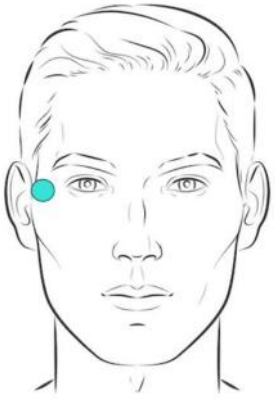

Figure 5. Skin location (blue dot) for cutometer assessment

Collection of skin surface for proteomics and epigenetic analysis: The collection will be performed using a noninvasive method, using corneodiscs (Corneofix®), a transparent adhesive disc with a 2 cm diameter.

#1: One corneodisc will be collected until saturation by a trained technician on one zone defined on the right side of the face under the eye and next to the nose at zone 1. This Corneodisc will be used for proteomics analysis.
#2: Eight corneodiscs will be collected by a trained technician on the glabella area (zone 2) . They will be used for epigenetic analysis for algorithm improvement.
Please refer to Figure 6 for the exact location of the corneodisc collection.

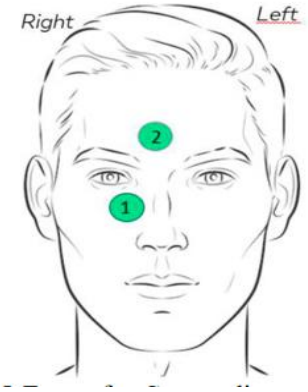

Figure 6. Zone 1 and 2 for corneodiscs collection

Collection of biological samples for microbiome analysis:
You will be asked if you have taken any antibiotics in the past 3 weeks. Skin swab for microbiome analysis will be performed on the left side of the face on a defined area of each subject at zone 1 and zone 3. Please refer to Figure 7 for exact location of microbiome skin assessment.

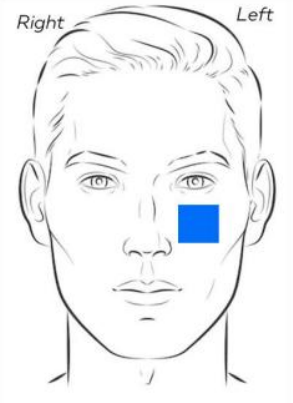

Figure 7. Zone 1 and 2 for microbiome analysis

Microbiopsy: The microbiopsy will be performed by a trained dermatologist/certified general practitioner after you give your consent to undergo this procedure. At least 1 hour prior to biopsy collection, a topical patch anesthetic will be applied to the investigational zone. Local anesthesia will be given with the application of a patch composed of two local anesthetics (lidocaine and prilocaine) acting by diffusion and inducing skin anesthesia of a few millimeters. The patch will be applied just after the standardized photos collection. The microbiopsy will be done on the left cheekbone. During the sampling, you will need to lie down. After microbiopsy, the sampling zone will be covered with bandage. Possible reactions at the biopsy site may include (but are not limited to) subjective sensations (pain, discomfort, burning, stinging, itching), bleeding, hematoma, skin redness, and dryness. Infection, scarring, or changes in skin

color at the biopsy site may occur. Healing takes place without stitches, reducing the risk of residual traces left by the biopsy. Sun exposure or UV-light sessions are strictly forbidden for 15 days after the microbiopsies collection. In case of unavoidable sun exposure, a sunscreen with a high protection index must be applied on the face (the product will be provided by the center). You will need to report to our study team if there is any abnormous discomfort on the following days of the microbiopsy collection.
Post procedure, a cream would be applied to the post biopsy site to facilitate wound healing. This would be non prescriptive and determined by the proceduralist and may include commonly applied post procedural creams such as antiseptic gels, barrier cream, silicon gel and sunscreen. Refer to Figure 8 below for the exact location of skin collection for microbiopsy procedure.

Figure 8. Sampling zone (green cross) for the microbiopsy procedure

Hair fiber collection :

A trained technician will sample 1 cm^2 of hair fibers from you in zone C. The root of the hair is required as close to the scalp as possible using curved stainless-steel scissors but without touching it (about 0.2cm from scalp).

Please refer to Figure 9 below for the location of hair collection.

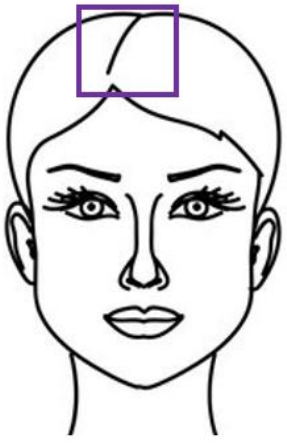

Figure 9 Zone for hair collection

Only the fiber will be collected and not the bulb.

The trained technician will secure the root with a clamp collar, transfer into aluminum-foil paper, label it and place it in a labelled envelope at room temperature.

All samples will be sent to a third party for analysis at the end of the study.

e) **Skin autofluorescence test**: You will place your arm on the device. The device will shine a light into your skin to measure the age of your skin. This procedure takes 10 minutes.

f) **Cognition test**: You will undergo a test called RBANS (a test entails immediate memory, visuospatial skills, attention, language and delayed memory) and this test will take roughly 30 minutes. This test will be done in a room with a trained study team member to ensure your comfort and privacy.

g) **Muscle strength and endurance**:
- **Handgrip strength**: You will stand upright and squeeze as hard as you can on a handgrip device, with your arm bent 90 degrees at the elbow. You will be given 3 attempts to perform your best in both hands.

- **8-RM Leg extension strength test**: You will sit on a leg extension chair with your back leaning against the backrest. You will perform leg extension with the initial weights of 10 kg. If you are able to perform 8 repetitions, without being able to do the 9th repetition, the weight will be recorded as 8-RM strength. If you are able to do more than 8 repetitions for the given weight, weight will be added on to every set, with a rest period of 2 mins, until 8-RM is achieved. For a validated repetition, a complete range of motion has to be performed.

h) **Cardiovascular assessment**
- **Resting blood pressure**: You will sit quietly for 5 minutes and have your blood pressure taken by an automatic blood pressure monitor. If your blood pressure is above 160/90 mmHg, it will be measured again after 5 minutes. If it is still consistently above 160/90 mmHg after repeated measurements over a 30-minute period, the site principal investigator or a physician at the Geriatric Clinic will examine you and decide whether you should be rescheduled for another visit, or if you will need to be withdrawn from the study.

- **Arterial stiffness**: This measures the age of your blood vessels. You will lie comfortably on an examination bed for 15 minutes, after which a blood pressure cuff will be placed around your arm to measure your blood pressure. Following that, it will be removed, and a blood pressure cuff will be placed around your thigh. The research staff will then measure the distance from your neck to your thigh with a measuring tape. This distance will inform us how fast your pulse travels in your major blood vessels, which is related to how stiff the vessels are. The research staff will then gently place a probe on your neck to detect the pulse. This procedure will take 30 minutes.

i) **Questionnaires**: You will be required to complete a few questionnaires to assess your socio-demographic information, present and past medical information, physical activity habits, quality of life, sleep quality, psychological status, and reproductive, skin and hair health. For most of these questions, you may answer "**Yes/No**". The questionnaires will take about 30 minutes to complete. All the questionnaires will be provided both digitally on the study platform as well as physical copies during the study visit.

j) Lifestyle monitoring:

- A ***3-day food diary*** will be provided to you via the study platform, and you will then record your routinemeals at **least 3 times a week (2 weekdays and 1 weekend)**. You will be reminded to complete the food diary 14 days before your scheduled appointment via the study platform.

7. Will there be reimbursement for participation?

The study procedures will be performed at no charge to you. There is no cost for participating in this study. However, the only direct cost incurred to you would be the transportation cost when travelling to the study site. Thus, you will receive a reimbursement amount equivalent to SGD $30 per visit as a reimbursement for transportation expenses (total of $120 upon completion of the study). You may choose to claim the reimbursement during each visit or cumulatively at the end of the study. If you consent to undergo a microbiopsy, you will be provided an additional $30 voucher at the end of visit 1 and visit 3 where you undergo a microbiopsy. However, you are free to decide at both visits if you want to consent to do the microbiopsy.

8. How will my privacy and the confidentiality of my research records be protected?

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 to which an organization has or is likely to have access. This includes medical conditions, medications, investigations, and treatment history.

All research documents/databases will be devoid of participant identifiers, only the facial image data collected will be identifiable. The participant identifiers will be kept in a source file that is kept separate from the working data. Working data will be entered on paper forms and electronic databases (Excel, SPSS, and IQVIA). They will then be stored in an assigned university laptop, NUS secure cloud (NUS Dropbox Enterprise, OneDrive) and data will be backed up to at least one encrypted external hard drive. Only the PI, co-investigator, research coordinators and limited IQVIA staff supporting the production platform will have access to the links to personally identifiable source data. For the identifiable facial image data, the PI, co-investigators, research coordinators and L'Oréal will have access to this data if the participant has consented to the use of their identifiable data for analysis purposes. Working data may be made available to L'Oréal who will process the data in accordance with our written instructions. The study remains PI-initiated and investigator-led under NUS governance, and L'Oréal is only involved in the design of the protocol for the skin assessments and analyses for this study and their role is limited to (e.g., providing laboratories testing support with no influence over study outcomes).

IQVIA is a service provider with service agreement in place between AHL (NUS) and IQVIA with clauses to protect all confidential study and other data. Access to participant data is enabled for limited 2 IQVIA employees, who are high skilled database administrators who are training to support platform for any enhancements, support and operational issues. There are multiple required measures in place to secure platform and data that includes:

- Audit logs for all data changes
- Access and authentication logs
- AUL (Authorized Users List)

- MFA (Multi-factored Authentication)
- Back-up and recovery
- Firewalls and registration based on IP for backend Admins and support team.
- Limited authorized IQVIA support team to production environment with regular audit on access and authentication.

To prevent unauthorized access, disclosure, or loss of data, all information collected during the research will be secured by data encryption and passwords (for electronic data) and under lock and key (for paper hardcopies). De-identified "research data" will be accessible by the PI, co-investigators, research coordinators, authorized service providers and relevant third parties. Identifiable facial image data will be accessible by the PI, co-investigators, research coordinators, authorized service providers and relevant third parties only if the participant has consented to the use of their identifiable data for analysis purpose. However, "personal data" such as participants' contact details will only be accessible by PI, PI-appointed research coordinators who are involved in setting up participants' appointments, sending reminders, and recontacting consented participants for incidental findings and limited IQVIA staff supporting the production platform. Additionally, if needed both "personal data" and "research data" will be made available for inspection by authorized regulatory monitors or legal authorities, as when called for.

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. All research data collected will be kept in accordance with the National University of Singapore's Research Data Management Policy. Research data (without personal identifiers) used in any publication will be kept for a minimum of 10 years before being discarded. Where any Personal Data is collected from you, we will keep the information confidential in accordance with the Human Biomedical Research Act and other applicable legal rules.

However, NUS, NUS Institutional Review Board, and the Ministry of Health will be granted direct access to your original data 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 authorizing (i) the collection, access to, use and storage of your "Personal Data", and (ii) the disclosure to authorized 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 the attached Informed Consent Form will be stored in Singapore. Only de-identified biological samples and/or data will be transferred out of Singapore.
All questions relating to the processing of your personal data may be directed to: longevitytrials@nus.edu.sg.

PART II: Information on this Human Biomedical Research

9. What is the nature of this biomedical research?

This is a prospective **6-month double-blinded, placebo-controlled longitudinal**

interventional study on prefrail, middle-aged to older (50-80 years) males to study the effect of a SIRT6 activator supplementation on biological age. This study aims to discover new information which may contribute to scientific and/or medical knowledge in the nutrition and geroscience field. Treatments or interventions used in this research are under evaluation and intended for research purposes. In this study, we intend to measure your biological age alongside with other health indicators such as your blood tests, skin health and physical functioning that may be related to your biological age and explore the potential of modulating these using a SIRT6 activator supplementation.

Definition of terms used
SIRT6 activator supplementation, a polymer of L-fucose and L-fucose-4-sulfate derived from brown macroalgae is available as a dietary supplement, safe for human consumption, and rarely causes irritation. SIRT6 activator exhibits dose-dependent SIRT6 stimulating activity and extends lifespan in model organisms.

Chronological age is the amount of time that has passed from your birth to the given date. It's your age in terms of years, months, days, etc. This is the primary way people define their age. It's also a primary risk factor for chronic diseases, mortality, and any impairments to bodily functions, such as hearing and memory. In contrast, biological age refers to how old a person seems. Also known as physiologicalor functional age, **biological age** differs from chronological age because it takes into consideration a number of factors other than just the day you were born. The basic idea behind biological ageing is that ageing occurs as you gradually accumulate damage to various cells and tissues in the body.

10. What is the purpose of this biomedical research?

The purpose of this study is to evaluate and investigate whether **SIRT6 activator supplementation can reduce biological age** in middle-aged to older (50-80 years) males. This is a **6-month double-blinded**, placebo-controlled longitudinal interventional study with the rationale to study the long-term effect of a SIRT6 activator supplementation in healthy middle-aged adults.

The **primary purpose** is to study the effect of daily SIRT6 activator supplementation (2.4 g/day/6 months), compared with placebo, on DNA methylation measured using GrimAge in prefrail, middle-aged to older (50-80 years) relatively healthy males in Singapore.

The **secondary purpose** is to study the effect of daily SIRT6 activator supplementation (2.4 g/day/6 months), compared with placebo, on biological (inflammatory, glycans) and clinical (frailty, quality of life, sleep, cognitive, body composition, muscular, cardiovascular, reproductive and skin ageing) markers of ageing.

11. What are the possible risks, discomforts, or inconveniences to me if I participate in this research?

There is no known side effect associated with this study procedure. While this study is considered and rigorously planned to minimize all potential adverse events, no study is completely risk-free. The anticipated risks to the participants are as follows:

SIRT6 activator supplementation has been declared to be safe, when taken according to the label. Fucoidan (SIRT6 activator**)** use within the range of the Dietary Reference Intake will not result in significant adverse effects, but participants may still experience side effects, which will be documented and reported to the PI. The PI will decide whether to withdraw the participant based on his/her clinical judgment.

Other possible risks, discomforts, or inconveniences anticipated in the procedures involved in this study.

a) **Blood draw:** There is some discomfort during venipuncture. There is also a risk of bruising, but this should resolve independently over a few days.
b) **Potential blood-thinning** effect of fucoidan: There is a possibility for fucoidan to have a blood-thinning effect, which could cause bleeding or prolonged wound healing. In case it occurs, please report to the study team immediately.
c) **AGE reader and colorimeter:** There is minimal exposure to UV-ray on your arm. However, the exposure is for about 12 seconds, which is less than the amount that you would expect from standing in outdoor sunlight for a few minutes.
d) For subjects accepting to undergo the microbiopsy procedure:

There are possible risks associated with lidocaine patch application procedures and the microbiopsy. Possible side effects associated with the lidocaine patch application include redness, swelling, rash or other allergic reaction, and subjective sensations (burning, stinging, tenderness). Unlikely, but serious side effects of lidocaine include drowsiness, mental/mood changes, ringing in the ears, dizziness, vision changes, tremors, numbness, headache, or backache. Since in this study the lidocaine is applied using a patch (topical application) these reactions are normally not expected. Possible reactions at the microbiopsy site may include (but are not limited to) subjective sensations (pain, discomfort, burning, stinging, itching), bleeding, hematoma, skin redness, and dryness. Infection, scarring, or changes in skin color at the microbiopsy site may occur. Healing takes place without stitches, reducing the risk of residual traces left by the microbiopsy. In case of any unforeseen circumstances, the research team will also ensure that the PI (Andrea B Maier) or clinically trained Co-investigators are within the vicinity of the testingsite on the study visit days.

12. What benefits can I expect from participating in the research?

There is no direct benefit from your participation. The bulk of the investigations performed in this study are for research purposes. One benefit to the participant arising from this study and the examinations is a report that details the results of this study procedure such as biological age which otherwise is not a standard clinical practice. This report may be beneficial to understand the process of ageing and discover the potential treatment. Other potential benefits include improved ageing-related physiological and physical functions, after a SIRT6 activator supplementation.

Research findings from this study and tests results such as BMI, blood sugar, blood lipids and total blood count will be provided to you. These findings can be further consulted with your treating physicians. The full report of your results will be provided only after the study has been completed.

13. Are there any alternative procedures or treatments available to me? What are the potential benefits and risks of such alternatives?

There are no alternative procedures or treatment available to you in this study. If you choose not to take part in this study, you will still receive standard care for your condition, if applicable.

14. If I am injured as a result of participating in this research, what are the compensation and treatments available to me?

It is unlikely that you will be injured during the course of this study. If you follow the directions of the PI/research staff in charge of this study. However, if you are injured due to the tests conducted, NUS will pay the medical expenses for the treatment of that injury without any legal commitment on your part to prove NUS is at fault. There are conditions and limitations to the extent of compensation provided. You may wish to discuss this with your PI. 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.

15. Do I have to incur any expenses by participating in this research?

The study procedures will be performed **at no charge to you**. There are no costs for participating in this study. The trial material (SIRT6 activator or placebo tablets) will be provided to you **free of cost.**

16. What will happen to the biological material taken from me?

In this study, participants consent to the collection of biological samples (blood) for analysis aimed at identifying biomarkers associated with biological age. Biomarkers can include cells, molecules, enzymes, hormones, genes, and physical characteristics that reflect normal or diseased processes in the body. Analysis may involve genetic material and molecular testing. Leftover samples will be stored long-term by the PI for potential future research on ageing and age-related diseases, with a minimum storage duration of 10 years.

All biological samples will be treated as donations to the study team and will not be returned. You will not have rights to commercial gains from the research. To protect your privacy and confidentiality, samples and research data will be de-identified, assigned unique identifiers, and stored securely. Participants can request the PI to discard remaining samples under specific conditions.

All biological samples and/or information containing your "Personal Data" that is collected for the purposes described in this PIS and ICF will be stored in Singapore. Only de-identified biological samples and/or data will be transferred out of Singapore, if required. Biological samples transferred out of Singapore may contain genetic information for genetic sequencing. To minimize any risk of re-identification through genetic information, research team will secure the dataflow and restrict analysis to their accredited laboratories only. De-identified samples will be used for future research conducted only by NUS Healthy Longevity Translational Research Programme and its collaborators. That might include genetic testing, such as Genome Wide Association Studies. Only de-identified samples will be used for any future research, including genetic testing.

17. Will my participation in this research involve the use of any information that will identify me?

Your personal data (i.e., **name, date of birth and partial NRIC, contact details**) will be collected for verifying your identity and contacting you for the purpose of the study. Additionally, your facial images may also be collected for the purposes of carrying out the study.

18. How will my personal identifiers collected from me be kept confidential?

To prevent unauthorized access, disclosure, or loss of data, all information collected in the course of the research will be secured by data encryption and passwords (for electronic data) and under lock and key (for paper hardcopies). Only the PI, co-investigators, research coordinators and limited IQVIA staff supporting the production platform will have access to your personal data. Your identifiable facial image data will only be accessible by the PI, co-investigators, research coordinators and L'Oréal if you have consented to sharing of this data. Your personal data will never be used in a publication or presentation. To protect your confidentiality, your research data will be coded (i.e., only identified with a code number, exception being the facial image data which remains identifiable). All personal data (e.g., names and contact information) will be kept separate from the research data, with the exception of the facial image data which remains identifiable. All participating subjects will be requested to provide the contact details of a person who can be contacted if needed, and this would be kept separate from the research data also. The link between your personal data and the code number will bekept

confidential by the principal investigator or a trusted third party.

Your identifiable information (e.g., names, Partial IC nos.) will not be disclosed, unless required by the applicable laws and regulations (e.g., Infectious Disease Act) or for inspection by authorized regulatory monitors or legal authorities, as when called for.

19. Will any identifiable information obtained from me be used for future biomedical research?

If you consent, your personal data (i.e., name, date of birth and partial NRIC) will be retained for a period of 10 years. We may contact you for participation in future research and/or follow-up in this study. The personal data will not be discarded upon study completion unless specified by participants.

20. Will I be re-identified in the event of incidental finding(s) arising during the biomedical research?

During the course of this study or future studies, there is a possibility that we might unintentionally come to know of new information about your health condition from the blood tests or other clinical tests that are unrelated to our research. These are called "**incidental findings**". "Incidental findings" are findings that have potential health or reproductive importance to 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 future life and/or health insurance coverage.

You will be asked to indicate whether you wish to be re-identified and notified in the case of any important incidental finding that is related to you. The discovery of an incidental finding, at the discretion of the University, will be communicated to you for the purpose of seeking medical advice or treatment. In the event that you have indicated not to be re-identified and notified, but the University has determined that the incidental finding is of clinical significance, you may still be contacted to decide if you wish to be notified of the incidental finding at that time.

If you agree to be re-identified and notified, your study doctor/a qualified healthcare professional will explain the incidental finding to you and discuss and advise you on the next steps to follow. 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.

21. Under what circumstances will I be re-contacted for further consent?

You will be re-contacted for further consent, including but not limited to changes in the proposed research, serious adverse events that would lead to a change in the proposed research.

22. Can I withdraw my consent to the research at any time?

Your participation in this study is completely voluntary. You may stop participating in this study at any time without giving any reason. 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 inform the Principal Investigator.

However, the data that has 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 reason for the withdrawal will be requested, however you are not bound to provide a reason for withdrawal. There will be no penalties or damages imposed on you should you

withdraw your consent to participate in this research. Once you are withdrawn from this study,no attempt will be made to further evaluate you or to collect additional data from you.

PI 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 the instructions required to complete the study adequately. If you have other medicalproblems 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 PI or his/her representative.

23. Will my personal data be shared and / or processed for use in research?

Your personal data may, for the purposes of use in this study, or future research studies after the completion of this study approved by the IRB, relevant laws and/ or the Singapore Government ("Research Studies"), be processed into de-identified data (De-identified Dataset). Such processing may be done by us or with the assistance of our authorized data service providers or data intermediaries. The De-identified Dataset may be further:

a) Combined or linked with other datasets (including but not limited to Government administrative data and research data such as Health, and health-related data, Social data, Education data, Birth and death data, Economic and housing data, Disease registries and databases); **or**

b) Shared for the purposes of the Research Studies approved by the IRB, relevant laws and/ or the Singapore Government, with other researchers, service providers, regulators or third parties, including:

    a. Healthy Longevity Translational Research Programme, Yong Loo Lin School of Medicine, National University of Singapore, MD11, 10, Medical Drive, 117456 Singapore

24. Will my personal data be processed overseas for use in research?

Only de-identified samples/data will be sent to external/overseas collaborators. Your data and the research data derived from the research may be processed and transferred to any overseas recipient. Such recipients are bound by legally enforceable obligations to protect your personal data to a standard comparable to the data protection laws of Singapore.

PART III: Information on the Removal and Use of My Tissue(s) for this Research

1. What is the tissue(s) that will be taken from me and what will they be used for?

a. *Blood Biomarkers*

Peripheral blood will be drawn from the antecubital vein by a nurse/ phlebotomist/ trained SAF medic. You will be requested to fast overnight, and a maximum of 46 mL of blood will be collected into blood collection tubes in each study visits 1 - 3. **This would be used to measure clinical and biochemical parameters.** The total volume of blood collection for each participant in this study is up to 141.5 mL (13.5 mL + 41 mL + 41 mL + 46 mL).

Table 1. Breakdown of the blood tubes and their intended uses for the screening visit.

Test(s)	Volume and type of tube(s)
Full Blood Count (FBC) and HbA1c, Glucose fasting	1 x 3 mL anticoagulant tubes = 3 mL 1 x 2 mL sodium fluoride tube = 2 mL
Insulin, lipid panel, protein panel, liver panel, renal panel, serology (HIV, Hepatitis B and C)	1 x 8.5 mL plain tube (gold top) = 8.5 mL
Total	**13.5 mL (3 tubes)**

Table 2. Breakdown of the blood tubes and their intended uses for visits 1-2.

Test(s)	Volume and type of tube(s)
Peripheral Blood Mononuclear Cells (PBMC)	3 x 9 mL anticoagulant tubes = 27 mL
Plasma and Buffy Coat Cells	1 x 9 mL anticoagulant tubes = 9 mL
Serum	1 x 5 mL plain tube (gold top) = 5 mL
Total	**41 mL (5 tubes)**

Table 3. Breakdown of the blood tubes and their intended uses for visit 3.

Test(s)	Volume and type of tube(s)
Peripheral Blood Mononuclear Cells (PBMC)	3 x 9 mL anticoagulant tubes = 27 mL
Plasma and Buffy Coat Cells	1 x 9 mL anticoagulant tubes = 9 mL
Serum	1 x 5 mL plain tube (gold top) = 5 mL
serology (HIV, Hepatitis B and C)	1x 5 mL plain tube (gold top) = 5mL
Total	**46 mL (6 tubes)**

b. *Skin and Hair Biomarkers*

Table 3. Breakdown of the skin and hair samples and their intended uses for visits 1-3.

Sample(s)	Test
Transparent adhesive discs	Stratum corneum proteomics and epigenetic analysis

Swabs	Skin microbiome
Hair samples	Fiber characterization
0.75mm microbiopsies	Transcriptomics, proteomic and skin DNA methylation

2. Will my tissue(s) be used for any purpose other than current research?

Yes, archived de-identified samples will be used for future research related to ageing and age- related diseases research conducted by Healthy Longevity Translational Research Programme and its collaborators (only). It might include genetic testing, such as Genome Wide Association Studies. Only de-identified samples will be used for any future research, including genetic testing.

Does this study involve the removal of human tissues from persons who lack mental capacity or understanding and intelligence to consent to the donation of their tissues for the study? If so, what are the proposed area(s) of research approved by the Institutional Review Board (IRB), where the IRB has waived the requirement that the removal of my tissue(s) be for therapeutic or diagnostic purpose?

No, this section is not applicable as this research study only involves subjects who have mental capacity and sufficient understanding and intelligence to consent to the donation of their tissue(s) for research.

3. What risks, discomforts and inconveniences will I expect if my tissue(s) is/ are removed from me?

You may experience some pain and bruising when blood is collected from your vein. Fainting is an occasional adverse event due to blood-taking. Appropriate first aid will be administered should any of these events occur. Please refer to Page 13 with regards to the potential risks and discomforts for the microbiopsy procedure.

4. Will I still retain my rights to my tissue(s) after it has/ have been removed from me?

Donation of your tissue(s) is voluntary. By donating your tissue(s), you will relinquish your rights to your tissue(s) and any intellectual property rights that may be derived from the use of your tissue(s).

5. If I am injured as a result of donating my tissue(s), what are the compensation and treatments available to me?

If you follow the directions of the PI in charge of this research study and you are injured during the donation of your tissue(s), the NUS will pay the medical expenses for the treatment of that injury. 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.

Injuries sustained due to this research will be covered by the National Clinical Trials Insurance.

6. Do I have to incur any expenses if I donate my tissue(s) for this research?

No. You do not have to incur any expenses for donating tissues for this research.

7. Will my donated tissue(s) be used in any ways that can identify me?

Biological samples collected from the participants will be coded (de-identified) with the same unique individual identifiers assigned to each participant. These de-identified biological samples will be stored within the NUS and can only be accessed by qualified laboratory personnel under the supervision of the PI or members of the study team. Biological samples transferred out of Singapore may contain genetic information for genetic sequencing. To minimize any risk of re-identification througeh genetic information, research team will secure the dataflow and restrict analysis to their accredited laboratories only. Samples will be stored until they are fully utilized or expired. Only de-identified samples/data will be sent to external/overseas collaborators (including L'Oréal's third-party laboratories) who will process the samples in accordance with our written instructions.

There may be potential use of the de-identified data and samples for future research, but this will only apply to samples/data of participants who have consented to allow such future usage of their samples/data.

8. Will the records that identify me in relation to my tissue(s) donation be kept confidential?

The PI will be responsible for the confidentiality of all study information. PI will ensure that the participant's identity is not made publicly available. To maintain subjects' confidentiality, all case report forms/data collection forms will be devoid of personal identifiers. Study participants will be identified only by unique identification numbers. All physical records will be kept locked. The research database will be password-protected and only accessible to authorized members of the study team. Linked personal data (e.g., name, date of birth, email address and telephone number) will be kept in a separate file under lock and key.

9. Will the identifiable information obtained from me in the course of tissue donation be used for future research?

Archival de-identified samples will be used for future research conducted by the PI and other team members in the Healthy Longevity Programme or other external collaborators.

10. What will happen to the tissue(s) taken from me upon completion of the research?

The tissues will be stored for a minimum of 10 years, for current and future research.

11. Will my tissue(s) be used in restricted human biomedical research?

Your tissue(s) will not be used in restricted human biomedical research involving human-animal combinations.

12. Will my tissue(s) be exported overseas or removed from Singapore?

De-identified samples will be used for future research conducted by the Healthy Longevity Programme and its collaborators (only). That might include genetic testing, such as Genome Wide Association Studies. Only de-identified samples will be used for any future research, including genetic testing. De-identified samples/data will be sent to external/overseas collaborators (including L'Oréal's third-party laboratories) for the

purpose of analysis for this study.

13. Will I be re-identified in the case of incidental finding(s) arising from the use of my tissue(s) in future research?

It is possible that during the research we may find you have pre-existing medical issues that are unrelated to our research. These are called “incidental findings”. “Incidental findings” are findings that have potential health or reproductive importance to 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.

You will be asked to indicate whether you wish to be re-identified and notified in the event of an important incidental finding that is related to you. The discovery of an incidental finding, at the discretion of the University, will be communicated to you for the purpose of seeking medical advice or treatment. In the event that you have indicated not to be re-identified and notified, but the University has determined that the incidental finding is of clinical significance, you may still be contacted to decide if you wish to be notified of the incidental finding at that time.

If you agree to be re-identified and notified, your study doctor/a qualified healthcare professional will explain the incidental finding to you and discuss and advise you on the next steps to follow. 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.

14. Will I be re-contacted for further consent for the use of my tissue(s)? If so, under what circumstances?

No, you would not be contacted for further consent for the use of tissue as consent has been given initially.

15. Can I withdraw my consent to the removal of my tissue(s) and/or use of my tissue(s) in research at any time?

You can also withdraw from the research at any time without giving any reasons, by informing the PI and all your tissue(s) collected will be discarded. However, this only applies if the tissue is individually-identifiable and has not been used for research. Please also note that the withdrawal of consent does not affect the research information obtained before the consent is withdrawn and such information may still be retained and used for research. There will be no penalties or damages imposed on you should you withdraw your consent to participate in this research.

You are entitled to refuse to participate or discontinue participation at any time in this research. Refusal to participate or withdrawal from participation will not affect your medical management or cause loss of benefits to which you are otherwise entitled.

Consent Form for Research Subjects

Protocol title:
Project SIRT6 activator

Principal Investigator with the contact number and organization:
Andrea B. Maier, MD, PhD, FRACP
Professor, NUS Academy for Healthy Longevity, Yong Loo Lin School ofMedicine, National University of Singapore
MD11 Clinical Research Centre, #03-01, 10 Medical Drive, Singapore 117597
Contact number: (+65) 66012839
Email: a.maier@nus.edu.sg; longevitytrials@nus.edu.sg

I hereby acknowledge that:

1. My signature is my acknowledgement that I have agreed to take part in the above research.

2. I have received a copy of this information sheet that explains the use of *human biological material / data* in this research. I understand its contents and agree to donate my *biological material / data* the use of this research.

3. I can withdraw from the research at any point of time by informing the Principal Investigator although if I have donated tissue for the research, I can only withdraw my consent to use my tissue if the tissue is individually identifiable and has not been used for research or it is practicable to discontinue further use of my tissue for research. I am aware that that the withdrawal of consent does not affect the research information obtained before the consent is withdrawn and such information may still be retained and used for research.

4. I will not have any financial benefits that result from the commercial development of this research.

5. For health information and/or human biological materials collected for use in future research related to ageing and age-related diseases research will be conducted by the Healthy Longevity Programme and its collaborators (which might include genetic testing), please select 1 of the 4 choices below:

   ☐ I agree to donate my coded *human biological material / data* collected for this research to be used in future research. The future research will be subject to an Institutional Review Board's approval. **OR**

   ☐ I agree to donate my *human biological material / data* collected for this research to be used in future research. However, I would like all personal data removed from my biological samples / data so that no one can link the samples / data to me. The future research will be subject to an Institutional Review Board's approval. **OR**

   ☐ I agree to donate my *human biological material / data* collected for this research to be used in future research which may include testing and development by commercial firms. However, I would like all personal data removed from my biological samples / data so that no one can link the samples / data to me. The future research will be subject to an Institutional Review Board's approval. **OR**

   ☐ I do not agree to donate my *human biological material / data* collected for this research to be used in future research. In addition, I would like to have left over biological samples destroyed after the completion of this research.

6. For purposes of re-contact for future research, please indicate:

   ☐ I *agree* to be re-contacted for future related studies. I understand that future studies will be subject to an Institutional Review Board's approval.

   ☐ I *do not agree* to be re-contacted for future related studies. I understand that future studies will be subject to an Institutional Review Board's approval.

7. For the purpose of re-contact for further consent

   ☐ I *agree* to be re-contacted for further consent under the circumstances identified in the Participant Information Sheet.

   ☐ I *do not agree* to be re-contacted for further consent under the circumstances identified in the Participant Information Sheet.

8. For purposes of re-contact and notified in the case of an incidental finding, please indicate

   ☐ I *agree* that I may be re-contacted and notified in the case of an incidental finding from this research, or any other medical issue is found during the course of this study or in future research, in order to facilitate my seeking proper medical advice. I understand that my participation in the research is not considered medical treatment, and that the researchers are not qualified medical practitioners able to provide diagnoses

   ☐ I *do not agree* I may be re-contacted and notified in the case of an incidental finding from this research, or any other medical issue is found during the course of this study or in future research, in order to facilitate my seeking proper medical advice. I understand that my participation in the research is not considered medical treatment, and that the researchers are not qualified medical practitioners able to provide diagnoses

9. For the purpose of using individually identifiable facial image data, please indicate:

   ☐ I agree that the sponsor and it's relevant collaborators may use my individually identifiable facial image data for the purpose of analysis and presentation to consumer panels for assessing apparent age

   ☐ I do not agree for the sponsor and it's relevant collaborators to use my individually identifiable facial image data for the purpose of analysis and presentation to consumer panels for assessing apparent age

10. For the purpose of undergoing the optional skin microbiopsy at Visit 1 and Visit 3, please indicate:

    ☐ I agree to undergo the skin microbiopsy at Visit 1 and Visit 3

    ☐ I do not agree to undergo the skin microbiopsy at Visit 1 and Visit 3

Name (Research Participant)	**Signature** (Research Participant)	**Date** <dd-mm-yyyy>

I, the undersigned, certify to the following:

(a) I am 21 years of age or older.
(b) I have taken reasonable steps to ascertain the identity of the research subject.
(c) To the best of my knowledge, the research subject had 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.
(d) I have taken steps to ascertain that the consent has been given voluntarily without any coercion or intimidation.

Name (Witness)	**Signature** (Witness)	**Date** <dd-mm-yyyy>

Note that the requirement of a witness is waived if the research is not invasive, not interventional and is not restricted HBR. (e.g., research that comprises solely of a survey or collection of information from research subjects)

Name (Consent Taker)	**Signature** (Consent Taker)	**Date** <dd-mm-yyyy>

The study has been explained to the research subject in_____[*State Language*]

☐ Check if this section is not applicable

Name (Translator)	**Signature** (Translator)	**Date** <dd-mm-yyyy>