CONFIDENTIAL

QIMR Berghofer
Medical Research Institute

Clinical Trial Protocol

The Sun-D Trial

PROTOCOL NUMBER: P3755

Version:7
Date: 25 May 2023

SPONSOR

QIMR Berghofer Medical Research Institute
300 Herston Road
Herston, Queensland, 4006
Australia

PRINCIPAL INVESTIGATOR

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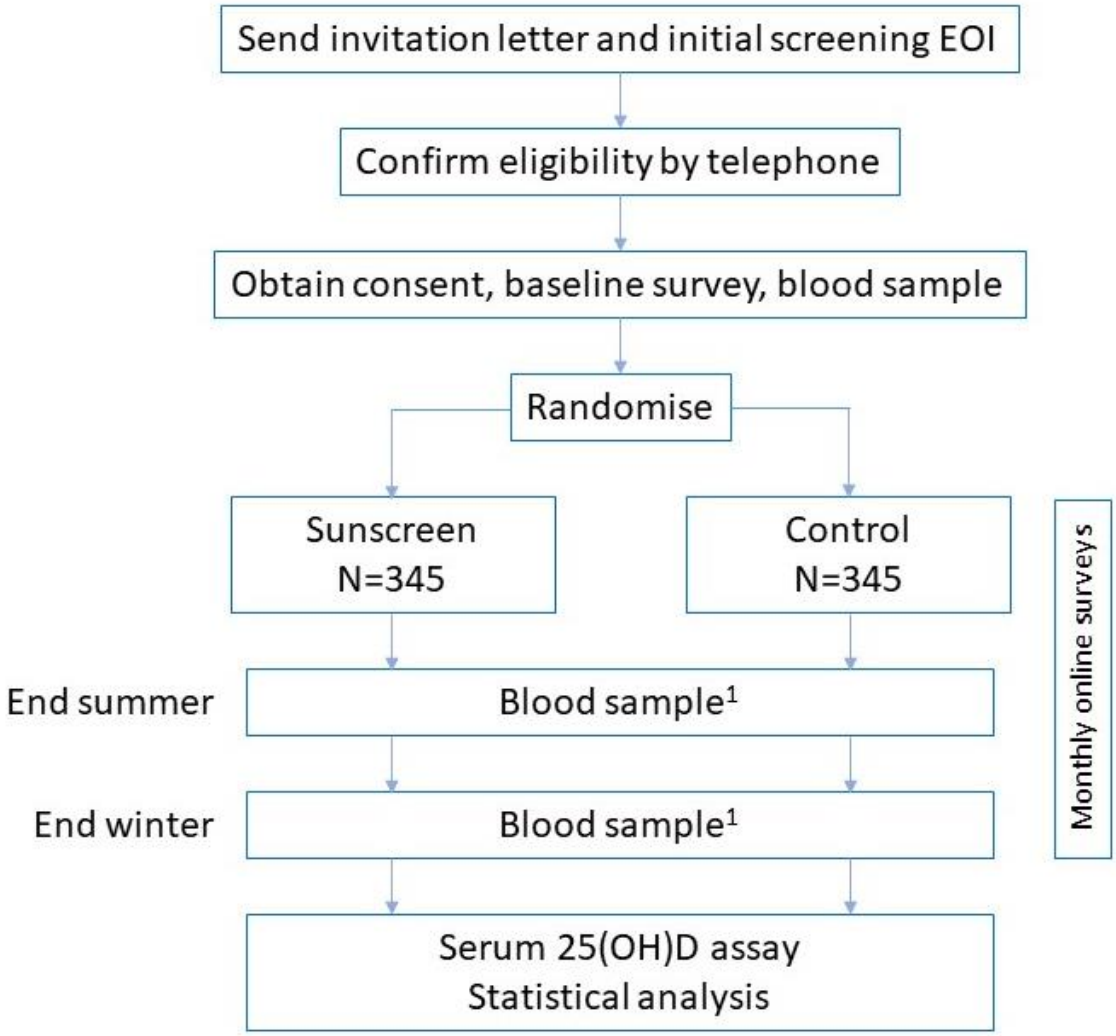
PROTOCOL AMENDMENT HISTORY

Protocol Version Number	Protocol Version Date	Primary Reason for Amendment
2	8/02/2022	1. Specify inclusion of ACT (Section 5.1 & 7.1) 2. Specify interview format (Section 6.1) 3. Addition of independent TMG member (Section 11.2.2 and appendix 1)
3	16/05/2022	1. Specify use of third party databases and mailing lists in recruitment activities (section 6.1) 2. Removal of Coles Myer specification for gift vouchers. (section 6.1)
4	29/06/2022	1. Eligibility age range amended to include 18-<30 and 65-70 year olds. 2. Further specification of mailing lists to be used for recruitment (section 6.1)
5	12/07/2022	1. Increased compensation for blood collection and removed 1 person per household limit (section 6.1) 2. Specified allergy exclusion criteria (section 6.4)
6	14/03/2023	1. Addition of Hamilton Sensitive sunscreen (sections 7.3, 7.5, 7.7 & 9.4)
7	25/05/2023	1. End of study definition updated (Section 5.4) 2. Retention point 5 updated to tri-monthly (section 6.1) 3. AE updated to bring in line with changes made in protocol version 6 (Section 7.10.1) 4. Inclusion of final survey (section 8.2.3)

PROTOCOL SYNOPSIS

Full Title:	The Sun-D Trial: the effect of high SPF sunscreen application on vitamin D
Short Title:	The Sun-D Trial
Project Number:	P3755
Objectives:	**Primary:** To determine whether routine application of high SPF sunscreen on all days when the ultraviolet (UV) index is forecast to be ≥3 leads to a decrease in 25 hydroxy vitamin D (25(OH)D) concentration. **Secondary:** (a) To determine if routine application of high SPF sunscreen affects 25(OH)D concentration within tertiles defined according to erythemally weighted UV radiation or baseline 25(OH)D concentration. (b) To understand determinants of changes in 25(OH)D concentration within the intervention group. (c) To determine if regular sunscreen application influences the incidence of actinic skin lesions.
Endpoint:	**Primary:** 25(OH)D concentration
Trial Design:	Open-label randomised controlled trial; phase 4; no placebo
Investigational Product(s):	SPF 50+ sunscreen containing chemical sunscreening agents, applied topically.
Number of Participants:	690
Key inclusion Criteria:	Aged 18 to 70 years; resident of one of the 4 eastern Australian states; willing to apply sunscreen daily when the maximum UVI is forecast to be ≥3; willing to have blood drawn on 3 occasions and to complete monthly online surveys; willing to limit supplementary vitamin D intake to 400 IU per day; able to give informed consent.
Key Exclusion Criteria:	Routinely applying sunscreen (other than cosmetics with maximum SPF 15); taking more than 400 IU vitamin D per day; previous allergic reaction to sunscreen; history of melanoma within the past 5 years.
Study Duration:	Estimated total study duration: 2.5 years Estimated participant involvement: 14 months Treatment duration: 12 months Estimated duration of recruitment period; 4 months

Study Schematic



[1] Blood samples will be collected by phlebotomists in commercial pathology laboratories and sent by courier to QIMR Berghofer. Aliquots of whole blood, serum, and plasma will be stored. At the end of the study samples will be assayed for 25(OH)D concentration.

SPONSOR SIGNATURE

The undersigned parties agree that the protocol was written in accordance with the World Medical Association Declaration of Helsinki — Ethical Principles for Medical Research Involving Human Subjects (Fortaleza, Brazil 2013), the NHMRC National Statement on Ethical Conduct in Human Research (2007, updated 2018), and the Integrated Addendum to ICH E6 (R1): Guideline for Good Clinical Practice E6 (R2) (November 2016) — with introductory comments of the Australian Therapeutic Goods Administration.

Protocol Writer Name	Signature	Date
Briony Duarte Romero		17/08/2021

I acknowledge and agree that I am responsible for conducting the study sponsored by QIMR Berghofer and will ensure that it is conducted to the above principles and QIMR Berghofer policy and procedures.

QIMR Berghofer Principal Investigator Name	Signature	Date
Rachel Neale		17/08/2021

This clinical trial protocol has been reviewed and approved by the Sponsor.

QIMR Berghofer Approving Authority Name	Signature	Date
Prof. Grant Ramm Deputy Director QIMR Berghofer Medical Research Institute		31/08/2021

COORDINATING PRINCIPAL INVESTIGATOR SIGNATURE

I agree to conduct the study in compliance with the protocol and all applicable legal and regulatory requirements including, but not limited to the following:

- World Medical Association Declaration of Helsinki – *Ethical Principles for Medical Research Involving Human Subjects*
- NHMRC *National Statement on Ethical Conduct in Human Research* (2007) incorporating all updates
- Notes for ***Guidance on Good Clinical Practice (CPMP/ICH/135/95)-Annotated with TGA comments (July, 2000 and Integrated Addendum to ICG E6(R1): Guidelines for Good Clinical Practice E6(R2) 9 November 2016)***

I will be responsible for oversight of all trial site personnel and activities and that the study will be conducted in accordance with the current HREC approvals.

I agree to inform all participants that the study interventions are being used for investigational purposes and I will ensure that the requirements related to obtaining informed consent are in accordance with International Council for Harmonisation (ICH) Guidelines for Good Clinical Practice (GCP) section 4.8 and local requirements.

I agree to report adverse events that occur in the course of the study to the Sponsor in accordance with ICH Guidelines for GCP section 4.11 and local requirements.

I have read and understand the information in the Investigator's Brochures, including the potential risks and side effects of the investigational product.

I agree to promptly report to the HREC all changes in the research activity and all unanticipated problems involving risk to participants. I will not make any changes to the conduct of the study without HREC and Sponsor approval, except when necessary to eliminate apparent immediate harm to patients.

I agree to maintain adequate and accurate records and make those records available in accordance with ICH Guidelines for GCP section 4.11 and local requirements.

I agree to ensure that all associates, colleagues, and employees assisting in the conduct of the study are informed about their obligations in meeting the above commitments.

I understand that the study may be terminated or enrolment suspended at any time by the Sponsor, with or without cause, or by me if it becomes necessary, to protect the best interest of the participants.

Signature:  Date:17/08/2021

Investigator Name: Rachel Neale

Investigative Site: QIMR Berghofer Medical Research Institute

LIST OF ABBREVIATIONS

AE	Adverse Event
CI	Clinical Investigator
CRF	Case Report Form
TMG	Trial Management Group
GCP	Good Clinical Practice
HREC	Human Research Ethics Committee
IB	Investigator's Brochure
IP	Investigational Product
NHMRC	National Health and Medical Research Council
PI	Principal Investigator
QIMR B	QIMR Berghofer Medical Research Institute
SAE	Serious Adverse Event
TGA	Therapeutic Goods Administration

Contents

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2 Introduction

2.1 Background Information

Skin cancer is a major burden: Skin cancer affects two in three Australian adults before the age of 70. Melanoma accounts for 10% of all new cancer diagnoses and over 1700 Australians die from melanoma each year. Keratinocyte cancers (squamous and basal cell carcinomas) are less fatal, but cause considerable morbidity and pose an enormous burden to the health system. In 2008-2009 management of keratinocyte cancers accounted for 8.1% of all health system expenditure on cancer in Australia (excluding cancer screening).[1]

Sunscreen can prevent skin cancer: Solar UV radiation (UVR) is the main environmental cause of skin cancer. Almost two-thirds of melanomas and essentially all keratinocyte cancers arising in Australia can be attributed to high ambient UVR.[2] Preventing skin cancer relies on reducing the amount of UVR that reaches the susceptible cells in the basal layer of the skin, and sunscreen is one of the most popular strategies used to achieve this. RCT evidence shows that daily sunscreen use can reduce the incidence of squamous cell carcinoma,[3] melanoma,[4] actinic keratoses (premalignant lesions),[5,6] and naevi.[7] In laboratory studies sunscreen also reduces UVR-induced mutations.[8] We estimated that approximately 10% of Australians who would have developed an SCC in 2008 and 14% of those who would have developed a melanoma had their cancer avoided by regular sunscreen use (defined as use when outdoors for at least 15 minutes).[2]

In light of these findings, in 2018 policy makers changed their position to recommend ***routine daily*** sunscreen use when the maximum UVI is forecast to be at least three, rather than only recommending sunscreen application prior to planned outdoors activities.[9] In much of Australia daily sunscreen application is required all year; application is not usually required in southern states in winter (Fig 1).

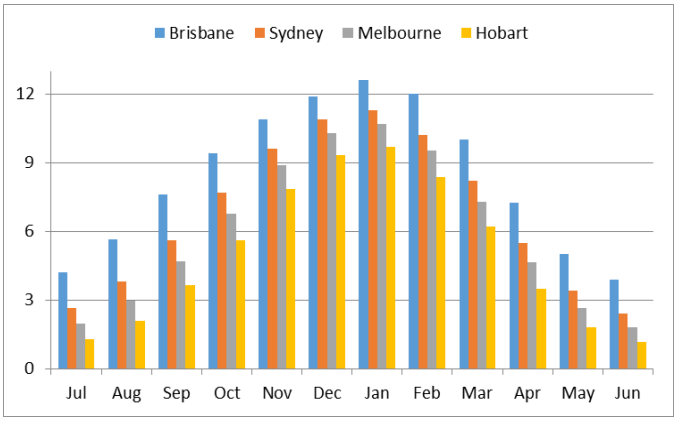

Figure 1: Average maximum UVI for selected Australian cities

Adequate vitamin D is important for bone health: Sun exposure of the skin is the main source of vitamin D for most Australians. Vitamin D plays a critical role in calcium homeostasis and is vital for the mineralisation of bone. Vitamin D deficiency causes rickets and osteomalacia, and is a risk factor for fractures[10] and falls.[11] The 25(OH)D concentration that constitutes sufficiency for bone health is unclear and controversial; recommendations from international organisations range from 25 to 75 nmol/L.[12] Australian peak bodies support a value of 50 nmol/L to denote vitamin D adequacy, but advise 60-70 nmol/L at the end of summer to avoid vitamin D deficiency in winter.[13]

Vitamin D is associated with other health outcomes: 25(OH)D concentration has been inversely associated with risk of over 100 different health outcomes. Arguably the most well established are acute respiratory illness[14] and total mortality.[15] Other important contributors to disease burden, such as colon cancer and cardiovascular disease, have been consistently associated with low 25(OH)D concentration in cohort studies, but RCTs have not shown a benefit of supplementation. It is thus not clear whether or not these associations are causal. However, if they are, a higher 25(OH)D concentration than needed for bone health may be required to reduce risk.

Vitamin D deficiency is prevalent, even in Australia: The most reliable data for Australia come from the Australian National Health Survey (NHS, 2011-2012).[16] Almost a quarter of

the population (23%) had a 25(OH)D concentration of <50 nmol/L (winter: 36%; summer: 14%) with prevalence higher in southern than in northern states (Figure 2).

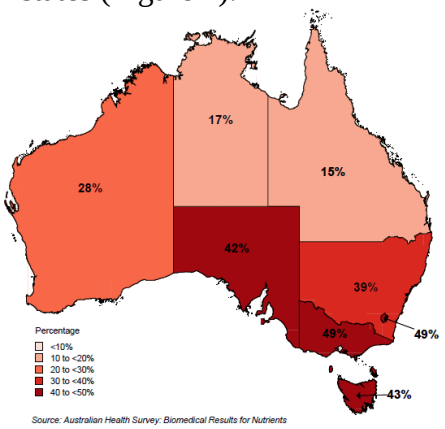

Figure 2: Prevalence of (25(OH)D) concentration < 50 nmol/L by state

Diseases related to vitamin D deficiency cause considerable health burden: There has not been a formal analysis of the burden of disease attributable to current levels of vitamin D deficiency. However, AI Lucas and colleagues estimated that under a scenario in which global UVR exposure was reduced to very low levels, the resultant vitamin D deficiency would cause four billion cases of bone disease with an associated disease burden of 3.3 billion disability-adjusted life years.[17] Studies suggest that a substantial proportion of annual deaths could be avoided by increasing 25(OH)D concentration to ~100 nmol/L: 16% for Canada;[18] 18% for New Zealand.[19] Our calculations show that ~9% of hip fractures and hospitalisations for falls in Australia may be attributable to low vitamin D (manuscript under review).

Other benefits of UVR exposure are not proven: A number of other beneficial effects of sun exposure, not mediated through vitamin D pathways, have been posited but these are not proven. Such effects include reduction of blood pressure, possibly through UVA-mediated release of nitric oxide stores in the skin, and immunomodulation through a wide range of mechanisms.[20]

Sunscreen can block vitamin D production: Sunscreens are designed to prevent erythema (sunburn), and the UVR wavelengths that cause erythema are largely the same as those that induce vitamin D synthesis. Thus, in theory, sunscreens that are effective at preventing erythema will also prevent vitamin D production. Our ***systematic review*** identified four experimental studies in humans; all showed that sunscreen markedly abrogated vitamin D production induced by exposure to artificially generated UVR.[21] The 69 observational studies were generally of poor quality and largely uninterpretable due to intractable confounding. Two RCTs assessing the effect of daily sunscreen application on 25(OH)D concentration, one in Nambour, Queensland (The Nambour Trial)[22] and one in Maryborough, Victoria,[23] showed that provision of sunscreen and advice to use it daily reduced skin cancer and premalignant lesions, showing that sufficient sunscreen was applied to prevent damage to the skin. Neither study found a difference in 25(OH)D concentration between the intervention and non-intervention groups. However, both used sunscreens with SPF of ~16, and took place where/when the maximum UVI was much greater than three. ***There have been no randomised field trials of sunscreens with a very high SPF, and it is plausible that these may influence vitamin D, particularly when the UVI is relatively low but above that at which sun protection is advised (e.g., UVI of 3-5).***

Concern about vitamin D is a barrier to sunscreen use: The public are exposed to frequent messages about the importance of vitamin D. An analysis of newspaper articles published from 1993 to 2006 found that Australians were exposed to mixed messages about sun protection;[24] 9% of articles relating to sun protection referred to vitamin D issues, and the vitamin D theme became more prominent over time. For example: *'Sunsmart Aussies are paying the price for covering up. While skin cancer rates have dropped, a lack of sunlight is causing serious vitamin D deficiencies'* (Herald Sun 2002). Such information is still promulgated almost two decades later; for example, '*Too much sunscreen is making us vitamin D deficient by blocking the good side of sunshine'* (Daily Mail Australia 2017). This opinion is supported by some scientists; e.g., this statement appeared in 2015: *'Among the reasons vitamin D deficiency is so widespread are the public health messages from the U.S. Surgeon General, the Institute of*

Medicine, and the World Health Organization, all of whom promote … covering the skin with clothing or sunscreen when out in the sun'.[25]

General practitioners (GPs) are also concerned: Concern about vitamin D deficiency is also evident among Australian GPs, as shown by the ~100-fold increase in vitamin D testing since 2000.[26] A survey of GPs in 2009 found that: (i) 83% were concerned that their patients were not getting enough vitamin D; (ii) 68% agreed that skin cancer prevention messages contributed to vitamin D deficiency; and (iii) only 32% agreed that it is more important to stay out of the sun than it is to get enough vitamin D.[27] Our recent qualitative study among GPs found that most GPs interviewed were unsure about how to advise their patients regarding sunscreen use in order to avoid vitamin D deficiency (unpublished data).

These messages are undermining decades of successful sun protection. A 2008 study of Queenslanders found that 32% agreed with the statement that sun protection could lead to insufficient vitamin D, 21% had already changed their sun protective behaviours due to concerns about vitamin D and 16% intended to.[28] Similarly 24% of 1002 people recruited from 4 Australian states were concerned about not getting enough vitamin D, and the odds of not applying sunscreen was three times higher in those concerned compared with those not concerned about vitamin D.[29] The 2016 National Sun Survey found that 28% of Australian adults were concerned about their vitamin D. People concerned about vitamin D were more likely to exhibit protanning beliefs and to be sceptical about sunscreen safety, and less likely to use sun protection.[30]

2.2 Study Rationale

Sunscreen is applied topically. Cancer Council recommendations are to use sunscreen with SPF at least 30+. We will use an SPF 50+ sunscreen. This is the highest SPF available in Australia and is widely used. It is therefore important to assess its effect on vitamin D.

Sunscreen is tested at a thickness of 2 mg/cm^2. In reality participants do not use this much, and we aim to test the effect of real-life application. Participants will be advised to apply sufficient sunscreen to result in a thick even coverage.

One year of intervention is sufficient to detect the effect of sunscreen application on 25(OH)D concentration at the end of summer and the end of the following winter. If sunscreen reduces 25(OH)D production during summer, this may manifest in markedly lower 25(OH)D at the end of winter, potentially leading to vitamin D deficiency.

Participants will be recruited across the 4 eastern Australian states to ensure maximum variability in ambient erythemally weighted UV radiation. Those older than 70 years will not be recruited as they are likely to be infrequent mobile phone users. Analyses adjusted for baseline 25(OH)D will ensure trial results apply to a broader age range.

Hypotheses

1. Compared with the control group, those in the intervention group will have a lower mean 25(OH)D concentration (by at least 10 nmol/L) at the end of summer or winter;
2. There will be a difference in 25(OH)D of at least 10 nmol/L between the treatment groups at the end of summer or winter in all strata defined by tertiles of ambient UV radiation and baseline 25(OH)D concentration;
3. Participant factors (such as body mass index) will influence the change in 25(OH)D concentration among people who are compliant with the intervention.
4. Participants in the intervention group will have a lower incidence of actinic skin lesions during the trial and over the subsequent 2 years.

3 Potential Risks and Benefits

3.1 Potential Risks

Reaction to sunscreen: people can experience topical reaction to sunscreen. We will not enrol people who have previously experienced a reaction to sunscreen or other topical products. Reactions are mostly self-limiting and do not need medical intervention. Participants will be asked to cease using the sunscreen, and to notify the study team if this occurs.

Lowered 25(OH)D concentration: the aim of this study is to determine if regular sunscreen application reduces 25(OH)D concentration. It is thus possible that this will occur. Low 25(OH)D concentration for ≤1 year is very unlikely to harm musculoskeletal health, particularly in people aged under 65 years. Further, the negative consequences of low 25(OH)D concentration are thought not to markedly increase until 25(OH)D is <30 nmol/L. In the Australian Health Survey only 7% of people had this degree of vitamin D deficiency; the mean 25(OH)D concentration was 65 nmol/L.

Sunburn: participants may assume they are protected from sunburn via a single daily application of sunscreen. We will provide baseline and regular advice throughout the study that if people are outside for more than a few minutes when the UV index is ≥3 additional sun protection measures should be used.

Blood collection: The risks associated with having blood collected (occurring on 3 occasions) are low but include excessive bleeding, fainting or feeling light-headed, haematoma, infection. We will minimize these risks by having blood drawn at pathology collection centres who employ qualified phlebotomists.

3.2 Potential Benefits

Direct benefits to participants

1. Participants in the sunscreen group will be provided with a one-year supply of sunscreen. Use of this may reduce future risk of skin cancer, premalignant lesions, and skin ageing.
2. All participants will be provided with their 25(OH)D concentration results at the end of the study. If participants have low 25(OH)D this will enable further investigation and treatment with their usual GP (this advice will be provided in the accompanying letter). Advice about their 25(OH)D results will provide them with information about the seasonal variability in their own vitamin D.

Broader benefits of the study

Finding the balance between the risks and benefits of sun exposure is extremely challenging. The Cancer Council Australia and other organisations now advise daily sunscreen use to reduce UV radiation-induced damage arising from incidental exposure. Sunscreen blocks vitamin D production in experimental settings but there are no data about the effect of frequent application of high SPF sunscreens in community settings. Despite this, there is a widely held perception that using sunscreen will increase the risk of vitamin D deficiency and this is undermining skin cancer prevention messages. The Sun-D Trial will either lead to a reconsideration of sunscreen policy or reassure the public about the safety of sunscreens with respect to vitamin D. ***This trial will thus impact health, irrespective of the findings.***

4 Aims and Objectives

4.1 Research Question

Does frequent application of high SPF sunscreen reduce 25(OH)D concentration in serum?

4.2 Study Objectives

4.2.1 Primary Objective

The primary objective is to determine whether participants randomised to provision of a broad-spectrum SPF 50+ sunscreen, and advice to apply it to all body parts uncovered by clothing on all days when the UVI is forecast to reach 3, have a lower mean 25 hydroxyvitamin D (25(OH)D) concentration at the end of either summer or winter than those randomised to usual discretionary sunscreen use.

4.2.2 Secondary Objectives

Secondary objectives are to:

- Determine whether the intervention affects 25(OH)D concentration at the end of winter or summer within tertiles of:
    - Erythemally weighted ambient UV radiation at the postcode of usual residence
    - Baseline 25(OH)D concentration
- Identify environmental and participant factors that influence the change in 25(OH)D concentration in sunscreen users.
- Identify barriers to knowledge and attitudes about sun protection, and facilitators and barriers to regular sunscreen use.
- Determine if randomisation to regular SPF 50+ sunscreen application reduces the incidence of malignant and pre-malignant skin lesions.

4.3 Study endpoint measures

- 25(OH)D concentration at end of summer and end of winter, and averaged across these time points.
- Compliance with sunscreen use.
- Malignant and pre-malignant skin lesions.

5 Study Design

5.1 Overall Study Design

Phase: Phase 4 RCT to determine effect of sunscreen application on serum 25(OH)D concentration.

Randomisation: Randomised computer-generated randomisation in a 1:1 ratio, stratified using permuted blocks by state of residence (QLD; NSW/ACT; VIC; TAS), age (18-44; 45-70), and sex. We will use cluster randomisation to ensure participants from the same household are randomised to the same study arm.

Control: Standard Cancer Council information to protect the skin when outdoors for more than a few minutes when the UV Index is ≥3, provided at baseline.

Blinding: Open label. Blood samples and data will be analysed blinded to study group.

Rationale: An RCT is needed to determine the effect of regular sunscreen application, as observational studies are frequently confounded by indication. It would be unethical to use a placebo sunscreen. We will recruit people who are not already using sunscreen routinely to avoid contamination in the control group, and advise that we want them to continue their usual behaviour during the course of the trial.

5.2 Number of Participants

690

5.3 Expected Duration of Study

Total study period: 17 months

Recruitment period: 4 months

Treatment period: 12 months

Follow-up period: Blood will be collected in the month after treatment finishes (i.e. month 13 after randomisation).

5.4 End of study Definition

6 The end of the study will occur when all participants have provided the final blood sample (winter 2023), and completed the final survey.Study Population Selection and Recruitment

6.1 Participant Recruitment and Retention Strategies

Participants will be recruited primarily from the Australian Electoral Roll. We will also enable volunteer recruitment, through use of third party databases and mailing lists such as the Join Us Register and university mailing lists (pending necessary approvals from each organisation), supported by traditional and social media. Participants enrolled in other QIMR Berghofer-sponsored studies (e.g., QSkin, the D-Health Trial), or who have subscribed to QIMR mailing lists, will be advised of the opportunity for them or their family/friends to participate, with HREC approval for the relevant study.

Recruitment approach

1. Invitation letter, including an eligibility questionnaire to conduct an initial eligibility screen (completed on paper or online). Volunteers will be able to access the eligibility questionnaire through a publicly available link.
2. Phone call to people who are eligible on the eligibility questionnaire to confirm eligibility criteria.
3. Email link to participant information sheet, consent form, questionnaire.
4. Email/mail pathology request form (according to participant preference).
5. Randomisation after consent form, questionnaire, and blood sample received.

Retention strategies

All participants:

1. Will receive a $50 e-voucher card for each sample returned to QIMR Berghofer, as compensation for their time;
2. Will be informed of all 25(OH)D test results at the end of the study

Intervention group only:

1. Will receive weekly reminders, including information about the forecast UVI
2. Be invited to a closed Facebook group providing access to videos, hints about sunscreen application, sunscreen and sun exposure facts etc.
3. Regular email updates about study progress, including short videos to encourage application
4. Advice about how to download and use the SunSmart App which displays the daily forecast UVI for their location.
5. After the first two weeks and then tri-monthly we will contact participants in the intervention group to identify barriers to sunscreen use and to suggest solutions. Interviews will be conducted over Zoom or by telephone, and recorded, with consent from the

participant at the time of contact. At enrolment participants will be asked to nominate their preferred contact mode including preference for video or non-video call.

All materials will be approved by the HREC prior to use. With respect to Facebook posts, any study updates or comments on new findings will be submitted for approval prior to posting. Posts that are designed to create engagement or encourage sunscreen application (e.g., tell us what you do to remember your sunscreen application; or don't forget sunscreen application even in lockdown) will not be submitted for approval. Similarly, we will respond to participant questions posted on Facebook in the Facebook forum, provided the advice is consistent with the PICF and protocol.

6.2 Informed Consent

People who express interest in taking part in the study, and whose expression-of-interest (EOI) form suggests they are eligible will be telephoned to confirm eligibility and ensure they understand the required commitment if they decide to proceed. Those who are still interested will be emailed a link to the participant information and consent form (PICF). They will be able to download a PDF of the PICF, and a copy of their completed questionnaire will be emailed to them and the Sun-D email account.

The PICF will describe the purpose of the study, the procedures to be followed, and the risks and benefits of participation. A helpline will be available for potential participants who have additional questions. Participants will be asked to consent online, after which they will be asked to complete the baseline questionnaire online. When consent and questionnaire are complete, participants will be provided with either online (printable) or hard copy pathology collection form. When the blood sample is received, the participant will be randomised and the study intervention will begin.

6.3 Inclusion Criteria

In order to be eligible to participate in this study, an individual must meet all of the following criteria:

- Provide electronic consent to participate
- Willing to comply with all study procedures and be available for the duration of the study
- Aged 18 to 70
- Resident of Queensland, New South Wales, Victoria or Tasmania
- Fitzpatrick skin type 1 to 4

Women of reproductive potential may be recruited. There are no specific contraceptive requirements.

6.4 Exclusion Criteria

People will be excluded if they are unable to provide consent or unable to communicate well enough in English to understand study requirements. In addition, they will be excluded if they:

- Have a history of allergic skin reaction to sunscreen
- Have an autoimmune condition that affects the skin, such as psoriasis, lupus of the skin, scleroderma
- Have a history of melanoma within the past 5 years
- Are currently using sunscreen on a regular basis (i.e., > 2 days per week), excluding makeup or moisturiser with max SPF 15+ on the face
- Are taking or plan to start taking > 400 IU/day of supplementary vitamin D
- Do not have a phone

- Do not have access to electronic device suitable for survey completion and receiving reminders.

7 Study Intervention

7.1 Intervention Assignment / Randomisation Procedures

Participants will be randomised into one of the two groups, (the sunscreen intervention or control group), using permuted block randomisation within strata defined according to state of residence (QLD, NSW/ACT, VIC, TAS), age (18-44, 45-70), and sex (M, F). Study staff and investigators will be blinded to the allocation sequence. Once all baseline components are returned the database will automatically apply the next record in the allocation sequence (within the relevant stratum).

7.2 Blinding Procedures and Code Break

As it would be unethical to provide placebo sunscreen products, the study will be an open-label RCT. Therefore, following randomisation, participants and study staff will be aware of group assignment. However, analysts and laboratory staff will be blinded to group assignment. This will be achieved in two ways:

Analysts – A researcher external to the study team will generate preliminary datasets containing replacement identification numbers and new assignment codes which have no relationship to the original assignment. Once statistical code has been finalised the external researcher will execute the programs to produce results for the actual randomisation allocation.

Laboratory staff – Laboratory staff will not have access to the dataset containing participant allocation codes, and samples will be labelled with the participant identifier only.

7.3 Study Intervention Description

Both groups will be directed to the Cancer Council sun protection information at the start of the study. The control group will receive no further intervention.

Participants in the intervention group will be supplied with Hamilton Active Family SPF 50+ (500 mL) and instructed to apply a generous even layer to all skin not covered by clothing every day when the maximum UVI is forecast to be ≥ 3. A separate facial sunscreen will be offered and supplied if preferred; Hamilton Everyday Face SPF 50+ (75gm). Hamilton Sensitive will also be available and provided on request to participants who are not able to tolerate Hamilton Active Family and/or Hamilton Everyday Face sunscreens.

Hamilton Active Family:

Active ingredients: Octyl Salicylate 5%, Homosalate 10%, Butyl Methoxydibenzoylmethane 4%, Octocrylene 8%.
Preservatives: Phenoxyethanol, Benzyl Alcohol, Hydroxybenzoates

Hamilton Everyday Face:

Active ingredients: Octocrylene 3%, Butyl Methoxydibenzoylmethane 3%, 4-Methylbenzylidene Camphor 2%, Ethylhexyl Triazone 2%
Preservatives: Phenoxyethanol

Hamilton Sensitive:

Active ingredients: 4-Methylbenzylidene Camphor 4%, Butyl Methoxydibenzoylmethane 4%, Octocrylene 4%, Ethylhexyl Triazone 3%
Preservatives: Caprylyl glycol, octanohydroxamic acid, glycerol

Sunscreen will be mailed to participants at the beginning of the trial. Replacements will be sent as requested. All product will be labelled as follows:

SUN-D STUDY SUNSCREEN

For participant use only

Participant ID: _____
Participant Name: _____
Directions for use: Apply liberally to exposed skin, when the maximum UV index is forecast to reach 3.

PLEASE RETAIN PACK FOR RETURN TO SUN-D TRIAL

Phone contact 1300 XXX XXX **Dispensed on:** dd/mm/yyyy **Item number:** PXX **EXP:**mm/yyyy
P3755 Prof Rachel Neale - QIMR Berghofer Medical Research Institute, Locked Bag 2000, Royal Brisbane Hospital, Q 4029

Note: Study labels will be fixed to the front of the product leaving the storage advice, ingredients list, and other important product information visible on the back of the pack.

7.4 Storage and Handling

The IP will be held at room temperature in a secure QIMR Berghofer facility that has temperature logging enabled. Any temperature deviations above 30 degrees Celsius will be recorded, although short elevations will have minimal impact on the sunscreen product.

Participants will be instructed to store sunscreen in a cool place (below 30º C) away from sunlight as per the manufacturer's instructions.

7.5 Dispensing and Accountability

Key Pharmaceuticals will provide Hamilton Active Family SPF 50+ (500 mL lotion in bottle with pump dispenser), Hamilton Everyday Face SPF 50+ (75 gm cream in tube) and Hamilton Sensitive (265 mL lotion in bottle) to QIMR Berghofer.

When a participant is randomised to the intervention group they will be dispensed an initial quantity of sunscreen suitable to their location (calculated based on the expected amount of sunscreen required for the following 6 months). All participants in the intervention group will be provided with 500 mL pump packs of general use sunscreen. Those who wish to use it will also be provided with facial sunscreen.

A letter and product labels will be printed, identifying the participant and providing instructions for storage, use, and product return. Labels will be fixed to the front of each tube/bottle of sunscreen and packed together with the letter for posting. Address labels will be attached to each pack, and the contents of the pack will be checked against the dispense report to ensure the correct type and quantity of sunscreen has been dispensed.

At the time of each monthly survey, participants will be asked to indicate if they need replacement sunscreen, and the type required (general and/or face). These will be dispensed as above.

Participants will be provided with a return satchel, and asked to store all empty bottles/tubes in the satchel for return at the conclusion of the study.

The Sun-D database will keep an up to date log of sunscreen supplies (type, quantity, dispense date, item number and batch information) dispensed to participants. Sunscreen bottles returned will be logged, along with the weight of each bottle. Quantities for each dispensed bottle will be updated in each tri-monthly participant interview and finalised at the conclusion of the intervention.

Note: we will offer additional sunscreen to families to minimise use of study sunscreen by other family members. It will be labelled as family use sunscreen. Sunscreen sent to families will also be captured in the Sun-D database.

7.6 Intervention Administration and Dose justification.

Following randomisation the control group will be instructed to maintain their usual sunscreen routine.

Participants in the intervention group will be instructed to apply the provided sunscreen liberally to all skin not covered by clothing every day when the maximum UVI is forecast to reach 3. The intervention is based on current recommendations for sunscreen use, for people living in Australian and New Zealanders,[31] and aims to assess the impact of this advice on 25(OH)D concentration at the end of summer and winter.

The intervention will last 1 year. Within individuals, 25(OH)D concentration is relatively stable from year to year but will fluctuate by season. The intervention period has been chosen to allow for this seasonal variation. A 1-year intervention will provide adequate data to answer the research question.

In line with the selection criteria (see 6.3-4) we will request participants limit supplementary vitamin D intake to 400 IU/day for the duration of the study. However, once randomised, participants will not be withdrawn for taking more than 400 IU/day. Vitamin D dose information will be captured in monthly surveys to assist in trial monitoring and for use in analyses at the conclusion of the study.

7.7 Intervention Dose Modifications

No dose modifications will be required. Participants who experience an adverse reaction (i.e., a skin rash) will be withdrawn if symptoms do not resolve and no other cause is identified.

NOTE: Participants withdrawing due to adverse reaction will be invited to continue monthly surveys and provide bloods in according to their planned schedule.

7.8 External monitoring

The investigational product is classified as a therapeutic sunscreen, and is therefore subject to additional regulatory requirements external to the trial. In light of this, it is possible that product quality, contamination and labelling issues may be revealed during the course of the trial. Should any issues become apparent, participants will be notified and advice provided in line with the TGA recommendations. Study staff will confirm advice is received and acted on appropriately by telephone and/or email contact with each individual.

7.9 Intervention / Treatment Compliance

We will use self-reported frequency from the monthly surveys as the primary measure of the number of days sunscreen was applied. Compliance will be calculated as the number of days applied divided by the number expected. Any Sunscreen bottles returned to QIMR B will be

weighed and their weights recorded in the Sun-D REDCap database. Participants will not be withdrawn for being non-compliant. However, compliance information will be routinely collected at each monthly survey. Participants reporting significant non-compliance will be contacted for further review in an effort to identify barriers and suggest solutions where possible. Compliance data will also be reviewed regularly by the Trial Management Group (TMG) – see section 11.2.2 and appendix 1.

We will update information on sunscreen supply during tri-monthly interviews with intervention group participants and again at the conclusion of the intervention period.

Note: The number of days expected will be estimated based on the number of days where the forecast maximum UVI at the closest town was ≥3 (using data from the Bureau of Meteorology).

7.10 Discontinuation of Intervention and Withdrawal of participants

7.10.1 Criteria for Discontinuation

Participants can withdraw from the study at any time by notifying us in writing, or via email or phone. Those in the sunscreen arm can discontinue using the study sunscreen at any time. They will be invited to continue surveys and blood collections as scheduled.

Participants who cease the monthly surveys will be invited to continue blood collections as scheduled.

Participants will be withdrawn from the study for any of the following reasons:

- Withdrawal of informed consent
- Experience an ongoing reaction to the sunscreen product (sunscreen group only)
- Death
- Discontinuation of the study by the Sponsor, a Regulatory Authority, or a Human Research Ethics Committee

7.10.2 Handling of Participant Discontinuation and Withdrawal

Participants do not have to give a reason for their withdrawal. Information already collected will be destroyed at their request.

The following information will be captured in the Sun-D Trial database for all participants who withdraw / are withdrawn from the study at the time of withdrawal:

- Date of withdrawal
- Reason for withdrawal: (including an option for no reason given)
- Willing to keep completing surveys: yes / no
- Willing to keep giving blood samples
- Willing for us to keep information already collected: yes / no (details if any caveats)
- Willing for us to obtain information in the future (MBS/PBS records): yes / no

No withdrawn participants will be replaced.

7.11 Premature Termination or Suspension of Study

The Sponsor, Principal Investigator(s), Human Research Ethics Committee (HREC) and Regulatory Authorities independently reserve the right to discontinue the study at any time for safety or other reasons. This will be done in consultation with the Sponsor where practical. In the occurrence of premature trial termination or suspension, the above mentioned parties will be notified in writing by the terminator/suspender stating the reasons for early termination or

suspension (with the exception of the sponsor's responsibility for notifying the Regulatory Authorities). After such a decision, the Sponsor and the Investigator will ensure that adequate consideration is given to the protection of the subjects' interests. The investigator must review all participating subjects as soon as practical and complete all required records.

8 Study Procedures and Assessments

8.1 Schedule of Assessments

	Study year	1				2				3			
	Calendar year	2021		2022				2023				2024	
	Quarter	Q3	Q4	Q1	Q2	Q3	Q4	Q1	Q2	Q3	Q4	Q1	Q2
Stage 1	Set-up												
Stage 2	Participant recruitment (invitations sent, EOIs completed, screening calls conducted and baseline materials returned)												
	Intervention and follow-up (Intervention, monthly surveys completed and blood samples returned)												
Stage 3	25(OH)D assays												
	Data analysis and publication												
	Stakeholder meeting												

Note: Year 1 begins on 1 July 2021; Participants will be involved only in stage 2, beginning with recruitment in the first half of 2022, just prior to the start of study year 2 and ending with the final blood collection in the third quarter of 2023. The intervention and follow-up are described in more detail below (section 8).

8.2 Study Assessments

8.2.1 Recruitment / Baseline

On receipt of completed eligibility questionnaire, potentially eligible people will be contacted by phone to confirm their eligibility information, as well as willingness and ability to adhere to study requirements. After phone contact, people who are eligible and willing to take part will be sent a link to online:

- Trial information sheet and consent form
- Baseline questionnaire

Participants who complete the consent and baseline questionnaire will then be able to access a pathology request form, and asked to provide a blood sample before the end of September 2022. Participants will be able to request a hard copy of the request form. Randomisation will take place once both consent and baseline questionnaire have been completed and checked, and the baseline blood sample has been received by sample processing at QIMR Berghofer.

8.2.2 Follow-up

Following randomisation participants in the intervention group will receive sunscreen supplies as described above (see section 7.5). They will also be provided with access to a short video clip showing optimal sunscreen application. In addition, the following reminders and support will be provided:

- Weekly reminders, including information about the forecast UVI
- Invitation to a closed Facebook group providing access to videos, hints about sunscreen application, sunscreen and sun exposure facts etc.
- Regular email updates about study progress, including short videos to encourage application
- Advice about how to download and use the SunSmart App which displays the daily forecast UVI for their location.
- After the first two weeks and then bi-monthly we will telephone participants in the intervention group to identify barriers to sunscreen use and to suggest solutions.

8.2.3 Surveys

Baseline questionnaire

The baseline questionnaire will capture information about: demographics; phenotype, including sun susceptibility; lifestyle; skin cancer history; sun exposure behaviour; use of supplementary vitamin D.

Follow-up surveys

Each month all participants will be asked to complete a short online survey which will capture information about: sunscreen use, time outdoors, clothing when outdoors, use of vitamin D supplements, adverse events.

Final Survey

At the end of the final month of participation, each participant will receive a final survey. This survey will include all questions asked in the monthly follow-up surveys, and in addition, will contain a short section capturing travel information, attitudes towards vitamin D, sun exposure, sunscreen, and participant feedback.

8.2.4 Blood collection

Three blood samples will be collected from eligible participants who have completed the consent form and baseline survey.

Sample 1

The baseline blood sample will be collected in winter to early spring: (Jun – Sept 2022). Eligible participants will be required to provide a baseline blood sample before the end of September in order for randomisation to take place.

Samples 2 and 3

The second and third samples will be collected at end of summer (Feb – March 2023), and at the end of the intervention phase (winter to early spring: Jul – Sept 2023).

Participants will be provided with either online (printable) or paper pathology collection forms to be presented at their local participating pathology laboratory. Blood samples will then be returned to QIMR Berghofer for processing and storage.

8.2.5 Data linkage

Linkage to Medicare Australia will enable capture of information about skin cancer treatments. This data will be used to assess if regular high SPF sunscreen application reduces the incidence of malignant and pre-malignant skin lesions. Data linkage will be sought for the period between enrolment and up to four years post intervention.

8.2.6 Laboratory Assessments

All blood samples will be analysed at the end of the study. Serum 25(OH)D will be measured using a liquid chromatography tandem mass spectroscopy method. It will most likely occur at Metabolomics Australia, University of Western Australia, with whom we have an existing collaboration, although other companies may start to offer the same assay, so we will select appropriately at the time of testing. The assay is certified to the NIST-Ghent University Reference Measurement Procedure.[32] Laboratory staff will be blinded to the group assignment; samples will be randomly distributed across batches to avoid systematic differences between study groups or across time points.

9 Safety Assessments and Reporting

9.1 Adverse Event Definitions

We will capture adverse events that are potentially related to the sunscreen application. These will be skin rashes, sunburn, falls, and fractures (with the latter potentially related to lowered 25(OH)D concentration).

9.2 Assessment of Severity

The severity of all AEs will be graded using the following criteria:

Severity	Description
Grade 1 (Mild)	Sign or symptom is present, but it is easily tolerated, is not expected to have a clinically significant effect on the participant's overall health and well-being, does not interfere with the participant's usual function, and is not likely to require medical attention.
Grade 2 (Moderate)	Sign or symptom causes interference with usual activity or affects clinical status, and may require medical intervention.
Grade 3 (Severe)	Sign or symptom is incapacitating or significantly affects clinical status and likely requires medical intervention and/or close follow-up.
Grade 4 (Life-threatening)	Sign or symptom results in a potential threat to life.
Grade 5 (Fatal)	Fatal Sign or symptom results in death

9.3 Assessment of Causality

Skin rash will be reported to the study physician who will assess causality. For other adverse events, causality cannot be determined during the course of the study. It is not possible to link any individual sunburn event to the intervention, and 25(OH)D will not be measured until the end of the study, so it will not be possible to assess causality of falls and fractures.

The assignment of causality for skin rashes will be based on the definitions below

Relationship	Description
Unrelated	There is no evidence of any causal relationship
Possible	There is some evidence to suggest a causal relationship (e.g. because the event occurs shortly (within 24 hours) after administration of the trial medication). However, the influence of other factors may have contributed to the event (e.g. the participant's clinical condition, other concomitant treatments).

Probable	There is evidence to suggest a causal relationship and the influence of other factors is unlikely.
Definite	There is clear evidence to suggest a causal relationship and other possible contributing factors can be ruled out.

9.4 Procedures for Recording and Reporting Adverse Events and Serious Adverse Events

1. Participants (or their families) may contact the study at any time after randomisation to let us know of an adverse event– they will be provided with a fridge magnet including the telephone number to facilitate this. These events will be recorded in the Sun-D database.

2. Each month participants will be asked to complete a short online survey in which they will be asked to report sunburn, falls, and fractures, including frequency, and severity.

Participants reporting skin rashes will be asked about symptom onset, with respect to sunscreen application, and about any other dietary or lifestyle changes that may have contributed. Participant reporting skin rashes will be offered Hamilton Sensitive sunscreen in place of Hamilton Active Family and/or Hamilton Everyday Face sunscreen and study staff will maintain regular contact with the participant to track symptoms. If a skin rash persists with use of Hamilton Sensitive and is assessed as being probably or definitely related to the study sunscreen, the participant will be withdrawn.

An adverse event report, capturing events reported in monthly surveys and by ad-hoc reporting, will be compiled monthly and provided to the TMG and the research office for review.

In the unlikely event that a participant experiences a skin rash that is possibly, probably or definitely related to the study medication, with severity ≥3, the event will be reported to the sponsor within 24 hours of notification.

9.5 Clinical Laboratory Abnormalities

25(OH)D concentration will be measured at the end of the study. Participants will be notified of their results, and advised that if the concentration in any of the 3 samples was < 50 nmol/L they should discuss this with their regular doctor.

9.6 Laboratory Specimen Preparation, Handling, Storage and Shipment

Each participant will be asked to provide 3 blood samples (up to 17 ml/sample). At each time point (sample 1, Jun-Sept 2022; sample 2, Feb-Mar 2023; sample 3, Jul-Sept 2023) participants will be provided with either online (printable) or paper pathology collection forms to be presented at their local participating pathology laboratory. Informed consent for blood collection will be included with trial consent and obtained prior to enrolment.

Pathology laboratories will be instructed to label samples (with study identification number) and return (at ambient temperature) within 48 hrs to QIMR Berghofer sample processing unit. Once received, samples will be processed and stored in a -80°C freezer.

One serum aliquot will be used for estimation of serum 25(OH)D. Testing will be performed at the conclusion of the trial. While this will most likely occur at Metabolomics Australia, other companies may be offering this service at the time the testing is required, so we will investigate other options at that time.

To ensure the laboratory remains blinded, laboratory staff will not have access to the dataset containing participant allocation codes, and samples will be labelled with the participant identifier (as above) only.

10 Statistics

10.1 Sample Size

We have based our sample size calculations on the ANCOVA analyses, considering the following factors:

1. A minimum difference in 25(OH)D concentration between treatment groups of 10 nmol/L; this is beyond the margin of assay error and a smaller difference is unlikely to be clinically relevant.
2. 90% power and 5% significance using a one-tailed test. A one-tailed test is appropriate because if sunscreen use increases 25(OH)D concentration this will not be of clinical or public health relevance (given the very high 25(OH)D needed before toxicity occurs).
3. Correlation between baseline and subsequent 25(OH)D values of 0.6 and standard deviation of 20 nmol/L: Based on a study in which 25(OH)D was measured on 333 participants from Brisbane and Canberra in all 4 seasons (R Lucas, personal communication).
4. Non-compliance in the intervention group of 20%, and 10% uptake of daily sunscreen application in the control group.
5. Loss to follow-up of 20%.

The sample size required per group is 115. We require fully powered analyses within tertiles of ambient UVR and baseline 25(OH)D in order to devise appropriate public health and clinical messages. Thus the total sample size to be recruited is 345 per group (690 in total). With 552 participants (80%) completing the study the non-inferiority margin (90% power, α=0.05) is 4.5 nmol/L.

10.2 Analysis Objectives and Endpoints

The **primary aim** is to determine whether participants randomised to provision of a broad-spectrum SPF 50+ sunscreen, and advice to apply it to all body parts uncovered by clothing on all days when the UVI is forecast to reach 3, have a lower mean 25(OH)D concentration at the end of either summer or winter than those randomised to usual discretionary sunscreen use.

Secondary aims are to:

a. Determine whether the intervention affects 25(OH)D concentration at the end of winter or summer within tertiles of:
   i. Erythemally weighted ambient UV radiation at the postcode of usual residence
   ii. Baseline 25(OH)D concentration
b. Identify environmental and participant factors that influence the change in 25(OH)D concentration in sunscreen users.
c. Assess the effect of frequent sunscreen application on malignant and pre-malignant skin lesions during the study and over the following 2 years.

10.3 Statistical Analysis Plan

Intention-to-treat analyses: Our main analyses will follow an intention-to-treat approach. 25(OH)D values in the Australian population are approximately normally distributed so we will model 25(OH)D as a continuous outcome using longitudinal analysis of covariance (ANCOVA). We will include treatment group (daily sunscreen or control), time, and the

interaction between treatment and time to estimate the difference in 25(OH)D concentration between treatment groups at the end of summer and at the end of winter. This method has been shown to reliably estimate the effect of treatment, accounting for any differences in the baseline value of the outcome measure.[33] All models will be adjusted for the variables used to stratify the randomisation and will include baseline 25(OH)D concentration as a covariate and participant as a random effect.

We will perform the analyses within the whole cohort and separately within tertiles defined according to: (1) average ambient UVR; and (2) baseline 25(OH)D concentration.

The incidence of skin lesions between the two groups will be assessed using Poisson regression.

Sensitivity analyses: To assess the effect of lack of compliance with the sunscreen intervention in the sunscreen group, and any routine sunscreen use in the control group, we will perform:

(a) An as-treated analysis using propensity score adjustment to minimise confounding. We will categorise sunscreen use into low (<30% of eligible days), moderate (30 to <70%), and high (≥ 70%). A generalised boosted model will be used to estimate the propensity score for sunscreen use, from which we will derive inverse probability of treatment weights. These will be used as weights in the ANCOVA models, both overall and within strata.

(b) Instrumental variable principal stratification to estimate the complier average causal effect, using the randomised allocation as the instrumental variable.[34] This method preserves the randomisation

Those in the intervention group will be classified as compliant if they used sunscreen on at least 70% of eligible days, and those in the control group will be classified as compliant if they used sunscreen on fewer than 20% of eligible days.

11 Responsibilities

11.1 Investigator

The investigator will ensure that this study is carried out in accordance with the World Medical Association Declaration of Helsinki – Ethical Principles for Medical Research Involving Human Subjects, the NHMRC National Statement on Ethical Conduct in Human Research (2007) incorporating all updates and the - Notes for Guidance on Good Clinical Practice (CPMP/ICH/135/95)-Annotated with TGA comments (July, 2000 and Integrated Addendum to ICG E6(R1): Guidelines for Good Clinical Practice E6(R2) 9 November 2016)

11.1.1 Reporting to the Human Research Ethics Committee (HREC)

This protocol, the Participant Information and Consent Form and any other material that will be provided to participants will be submitted to the QIMR Berghofer HREC for approval prior to participant accrual. If approval is suspended or terminated by the HREC, the investigator will notify the Sponsor immediately.

It is the responsibility of the investigator to report study progress to the HREC at least annually, or as otherwise required by the HREC.

The investigator will be responsible for reporting serious adverse events and other applicable safety information to the HREC in accordance with the guidelines of the HREC.

11.1.2 Obtaining Informed Consent from Participants

Before enrolment into the study, each prospective participant will be given a full explanation of the nature and purpose of the study, and a copy of the Participant Information and Consent Form to review. Once the essential study information has been provided, the participant will

be asked to provide consent to participate in the study by completing online consent. The participant will be provided with a copy of their consent form to keep.

11.1.3 Protocol Modifications

The Investigator will not modify the protocol without first obtaining the agreement of QIMR Berghofer in writing. No changes to the protocol may be implemented without prior approval of QIMR Berghofer and the QIMR Berghofer HREC, unless where required to eliminate immediate risk to study participants.

It is the responsibility of the Investigator to submit the amendment to the QIMR Berghofer HREC for approval and provide a copy of the written HREC approval to the Sponsor. Protocol amendments should be signed by the lead investigator and the original signature page(s) should be forwarded to the Sponsor. Any training that is required by the amendment must be documented by the investigator and relevant site personnel. If a protocol amendment requires changes to the Participant Information and Consent Form, the revised Participant Information and Consent Form must be approved by the appropriate HREC.

11.1.4 Protocol Compliance, Deviations and Serious Breaches of GCP

All deviations from the approved protocol will be documented and reported to the Sponsor. Those deviations deemed to have a potential impact on the integrity of the study data, patient safety or the ethical acceptability of the trial will be classified as protocol violations and reported to the HREC as per HREC guidelines.

11.1.5 Data Capture

The investigator or appropriately delegated study staff members will enter all protocol-required data into a Case Report Form (CRF) (electronic – held within REDCap) for each participant enrolled in the study.

11.1.6 Essential Document Maintenance, Access and Retention

The investigator will maintain adequate and accurate records for this study, in compliance with ICH GCP Section 8. The investigator is responsible for maintaining the Investigator Site File, comprising the signed protocol / amendments, informed consent forms, CRF, curriculum vitae, financial disclosure forms, training records, Site Signature and Delegation Log and other applicable documents and correspondence.

Upon request, the investigator(s) / institution(s) will permit direct access to source data / documents for trial-related monitoring, audits, HREC review and regulatory inspection(s) by the Sponsor (or their appropriately qualified delegate) and Regulatory Authorities.

The investigator will ensure that all study documents and records are stored securely throughout the duration of the study. All study related documents and records are to be retained for a minimum of fifteen years after trial completion. Written agreement from the Sponsor must precede destruction of the same."

11.1.7 Confidentiality

Authorised personnel from QIMR Berghofer or its representatives, responsible HREC(s) or regulatory authorities may review medical records of study participants for monitoring or audit purposes to ensure compliance with this protocol and all applicable regulatory and legal requirements.

These parties will not disclose the identity of any research participant to a third party, unless permitted or required by law. All study participants will be assigned a unique identifier and no

identifying information is to be entered by the Investigator or study staff on any CRF, document or biological specimen provided to the Sponsor.

The investigator agrees that all study documents provided by the Sponsor will not be shared with third parties unless specific prior permission is granted in writing by QIMR Berghofer or such disclosure is required by federal or other laws or regulations.

11.2 Sponsor

11.2.1 Monitoring and Quality Assurance

Together with the QIMR Berghofer Research Office, the trial team will develop a Data and Safety Monitoring Plan (DSMP) commensurate with the size and complexity of the study, the level of risk to study participants, and phase of the study. The PI (or appropriately qualified delegate) will be responsible for carrying out the Data and Safety Monitoring of the trial according to the DSMP.

11.2.2 Safety and Data Monitoring and Oversight

The safety risks for participants in the Sun-D Trial will be minimal due to the fact that the trial will use an open label design, and requires usual application of an ARTG-listed product, which is readily available and widely used in the target population. To remain listed on the ARTG sunscreens are also subject to ongoing regulatory requirements and safety monitoring.[35] In addition, the enrolment process will screen out people who have a known history of allergic reaction to sunscreen products. There is also a minor safety risk associated with blood collection which will be minimised by contracting trained professionals to perform this task.

The trial will be conducted from a single site and will involve only a small number of staff. This will eliminate the risk of data inconsistencies between sites and the small team size will reduce the risk of inconsistencies produced by multiple study staff. The site has extensive experience in successfully conducting high quality large-scale clinical trials and many of the systems successfully employed in previous trials will be used in the Sun-D Trial.

As a result it is expected that the experience and qualifications of the investigator team will be sufficient to monitor its safety and success, and where necessary, take appropriate action. This will be achieved as follows.

A Trial Management Group (TMG) will be assembled. The TMG will include a subset of the investigator team and one independent member, with suitable qualifications and experience. A list of TMG members and summary of their relevant qualifications and experience is outlined in appendix 1. The project manager will provide the TMG with monthly reports including details of:

- Recruitment/Withdrawals (depending on study phase)
- Compliance
- Contamination
- Adverse events
- Survey and blood sample response rates

11.2.3 Public Registration of Clinical Trial

QIMR Berghofer Research Office will assume responsibility for including this clinical trial on a publicly accessible clinical trial register, and will ensure that the listing remains current throughout the course of the clinical trial.

11.2.4 Insurance and Indemnity

QIMR Berghofer adheres to the Medicines Australia "Guidelines for Compensation for Injury Resulting from Participation in a Company-Sponsored Clinical Trial," and holds a No-Fault Compensation for Clinical Trials insurance policy. The study sponsor agrees to indemnify the investigator(s) from any claims for damages for unexpected injuries, including death, that may be directly caused by the participant's participation in the study, but only to the extent that the claim is not caused by the fault or negligence of the participants or investigator(s), hospital, institution, ethics committee"

11.2.5 Data Management and Record Keeping

There will be no hard copy case report forms used in Sun-D. Instead, all participant information (eg randomisation code, date of randomisation, adverse events, survey return, blood sampling) will be captured and managed using REDCap[36,37] electronic data capture tools, purpose built to suit the Sun-D Trial project requirements and hosted on the secure QIMR Berghofer network that is backed up daily (see appendix 2).

REDCap is a secure web-based software platform designed for research activities. It includes a built-in audit trail, which captures all user activity, including data manipulation, data exports, and all pages viewed by each user.

11.2.6 Biological Sample Retention

Samples will be retained to enable future examination of the potential effects of regular sunscreen application on UV-induced damage in the skin. Participants will be asked to consent to future use of their samples in their baseline consent form, on the understanding that any future projects will receive HREC approval, but that they will not be notified about the use of samples.

Samples will be maintained in the QIMR Berghofer central processing laboratory, and discarded after 10 years if they have not been used prior to then.

11.2.7 Study Reporting and Publication

Publication and reporting of results and outcomes of this trial will be accurate and honest, undertaken with integrity and transparency and in accordance with QIMR Berghofer's Publication Policy. Publication of results will be subjected to fair peer-review. Authorship will be given to all persons providing significant input into the conception, design, execution or reporting of the research according to QIMR Berghofer Statement of Record Integrity. No person who is an author, consistent with this definition, will be excluded as an author without their permission in writing. Authorship will be discussed between researchers prior to study commencement (or as soon as possible thereafter) and reviewed whenever there are changes in participation. All conflicts arising through disputes about authorship will be reviewed by the QIMR Berghofer Director. Acknowledgment will be given to collaborating institutions and hospitals and other individuals and organisations providing finance or facilities. Participant confidentiality will be maintained by referring to individual participants by their identifying code used in the trial. Data will not be released publicly until the manuscript is accepted for publication. In the case of no publication, information will only be released to the public and media in accordance with QIMR Berghofer's Corporate Media Strategy Policy.

12 References

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13 Appendices

13.1 Appendix 1: Trial Monitoring Group (TMG): Member Qualification and experience summary

QIMR Berghofer-based TMG members

Prof Rachel Neale

Prof Neale has a PhD in epidemiology. She is internationally recognised for her expertise in skin cancer, sun exposure measurement, sunscreen, vitamin D, and clinical trials She leads Australia's largest medication trial (the D-Health Trial) with over 21,000 people enrolled and supplemented for 5 years, and her leadership has led to extremely high quality data (e.g. over 80% retention, over 80% compliance, over 98% survey return).

Prof David Whiteman

MBBS, PhD. Prof Whiteman is a medical epidemiologist with a long-standing global reputation for his work on melanoma and other cancers of the skin. Professor Whiteman leads the highly successful QSkin Study, a cohort of over 40,000 Australians focused on skin cancer.

A/Prof Gunter Hartel

A/Prof Hartel has a PhD in statistics and leads the statistics unit at QIMR Berghofer. He has particular expertise in analysis of randomised controlled trials, developed during 14 years as the head of statistics for a large biopharmaceutical company (CSL Ltd). He has played a vital role in the design of the Sun-D Trial, ensuring that the proposed design and sample size are robust.

Dr Mary Waterhouse

Dr Waterhouse is an early career researcher with a PhD in mathematics and experience as a consultant biostatistician. She is the lead statistician of the D-Health Trial, requiring extraordinarily complex data manipulation and analysis.

A/Prof Donald McLeod

Dr McLeod is an endocrinologist and early career researcher. He combines his research with clinical practice as a consultant endocrinologist, and brings important clinical knowledge regarding vitamin D deficiency and its consequences to the interpretation of the trial data. He will also be the study physician, ensuring that adverse events are reported in line with the protocol and causality is assigned appropriately.

A/Prof Louisa Gordon

A/Prof Gordon is a health economist with an international reputation in the economics of skin cancer prevention. Her modelling work related to sunbed use has resulted in changes in sunbed policy in Australia and internationally.

External TMG members

Adjunct A/Prof Craig Sinclair

A/Prof Sinclair is the director of the World Health Organisation's Collaborative Centre for UV radiation and head of prevention at the Cancer Council Victoria. He is also Chair of Standards Australia Sunscreen Product technical committee.

Prof Robyn Lucas

Prof Lucas is a medical epidemiologist who is renowned for her work in balancing the risks and benefits of sun exposure. She led the health chapter of the United Nations Environmental Effects Assessment Panel from 2011 until March 2019. She is principal investigator of a randomised controlled trial that has used many of the techniques that will be implemented in the Sun-D Trial.

Independent TMG member

Prof Claire Vajdic

Prof Vajdic is a cancer epidemiologist and public health researcher. She is the head of the Cancer Epidemiology Research Unit at the Centre for Big Data Research in Health where her work focuses on reducing the burden of cancer on individuals and on the Australian health care system. She is recognised nationally and internationally as a leader in research using linked administrative health data.

13.2 Appendix 2: QIMR Berghofer Web Application Security

QIMR Berghofer hosted web applications are protected by multiple security measures, which combine to provide a high level of safety for data and infrastructure.

Security measures employed are:

Enterprise Firewall

All systems at QIMR Berghofer exist behind an enterprise grade firewall. The firewall blocks traffic that is not sent to the appropriate to specific devices in a specific manor.

Application Security Firewall

The application security firewall scans for known security exploits that target web applications. These include the OWASP top 10 security threats. The list of known exploits is automatically updated to include new variants as they identified.

Intrusion Protection

Intrusion protection systems scan traffic for known and unknown security threats. This usually operates at a lower level that the application security firewalls. As with the application security firewall, a list of known exploits is automatically updated. This solution is also provided by a different vendor to the application security firewall, providing a greater protection.

Anti-Virus

All servers hosting a web application run up-to-date antivirus software which includes on access scanning. This provides a high level of anti-virus protection

Security Patching

All servers hosting a web application are regularly patched with the latest security updates. These updates are designed to fix known vulnerabilities in operating systems and software that can host web applications.

Secure Physical Access

All servers hosting a web application have restricted physical access. Only members of the ITS department can physically access the computers.

Secure Remote Access

All servers hosting a web application have restricted remote access. Only authorized system administrators can log in to the servers to run applications or change the configuration.