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Title: The ACEMID Cohort Study: protocol of a prospective cohort study using 3D total body photography for melanoma imaging and diagnosis

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Abstract

Introduction

Three-dimensional (3D) total body photography may improve early detection of melanoma and facilitate surveillance, leading to better prognosis and lower healthcare costs. The ACEMID Cohort Study will assess long-term outcomes from delivery of a precision strategy of monitoring skin lesions using skin surface imaging technology embedded into health services across Australia.

Methods and analysis

A prospective cohort study will enrol 15,000 participants aged 18 years and above, across 15 Australian sites. Participants will attend study visits according to their melanoma risk category: very high risk, high risk, or low/average risk, every 6, 12, and 24 months, respectively, over 3 years. Participants will undergo 3D total body photography and dermoscopy imaging at study visits. A baseline questionnaire will be administered to collect socio-demographic, phenotypic, quality of life and sun behaviour data. A follow-up questionnaire will be administered every 12 months to obtain changes in sun behaviour and quality of life. A saliva sample will be collected at the baseline visit from a sub-sample.

Ethics and dissemination

The ACEMID Cohort study was approved by the Metro South Health Human Research Ethics Committee (Approval number: HREC/2019/QMS/57206) and the University of Queensland Human Research Ethics Committee (Approval number: 2019003077). The findings will be reported through peer-reviewed and lay publications and presentations at conferences.

Trial registration Australian New Zealand Clinical Trials Registry (ANZCTR12619001706167).

Key words: melanocytic naevi, moles, melanoma, skin cancer, imaging, early detection, screening, 3D total body photography

Strengths and limitations of this study

- The ACEMID Cohort Study will establish the largest, world-first, prospectively collected standardised 3D total body skin surface image data collection.
- Comprehensive collection of data on personal, immunological, genetic, and clinical risk factors.
- Large sample size, recruited across 15 metropolitan and regional sites in three Australian eastern states.
- Central and western Australia are not represented, which could lead to underrepresentation of Indigenous Australians.

INTRODUCTION

Australia has the highest incidence rate of melanoma in the world, in both males (42 per 100,000 person-years) and females (31 per 100,000 person-years).[1] Melanoma is the most common invasive cancer in Australians aged 20-39 years and in the whole population it is the third most commonly diagnosed cancer in both males and females.[2] The lifetime risk of being diagnosed with invasive melanoma tripled in Australia between 1982 and 2020, mainly driven by increasing incidence among the older population, and despite melanoma incidence decreasing in younger generations who have benefited from sun protection campaigns.

The burden of melanoma on healthcare systems is significant and increasing.[3] The number of melanoma-related hospitalisations increased by 63% during 2002-2014,[4] and melanoma and keratinocyte skin cancers (including basal cell carcinoma and squamous cell carcinoma) represent over a quarter of all cancer-related hospitalisations in Australia. In addition, people living in regional or remote Australia are often disadvantaged in their access to primary healthcare and diagnostic services, which may adversely affect prognosis.[5, 6] In 2021 in Australia, the mean first-year costs of melanoma per patient ranged from AUD$644 (95% uncertainty interval [UI]: $642 to $647) for melanoma in situ to AUD$100,725 (95%UI: $84,288 to $119,070) for unresectable stage III/IV disease. Australia-wide direct health system costs for newly diagnosed patients with melanoma were just under AUD$400 million.[7] Furthermore, the quality of life for people diagnosed with melanoma and their family and friends has been shown to be negatively impacted, especially due to the fear of melanoma recurrence.[8] Identifying melanomas at an early stage is associated with good prognosis,[9] leading to reduced healthcare costs and better quality of life. Difficulties in accurately diagnosing melanoma and other skin cancers also contribute to many additional excisions for benign lesions, leading to additional costs for people and the healthcare systems. [10, 11]

The clinical diagnosis of skin cancers relies heavily on visual observation of the skin surface with the assistance of dermoscopy. Clinical images can be used to monitor skin lesions, document locations of skin lesions and monitor response to treatment. Dermatologists have traditionally employed direct visual assessment, clinical memory recall and, if available, two-dimensional (2D) digital images of the skin lesions. However, this approach is imperfect and manipulation of a three-dimensional (3D) surface such as the human skin into a 2D format can compromise accuracy. Composing a body map of a patient via 2D imaging is also time-consuming; it requires multiple separate images of the patient to be taken in a variety of different anatomical positions that may overlap or conversely fail to include lesions that have not been captured from a specific camera angle.

Our team has established the Australian Centre of Excellence in Melanoma Imaging and Diagnosis (ACEMID). The 3D total body imaging technology that is the screening modality for the ACEMID Cohort Study will allow for objective and secure imaging and collection of 3D avatars, which will be cleansed and stored securely on a national research repository.[12] Such 3D avatars enable documentation of the skin surface (except soles of

feet, scalp and areas covered by underwear) to unprecedented levels of detail. Here, we describe the protocol for the ACEMID Cohort Study that uses 3D total body photography to monitor lesions for the early detection of melanoma over a 3-year period.

METHODS AND ANALYSIS

Study design and setting

This is a prospective population-based cohort study, stratifying participants based on their calculated risk of melanoma, to undergo risk-appropriate regularity of 3D total body photography of skin lesions over a 3-year period. The delivery of 15 total body 3D imaging systems with integrated data infrastructure will be implemented across metropolitan and regional areas in the states of Queensland (QLD), New South Wales (NSW) and Victoria (VIC) in Australia.

The main aims of this study are to:

- Establish a large prospectively collected standardised 3D total body skin surface image database with tagged dermoscopy, together with scanning of pathology slides collected from excised lesions and other relevant participant information, including genomic data and Medicare claims data.
- Develop novel diagnostic algorithms using the image repository to overcome the current high degree of variability in diagnostic accuracy of melanoma and other skin cancers.
- Prospectively validate available melanoma risk tools to inform individualised risk-stratified screening and surveillance programs for the Australian population.
- Reduce the overarching burden, morbidity and mortality associated with melanoma, by helping ensure that specialist skin cancer services are targeted effectively and equitably to Australians most in need.
- Assess patient acceptability of new technologies, including 3D total body skin surface imaging, telehealth and novel diagnostics, and examine the impacts of these modalities on quality of life.
- Model the potential quality of life benefits and cost savings to the patient and the healthcare system associated with a targeted and accurate screening approach.

Study population

This study will recruit 15,000 people aged 18 years and over, across 15 sites across three eastern States of Australia at varying latitudes and in metropolitan and regional locations.

Patient and Public Involvement

Prior to obtaining funding for this project, members of the public previously involved in skin cancer research were invited to provide feedback to help inform our research plan. The ACEMID Project formed a Consumer

Working Group consisting of key researchers, representatives from melanoma advocacy groups and consumer representatives. This group has been heavily involved in the study design and progress and will continue to contribute for the duration of the study. A consumer representative will also be member of the ACEMID Executive Committee and consumers will take part in each of the three State Steering Committees. We will also conduct regular consumer forums to keep participants and the public involved in our research. Furthermore, participants will also receive regular updates on the progress of the study and other information via a study newsletter and a study website.

Inclusion criteria

Australians are eligible to participate in the ACEMID Cohort Study if they are aged 18 years or older, willing to attend multiple study visits and have a medical practitioner that can be contacted by the study team. People at any level of melanoma risk are eligible to participate.

Recruitment

A risk-stratified sample of participants will be recruited using several channels, including medical referrals, social media and traditional media (such as television news reports). Participants from previous and existing skin cancer research studies will also be invited to participate in this study. People who would like to participate are able to register their interest by sending an email to the study email address or via the contact form on the study website.

People who express interest to participate in the study or are referred to participate in the study will be contacted via telephone. At clinical sites, potential participants may be recruited during their dermatology appointments. During this contact (via telephone or in clinic), individuals will be provided with study information. If the potential participant would like to proceed, their eligibility and their risk for melanoma will be assessed, and participants will be enrolled until each risk category is filled.

Melanoma Risk Group and Intervention

At enrolment, participants will be stratified into 3 groups: low/average, high and very high risk. All individuals with a previous history of melanoma will be allocated to the very high risk group as their risk of developing a subsequent primary melanoma is very high compared to the general population.[13] For people without a previous history of melanoma, we will categorise risk levels using a validated melanoma risk tool[14] that is available online through the Melanoma Institute of Australia (https://www.melanomarisk.org.au/FirstMelLand). The online risk tool provides an individual's personal risk (lower than average, average, higher than average) that approximately corresponds to the lower quarter, middle 50%, and top quarter, respectively, of the Australian population melanoma risk distribution, based on

traditional risk factors (hair colour, naevi, family history of melanoma, personal history of keratinocyte skin cancer, sunbed use), and in comparison to someone of the same age and gender and living in the same State.

Participants with a low or average risk of melanoma will undergo 3D total body photography and dermoscopy at baseline and at 24 months (2 study visits). Participants identified as having high risk of melanoma will be seen at the clinic for repeat 3D total body photography and dermoscopy every 12 months (baseline and 3 annual study visits). Participants in the very high-risk group will undergo 3D total body photography and dermoscopy every 6 months (baseline and 6 subsequent study visits) (Figure 1). The ACEMID medical practitioner will have discretion to see participants return sooner than scheduled to monitor any changes in suspicious skin lesions.

Baseline study procedures and data collected

At the baseline study visit, research staff will discuss the Participant Information and Consent Form with potential participants and give them an opportunity to ask any questions. If consent is obtained, participants will undergo 3D total body photography, dermoscopy, a skin examination for research purposes only, and may be asked to provide a saliva sample.

Questionnaire

Participants will be asked to complete a baseline questionnaire either prior to attending the baseline study visit or during the study visit. This baseline questionnaire will collect information on personal and demographic data, history of sun exposure, sun protection strategies, skin check and skin cancer history, perceived melanoma risk and quality of life. Health-related quality of life will be collected using the Australian Assessment of Quality of Life four domains (AQoL-4D) instrument.[15-17] Participants who have a history of skin cancer will also complete the Skin Cancer Quality of Life Impact Tool (SCQOLIT).[18]

Clinical data

Melanographers and/or dermatologically-trained medical practitioners will conduct a research skin examination. Eye colour and freckling density on the face, dorsum of right hand and shoulders will be recorded (none, mild, moderate, severe). Skin colour will be clinically assessed as being very fair, fair, medium, olive, brown or dark brown on the ventral upper arm (unexposed) and dorsal forearm (exposed). Height and weight of participants will be measured. Information relating to any suspicious lesions will be recorded, including recent changes in size, shape, elevation, bleeding, itch, previous biopsy, previous cryotherapy or other ablative treatments.

3D total body photography and dermoscopy

Participants will undergo 3D total body photography (excluding skin beneath underwear, scalp and soles of feet) using a VECTRA whole-body scanner (VECTRA WB360 Serial Number WB00009, Canfield Scientific Inc, Parsippany, NJ, USA). The scanner consists of 92 cameras with white or cross-polarised lighting, which simultaneously capture images to construct a digital 3D avatar of the participant, providing a record of all pigmented and non-pigmented skin lesions.

Each participant will undress to their underwear (underwear that exposes the most skin that the participant is comfortable with) with hair tied up if applicable. Participants will be instructed on the correct stance and posture for scanning; the 3D image will then be captured in approximately 5 seconds and the 3D avatar digitally will be constructed in approximately 10 minutes. Participants may be offered their images on a password-protected Universal Serial Bus device, for their reference and to take to routine visits to their medical practitioner if required.

Dermoscopic images (non-polarised or polarised depending on site dermatologist's discretion) will be taken of any skin lesions that are of concern to the study participant or dermatologically-trained melanographer using a Visiomed D200e dermatoscope (Canfield Scientific Inc, Parsippany, NJ, USA) attached to the VECTRA. Any lesions 5mm or greater in diameter will also be dermoscopically imaged, with a maximum of 50 lesions per participant.

Collection of biological samples

A convenience sample of participants will be asked to provide a saliva sample. Saliva samples will be collected using an Oragene DNA self-collection kit (DNA Genotek) according to the standards recommended by the Royal College of Pathologists of Australasia for medical genetic testing (Position Statement 3/2007), adopting the guidelines for Specimen Labelling at Point of Collection (1/2006). Depending on the available study resources, some participants may also be asked to provide a blood, tissue or urine sample at the baseline visit, as approved by the ethics committee. Donation of biospecimens including saliva, blood, urine, and/or tissue samples is voluntary, and will not affect the participant's inclusion in the cohort study if they do not wish to donate biospecimens.

Collection of Healthcare use

Medicare claims data through linkage from Services Australia has been approved (Services Australia EREC approval RMS1199) for 4.5 years of data from the participant's baseline visit date. This will include Medicare item number and description, provider charge, schedule fee (AUD$), patient out-of-pocket cost and prescribed medicines, for the duration of the study period. These de-identified data will be used to analyse the type, volume and cost of healthcare used per participant and for the cohort. Consent for this data is optional and will be obtained via a separate consent form.

Follow-up study procedures

Participants will undergo repeat 3D total body imaging, dermoscopy and clinical examination every 24, 12 or 6 months based on if they are in the low/average risk, high risk or very high risk group, respectively (Figure 1). At the 12-monthly follow-up visits, a follow-up questionnaire will be administered to assess changes in sun behaviour, skin cancer diagnoses and quality of life. Participants in the low/average group will complete their 12-month and 36-month questionnaire online. For all risk groups, at the 24-month follow-up visit, a questionnaire on the acceptability of 3D total body photography will also be administered to obtain feedback on this technology.

Identification of suspicious lesions

During the study period, lesions identified by the melanographer or study dermatologist as suspicious for malignancy will be referred to the participant's clinician for management. A report including images of any lesions requiring management will be sent to the participant's nominated treating medical practitioner. Any referrals will be followed up and pathology reports requested.

As per routine clinical practice, skin biopsies and excisions will be sent to accredited pathology laboratories to be processed and diagnosed using standard histology practices. Pathology reports of all skin biopsies or excisions in study participants will be collected by the study team. Following the generation of a pathology report, some of the slides used for microscopic diagnosis may undergo digital scanning (all melanomas, borderline lesions and 10% of benign lesions will be randomly selected). Whole slide scans will be reviewed by 2-3 pathologists to confirm diagnoses.

Participant reimbursement

Monetary reimbursements will not be provided to participants in this study.

Standard Operating Procedure adherence checks

Adherence at sites to the Standard Operating Procedures of the study will be monitored on a quarterly basis to ensure standardised quality of data produced at each of the 15 sites. These checks will be conducted by the respective ACEMID managers in QLD, NSW and VIC.

Data collection and storage

Clinical and questionnaire data will be recorded on the REDCap system, a secure study database software built by Vanderbilt University and hosted by Monash University, Melbourne, Australia (https://redcap.helix.monash.edu).

Pathology reports will be obtained from each State's (Queensland, New South Wales, Victoria) cancer registry and pathology laboratories; redacted and uploaded onto the REDCap database. Claims and health service data will be collected by linkage from the Medicare Benefits Schedule (MBS) and the Pharmaceutical Benefits Scheme (PBS), via a separate consent form approved by Services Australia.

Cleansed image data (de-identified and/or without demographic data) will be stored in the national ACEMID research repository. Access to the research repository will be controlled and governed by the ACEMID Data Governance Working Group using secure software platforms, including Extensible Neuroimaging Archive Toolkit (XNAT) and relevant Universities' Secure eResearch Platforms (SeRP) and Keypoint.

Participant data will be handled with utmost confidentiality. A participant log will be kept where a coded ID number will be allocated to each participant, which will be kept securely and separately from other data. All images, questionnaires, forms, medical reports, samples and genetic data will only have the participant ID number to protect their privacy.

Data Processing and analysis

Sample size

The ACEMID Cohort Study aims to recruit 15,000 participants, with quota sampling employed to recruit 3000 participants (20%) in the low/average melanoma risk group, 9000 participants (60%) in the high risk group and 3000 participants (20%) in the very high risk group.

Based on previous studies, from baseline to 36 months we anticipate a participant dropout rate of up to 20%, 10% and 10% in the low/average, high and very high risk groups, respectively.

Based on the melanoma incidence in previous studies conducted in New South Wales and Queensland,[19, 20] we conservatively expect to observe a melanoma incidence rate over the 3-year study follow-up of 0.4% (n=8), 2% (n=162) and 5% (n=135) in the low/average, high and very high risk groups, respectively.[21]

Power calculations were conducted to ensure the sample size is sufficient to detect associations between new melanomas (yes/no) and potential risk factors in both the high risk and very high risk groups. Based on the numbers above, we will have at least 80% power to detect a relative risk of 2 comparing risk factor presence and absence, for a risk factor that has prevalence 10% in each of the high and very high risk groups, assuming a two-sided alpha of 0.05. In analyses for which multiple comparisons may be of concern, for example broad-based genetic markers, a more stringent alpha may be appropriate. In this case with a lower alpha (0.001, two-sided) we will have at least 80% power to detect a relative risk of 2.3 in the high risk group, and 2.5 in the very high risk group, for a risk factor with prevalence of 10% in each group.

We expect a small number of new melanomas in the low/average melanoma risk group and therefore we examine power for associations between risk factors and new keratinocyte cancers in this group. Based on an expectation of approximately 67 keratinocyte cancers per 1 melanoma,[22] we anticipate 6.7% of the low/average risk group will develop a new keratinocyte cancer over 2 years of follow-up. Based on this, we will have 89% power to detect a relative risk of 2, for a risk factor that is prevalent in only 10% of the low/average risk group with 89% power and assuming a two-sided alpha of 0.05. As above, for analyses in which multiple comparisons may be of concern, with a two-sided alpha of 0.001, there is 91% power to detect a relative risk of 2.5, for a risk factor that is prevalent in only 10% of the low/average risk group.

Genomic analysis

The saliva samples will be processed to extract DNA. Once extracted, the DNA will be quantified using either the Nanodrop spectrophotometer or the Qubit 2.0 fluorometer along with the Qubit dsDNA BR Assay kits (Thermo Scientific). The DNA will be stored at a temperature of -20°C. A minimum of 2 micrograms of the extracted DNA will be submitted for genotyping.

Statistical analysis

For the cross-sectional data, descriptive statistical analyses including counts and proportions will be used to describe the total number of in situ and advanced melanoma, keratinocyte cancers, and pigmented and non-pigmented skin lesions (≥ 2mm and ≥ 5mm). These skin lesions will be analysed and summarised according to melanoma risk group, sex, age and body site. Descriptive statistics will be used to summarise dermoscopic features of pigmented skin lesions by body site. Cross-sectional associations will be quantified by regression methods suited to the measurement scale of each outcome.

To assess the unadjusted and adjusted strength of association between participants' phenotypic or genotypic characteristics and lesion outcomes, linear and log-linear (relative risk) regression models will be fitted, for continuous and binary/count outcomes respectively. Where multiple lesion outcomes per participant are included the model for mean outcome will be fit using generalised estimating equations with an exchangeable working correlation matrix and robust standard errors. The adjusted models will include explanatory factors (for example skin type) according to a causal diagram. Interaction terms will also be fitted where appropriate (for example phenotype and genotype) to explain lesion counts or distributions.

Additional longitudinal analysis will include spatio-temporal models to analyse lesion distribution patterns over time, and whether changes are associated with a naevus cluster, or a specific body site, in each of the risk groups. Age, sex, and residence-based geographical and socio-economic status related information are available to assess response bias effects. To further assess effects of response bias, we will compare traits including naevus counts to those of other studies in well-characterised community and clinical populations.

Performance of melanoma and keratinocyte risk prediction models based on self-reported risk factors will be assessed throughout the study period, overall and in different population subgroups. Discrimination will be assessed using area under the receiver operating characteristic curve (AUC) at a single time-point and c-index with censored data, and net reclassification improvement. Calibration will be assessed using calibration plots. Objective measures of phenotypic risk from imaging, together with behavioural and genomic risk factors, will be assessed in their ability to further discriminate risk of developing melanoma and keratinocyte cancers.

Macroscopic, dermoscopic and histologic imaging data, lesion history and de-identified participant risk data will be stored in a national research repository for development of diagnostic algorithms. Machine learning, including convolutional neural networks and support vector machine algorithms will be applied to training data sets and evaluated in test sets. The impact of including metadata, including genomic data and other risk factors, on diagnostic accuracy will be assessed in these analyses. The relative benefit of including macroscopic and dermoscopic data with histology image data will also be assessed.

Economic analysis

Utility-based quality of life will be assessed using scores from the AQoL-4D instrument at baseline, 12 and 24 months for the cohort during the study period, and used to calculate quality-adjusted survival at 24 months. Data relating to treatment costs, hospitalisations, participant time and effort required to participate, convenience of location, acceptability of the technology, out-of-pocket expenses and changes in productivity associated with referrals will be collected. Total costs, including use of AI-based diagnosis, and total outcomes expressed as QALYs gained for this cohort, will be calculated and reported as mean values with standard deviations and 95% confidence intervals. A comparison of healthcare use 12 months prior and 48 months after enrolment in the cohort study will be undertaken using MBS and PBS data. Mean annual and total healthcare use, costs and QALYs will be quantified for the cohort, pre and post inception. A budget impact analysis (BIA) will be modelled using best practice methods[23-25] over a 5 year timeframe. In this BIA, several scenarios will be investigated for the provision of services in a staged implementation in which 50% of eligible Australians will access 3D total body photography in year 1, subsequently rising to 60% in year 2, 70% in year 3, 80% in year 4 and 90% in year 5.

Ethics and dissemination

Ethics approval has been obtained by the Metro South Human Research Ethics Committee (approval number: HREC/2019/QMS/57206) and the University of Queensland Human Research Ethics Committee (Approval number: 2019003077). The trial is prospectively registered on the Australian New Zealand Clinical Trials Registry (ANZCTR12619001706167). The protocol adheres to the Standard Protocol Items Recommendations

for Interventional Trials (SPIRIT) statement.[26] The findings from this study will be circulated through peer-reviewed publications, conferences, policy documents and media outlets.

Conclusions

This project will create a large dataset which accurately represents each person's skin lesion microcosmos in detail, data that is not currently available. This project will therefore greatly improve the understanding of risk-stratified early detection of melanoma and demonstrate whether longitudinal imaging analyses and genomic information can improve risk prediction. This data will also be informative for image-based algorithm development, and clinician diagnostic support. Information obtained from this study may inform policies and clinical practice guidelines for early detection or prevention of melanoma, lead to better patient education and translation into adequate survivorship care. Overall results will be used to advise policy makers on the expected future projection of the use of healthcare resources and show the impact of melanoma prevention on long-term health outcomes. This program of research will also contribute towards developing evidence for a national targeted screening program for melanoma.

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Author contributions

UK, AEC, PFP, CH, GJM, VM, RLM, HPS, RW, MS, GK, EJP, RAM, MJ and ACEMID Research Team were all involved in developing the study protocol. AEC, PFP, GJM, VM, RLM, HPS, RW, MJ and others worked together on the funding proposal. RW provided support for the development of the statistical analysis plan. RLM and RAM provided the health economics analysis. All authors have reviewed, edited and approved the final version.

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Competing interests

HPS is a shareholder of MoleMap NZ Limited and e-derm consult GmbH and undertakes regular teledermatological reporting for both companies. HPS is a Medical Consultant for Canfield Scientific Inc, Blaze Bioscience Inc, and a Medical Advisor for First Derm.

VM has received speakers fees from Novartis, Bristol Myers Squibb, Merck, Janssen and conference sponsorship from L'Oreal.

PFP has consulted for Leo, Amgen, Abbvie, UCB, Sanofi, Janssen, Novartis, BMS, MSD, Pfizer and Lilly. PFP has received speakers fees from Janssen, Leo, Amgen, Sanofi, Lilly, Abbvie, UCB, Novartis, Merck and Pfizer.

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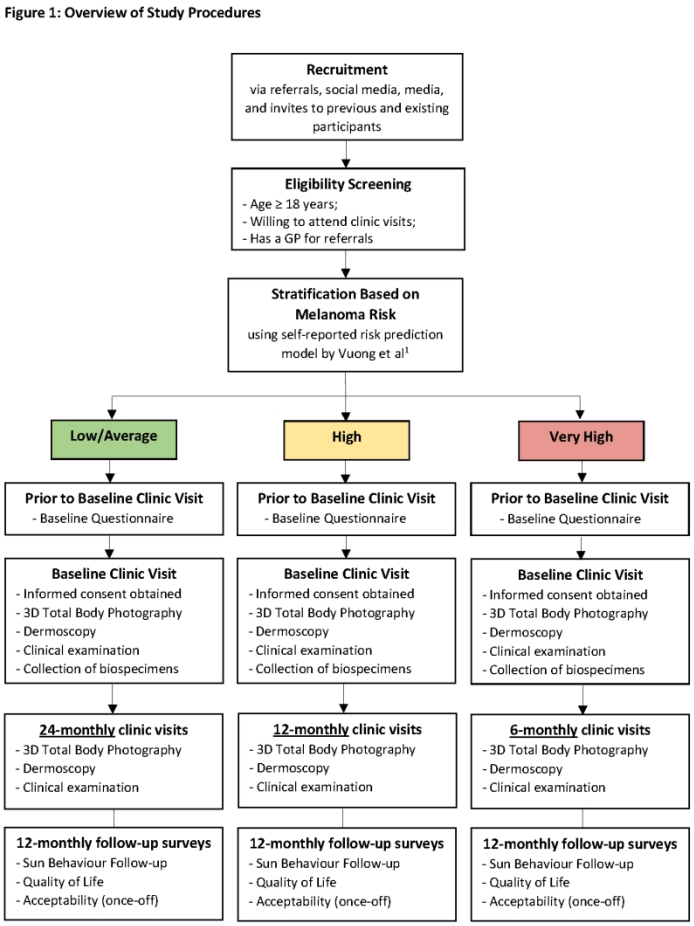

Figure 1: Overview of Study Procedures

531x752mm (79 x 79 DPI)

SPIRIT 2013 Checklist: Recommended items to address in a clinical trial protocol and related documents*

Section/item	Item No	Description
Administrative information		
Title	1	Descriptive title identifying the study design, population, interventions, and, if applicable, trial acronym
Trial registration	2a	Trial identifier and registry name. If not yet registered, name of intended registry
	2b	All items from the World Health Organization Trial Registration Data Set
Protocol version	3	Date and version identifier
Funding	4	Sources and types of financial, material, and other support
Roles and responsibilities	5a	Names, affiliations, and roles of protocol contributors
	5b	Name and contact information for the trial sponsor
	5c	Role of study sponsor and funders, if any, in study design; collection, management, analysis, and interpretation of data; writing of the report; and the decision to submit the report for publication, including whether they will have ultimate authority over any of these activities
	5d	Composition, roles, and responsibilities of the coordinating centre, steering committee, endpoint adjudication committee, data management team, and other individuals or groups overseeing the trial, if applicable (see Item 21a for data monitoring committee)
Introduction		
Background and rationale	6a	Description of research question and justification for undertaking the trial, including summary of relevant studies (published and unpublished) examining benefits and harms for each intervention
	6b	Explanation for choice of comparators
Objectives	7	Specific objectives or hypotheses
Trial design	8	Description of trial design including type of trial (eg, parallel group, crossover, factorial, single group), allocation ratio, and framework (eg, superiority, equivalence, noninferiority, exploratory)

Methods: Participants, interventions, and outcomes

Study setting	9	Description of study settings (eg, community clinic, academic hospital) and list of countries where data will be collected. Reference to where list of study sites can be obtained
Eligibility criteria	10	Inclusion and exclusion criteria for participants. If applicable, eligibility criteria for study centres and individuals who will perform the interventions (eg, surgeons, psychotherapists)
Interventions	11a	Interventions for each group with sufficient detail to allow replication, including how and when they will be administered
	11b	Criteria for discontinuing or modifying allocated interventions for a given trial participant (eg, drug dose change in response to harms, participant request, or improving/worsening disease)
	11c	Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence (eg, drug tablet return, laboratory tests)
	11d	Relevant concomitant care and interventions that are permitted or prohibited during the trial
Outcomes	12	Primary, secondary, and other outcomes, including the specific measurement variable (eg, systolic blood pressure), analysis metric (eg, change from baseline, final value, time to event), method of aggregation (eg, median, proportion), and time point for each outcome. Explanation of the clinical relevance of chosen efficacy and harm outcomes is strongly recommended
Participant timeline	13	Time schedule of enrolment, interventions (including any run-ins and washouts), assessments, and visits for participants. A schematic diagram is highly recommended (see Figure)
Sample size	14	Estimated number of participants needed to achieve study objectives and how it was determined, including clinical and statistical assumptions supporting any sample size calculations
Recruitment	15	Strategies for achieving adequate participant enrolment to reach target sample size

Methods: Assignment of interventions (for controlled trials)

Allocation:

Sequence generation	16a	Method of generating the allocation sequence (eg, computer-generated random numbers), and list of any factors for stratification. To reduce predictability of a random sequence, details of any planned restriction (eg, blocking) should be provided in a separate document that is unavailable to those who enrol participants or assign interventions

Allocation concealment mechanism	16b	Mechanism of implementing the allocation sequence (eg, central telephone; sequentially numbered, opaque, sealed envelopes), describing any steps to conceal the sequence until interventions are assigned
Implementation	16c	Who will generate the allocation sequence, who will enrol participants, and who will assign participants to interventions
Blinding (masking)	17a	Who will be blinded after assignment to interventions (eg, trial participants, care providers, outcome assessors, data analysts), and how
	17b	If blinded, circumstances under which unblinding is permissible, and procedure for revealing a participant's allocated intervention during the trial
Methods: Data collection, management, and analysis		
Data collection methods	18a	Plans for assessment and collection of outcome, baseline, and other trial data, including any related processes to promote data quality (eg, duplicate measurements, training of assessors) and a description of study instruments (eg, questionnaires, laboratory tests) along with their reliability and validity, if known. Reference to where data collection forms can be found, if not in the protocol
	18b	Plans to promote participant retention and complete follow-up, including list of any outcome data to be collected for participants who discontinue or deviate from intervention protocols
Data management	19	Plans for data entry, coding, security, and storage, including any related processes to promote data quality (eg, double data entry; range checks for data values). Reference to where details of data management procedures can be found, if not in the protocol
Statistical methods	20a	Statistical methods for analysing primary and secondary outcomes. Reference to where other details of the statistical analysis plan can be found, if not in the protocol
	20b	Methods for any additional analyses (eg, subgroup and adjusted analyses)
	20c	Definition of analysis population relating to protocol non-adherence (eg, as randomised analysis), and any statistical methods to handle missing data (eg, multiple imputation)
Methods: Monitoring		
Data monitoring	21a	Composition of data monitoring committee (DMC); summary of its role and reporting structure; statement of whether it is independent from the sponsor and competing interests; and reference to where further details about its charter can be found, if not in the protocol. Alternatively, an explanation of why a DMC is not needed

	21b	Description of any interim analyses and stopping guidelines, including who will have access to these interim results and make the final decision to terminate the trial
Harms	22	Plans for collecting, assessing, reporting, and managing solicited and spontaneously reported adverse events and other unintended effects of trial interventions or trial conduct
Auditing	23	Frequency and procedures for auditing trial conduct, if any, and whether the process will be independent from investigators and the sponsor

Ethics and dissemination

Research ethics approval	24	Plans for seeking research ethics committee/institutional review board (REC/IRB) approval
Protocol amendments	25	Plans for communicating important protocol modifications (eg, changes to eligibility criteria, outcomes, analyses) to relevant parties (eg, investigators, REC/IRBs, trial participants, trial registries, journals, regulators)
Consent or assent	26a	Who will obtain informed consent or assent from potential trial participants or authorised surrogates, and how (see Item 32)
	26b	Additional consent provisions for collection and use of participant data and biological specimens in ancillary studies, if applicable
Confidentiality	27	How personal information about potential and enrolled participants will be collected, shared, and maintained in order to protect confidentiality before, during, and after the trial
Declaration of interests	28	Financial and other competing interests for principal investigators for the overall trial and each study site
Access to data	29	Statement of who will have access to the final trial dataset, and disclosure of contractual agreements that limit such access for investigators
Ancillary and post-trial care	30	Provisions, if any, for ancillary and post-trial care, and for compensation to those who suffer harm from trial participation
Dissemination policy	31a	Plans for investigators and sponsor to communicate trial results to participants, healthcare professionals, the public, and other relevant groups (eg, via publication, reporting in results databases, or other data sharing arrangements), including any publication restrictions
	31b	Authorship eligibility guidelines and any intended use of professional writers
	31c	Plans, if any, for granting public access to the full protocol, participant-level dataset, and statistical code

Appendices

Informed consent materials	32	Model consent form and other related documentation given to participants and authorised surrogates
Biological specimens	33	Plans for collection, laboratory evaluation, and storage of biological specimens for genetic or molecular analysis in the current trial and for future use in ancillary studies, if applicable

*It is strongly recommended that this checklist be read in conjunction with the SPIRIT 2013 Explanation & Elaboration for important clarification on the items. Amendments to the protocol should be tracked and dated. The SPIRIT checklist is copyrighted by the SPIRIT Group under the Creative Commons "Attribution-NonCommercial-NoDerivs 3.0 Unported" license.

STROBE 2007 (v4) Statement—Checklist of items that should be included in reports of *cohort studies*

Section/Topic	Item #	Recommendation	Reported on page #
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract	1
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found	2
Introduction			
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	4-5
Objectives	3	State specific objectives, including any prespecified hypotheses	5
Methods			
Study design	4	Present key elements of study design early in the paper	5
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	5
Participants	6	(*a*) Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up	6-7
		(*b*) For matched studies, give matching criteria and number of exposed and unexposed	N/A
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	11-12
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	7-9
Bias	9	Describe any efforts to address potential sources of bias	11-12
Study size	10	Explain how the study size was arrived at	10-11
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	11-12
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding	11-12
		(*b*) Describe any methods used to examine subgroups and interactions	11-12
		(*c*) Explain how missing data were addressed	11-12
		(*d*) If applicable, explain how loss to follow-up was addressed	10-11
		(*e*) Describe any sensitivity analyses	N/A
Results			

Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed	N/A – protocol paper
		(b) Give reasons for non-participation at each stage	N/A – protocol paper
		(c) Consider use of a flow diagram	N/A – protocol paper
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders	N/A – protocol paper
		(b) Indicate number of participants with missing data for each variable of interest	N/A – protocol paper
		(c) Summarise follow-up time (eg, average and total amount)	N/A – protocol paper
Outcome data	15*	Report numbers of outcome events or summary measures over time	N/A – protocol paper
Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included	N/A – protocol paper
		(*b*) Report category boundaries when continuous variables were categorized	N/A – protocol paper
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	N/A – protocol paper
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	N/A – protocol paper
Discussion			
Key results	18	Summarise key results with reference to study objectives	N/A – protocol paper
Limitations			
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	N/A – protocol paper
Generalisability	21	Discuss the generalisability (external validity) of the study results	N/A – protocol paper
Other information			
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	13

*Give information separately for cases and controls in case-control studies and, if applicable, for exposed and unexposed groups in cohort and cross-sectional studies.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at www.strobe-statement.org.

BMJ Open

The ACEMID Cohort Study: protocol of a prospective cohort study using 3D total body photography for melanoma imaging and diagnosis

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Primary Subject Heading:	Dermatology
Secondary Subject Heading:	Public health
Keywords:	DERMATOLOGY, Adult dermatology < DERMATOLOGY, Epidemiology < ONCOLOGY, Dermatopathology < PATHOLOGY, PUBLIC HEALTH

Title: The ACEMID Cohort Study: protocol of a prospective cohort study using 3D total body photography for melanoma imaging and diagnosis

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Word count: 3955

Abstract

Introduction

Three-dimensional (3D) total body photography may improve early detection of melanoma and facilitate surveillance, leading to better prognosis and lower healthcare costs. The ACEMID Cohort Study will assess long-term outcomes from delivery of a precision strategy of monitoring skin lesions using skin surface imaging technology embedded into health services across Australia.

Methods and analysis

A prospective cohort study will enrol 15,000 participants aged 18 years and above, across 15 Australian sites. Participants will attend study visits according to their melanoma risk category: very high risk, high risk, or low/average risk, every 6, 12, and 24 months, respectively, over 3 years. Participants will undergo 3D total body photography and dermoscopy imaging at study visits. A baseline questionnaire will be administered to collect socio-demographic, phenotypic, quality of life and sun behaviour data. A follow-up questionnaire will be administered every 12 months to obtain changes in sun behaviour and quality of life. A saliva sample will be collected at the baseline visit from a sub-sample.

Ethics and dissemination

The ACEMID Cohort study was approved by the Metro South Health Human Research Ethics Committee (Approval number: HREC/2019/QMS/57206) and the University of Queensland Human Research Ethics Committee (Approval number: 2019003077). The findings will be reported through peer-reviewed and lay publications and presentations at conferences.

Trial registration Australian New Zealand Clinical Trials Registry (ACTRN12619001706167).

Key words: melanocytic naevi, moles, melanoma, skin cancer, imaging, early detection, screening, 3D total body photography

Strengths and limitations of this study

- The ACEMID Cohort Study will establish the largest, world-first, prospectively collected standardised 3D total body skin surface image data collection.
- Comprehensive collection of data on personal, immunological, genetic, and clinical risk factors.
- Large sample size, recruited across 15 metropolitan and regional sites in three Australian eastern states.
- Central and western Australia are not represented, which could lead to underrepresentation of Indigenous Australians.

INTRODUCTION

Australia has the highest incidence rate of melanoma in the world, in both males (42 per 100,000 person-years) and females (31 per 100,000 person-years).(1) Melanoma is the most common invasive cancer in Australians aged 20-39 years and in the whole population it is the third most commonly diagnosed cancer in both males and females.(2) The lifetime risk of being diagnosed with invasive melanoma tripled in Australia between 1982 and 2020, mainly driven by increasing incidence among the older population, and despite melanoma incidence decreasing in younger generations who have benefited from sun protection campaigns.

The burden of melanoma on healthcare systems is significant and increasing.(3) The number of melanoma-related hospitalisations increased by 63% during 2002-2014,(4) and melanoma and keratinocyte skin cancers (including basal cell carcinoma and squamous cell carcinoma) represent over a quarter of all cancer-related hospitalisations in Australia. In addition, people living in regional or remote Australia are often disadvantaged in their access to primary healthcare and diagnostic services, which may adversely affect prognosis.(5, 6) In 2021 in Australia, the mean first-year costs of melanoma per patient ranged from AUD$644 (95% uncertainty interval [UI]: $642 to $647) for melanoma in situ to AUD$100,725 (95%UI: $84,288 to $119,070) for unresectable stage III/IV disease. Australia-wide direct health system costs for newly diagnosed patients with melanoma were just under AUD$400 million.(7) Furthermore, the quality of life for people diagnosed with melanoma and their family and friends has been shown to be negatively impacted, especially due to the fear of melanoma recurrence.(8) Identifying melanomas at an early stage is associated with good prognosis,(9) leading to reduced healthcare costs and better quality of life. Difficulties in accurately diagnosing melanoma and other skin cancers also contribute to many additional excisions for benign lesions, leading to additional costs for people and the healthcare systems.(10, 11)

The clinical diagnosis of skin cancers relies heavily on visual observation of the skin surface with the assistance of dermoscopy. Clinical images can be used to monitor skin lesions, document locations of skin lesions and monitor response to treatment. Dermatologists have traditionally employed direct visual assessment, clinical memory recall and, if available, two-dimensional (2D) digital images of the skin lesions. However, this approach is imperfect and manipulation of a three-dimensional (3D) surface such as the human skin into a 2D format can compromise accuracy. Composing a body map of a patient via 2D imaging is also time-consuming; it requires multiple separate images of the patient to be taken in a variety of different anatomical positions that may overlap or conversely fail to include lesions that have not been captured from a specific camera angle.

Our team has established the Australian Centre of Excellence in Melanoma Imaging and Diagnosis (ACEMID). The 3D total body imaging technology that is the screening modality for the ACEMID Cohort Study will allow for objective and secure imaging and collection of 3D avatars, which will be cleansed and stored securely on a national research repository.(12) Such 3D avatars enable documentation of the skin surface (except soles

of feet, scalp and areas covered by underwear) to unprecedented levels of detail. Here, we describe the protocol for the ACEMID Cohort Study that uses 3D total body photography to monitor lesions for the early detection of melanoma over a 3-year period.

METHODS AND ANALYSIS

Study design and setting

This is a prospective population-based cohort study, stratifying participants based on their calculated risk of melanoma, to undergo risk-appropriate regularity of 3D total body photography of skin lesions over a 3-year period. The delivery of 15 total body 3D imaging systems with integrated data infrastructure will be implemented across metropolitan and regional areas in the states of Queensland (QLD), New South Wales (NSW) and Victoria (VIC) in Australia.

The main aims of this study are to:

- Establish a large prospectively collected standardised 3D total body skin surface image database with tagged dermoscopy, together with scanning of pathology slides collected from excised lesions and other relevant participant information, including genomic data and Medicare claims data.
- Develop novel diagnostic algorithms using the image repository to overcome the current high degree of variability in diagnostic accuracy of melanoma and other skin cancers.
- Prospectively validate available melanoma risk tools to inform individualised risk-stratified screening and surveillance programs for the Australian population.
- Reduce the overarching burden, morbidity and mortality associated with melanoma, by helping ensure that specialist skin cancer services are targeted effectively and equitably to Australians most in need.
- Assess patient acceptability of new technologies, including 3D total body skin surface imaging, telehealth and novel diagnostics, and examine the impacts of these modalities on quality of life.
- Model the potential quality of life benefits and cost savings to the patient and the healthcare system associated with a targeted and accurate screening approach.

Study population

This study will recruit 15,000 people aged 18 years and over, across 15 sites across three eastern States of Australia at varying latitudes and in metropolitan and regional locations.

Patient and Public Involvement

Prior to obtaining funding for this project, members of the public previously involved in skin cancer research were invited to provide feedback to help inform our research plan. The ACEMID Project formed a Consumer

Working Group consisting of key researchers, representatives from melanoma advocacy groups and consumer representatives. This group has been heavily involved in the study design and progress and will continue to contribute for the duration of the study. A consumer representative will also be member of the ACEMID Executive Committee and consumers will take part in each of the three State Steering Committees. We will also conduct regular consumer forums to keep participants and the public involved in our research. Furthermore, participants will also receive regular updates on the progress of the study and other information via a study newsletter and a study website, to aid study retention.

Inclusion criteria

Australians are eligible to participate in the ACEMID Cohort Study if they are aged 18 years or older, willing to attend multiple study visits and have a medical practitioner that can be contacted by the study team. People at any level of melanoma risk are eligible to participate.

Recruitment

A risk-stratified sample of participants will be recruited using several channels, including medical referrals, social media and traditional media (such as television news reports). Participants from previous and existing skin cancer research studies will also be invited to participate in this study. People who would like to participate are able to register their interest by sending an email to the study email address or via the contact form on the study website.

People who express interest to participate in the study or are referred to participate in the study will be contacted via telephone. At clinical sites, potential participants may be recruited during their dermatology appointments. During this contact (via telephone or in clinic), individuals will be provided with study information. If the potential participant would like to proceed, their eligibility and their risk for melanoma will be assessed, and participants will be enrolled until each risk category is filled.

Melanoma Risk Group and Intervention

At enrolment, participants will be stratified into 3 groups: low/average, high and very high risk. All individuals with a previous history of melanoma will be allocated to the very high risk group as their risk of developing a subsequent primary melanoma is very high compared to the general population.(13) For people without a previous history of melanoma, we will categorise risk levels using a validated melanoma risk tool(14) that is available online through the Melanoma Institute of Australia (https://www.melanomarisk.org.au/FirstMelLand). The online risk tool provides an individual's personal risk (lower than average, average, higher than average) that approximately corresponds to the lower quarter, middle 50%, and top quarter, respectively, of the Australian population melanoma risk distribution, based on

traditional risk factors (hair colour, naevi, family history of melanoma, personal history of keratinocyte skin cancer, sunbed use), and in comparison to someone of the same age and gender and living in the same State.

Participants with a low or average risk of melanoma will undergo 3D total body photography and dermoscopy at baseline and at 24 months (2 study visits). Participants identified as having high risk of melanoma will be seen at the clinic for repeat 3D total body photography and dermoscopy every 12 months (baseline and 3 annual study visits). Participants in the very high-risk group will undergo 3D total body photography and dermoscopy every 6 months (baseline and 6 subsequent study visits) (Figure 1). The ACEMID medical practitioner will have discretion to see participants return sooner than scheduled to monitor any changes in suspicious skin lesions.

Baseline study procedures and data collected

At the baseline study visit, research staff will discuss the Participant Information and Consent Form with potential participants and give them an opportunity to ask any questions. If consent is obtained, participants will undergo 3D total body photography, dermoscopy, a skin examination for research purposes only, and may be asked to provide a saliva sample.

Questionnaire

Participants will be asked to complete a baseline questionnaire either prior to attending the baseline study visit or during the study visit. This baseline questionnaire will collect information on personal and demographic data, history of sun exposure, sun protection strategies, skin check and skin cancer history, perceived melanoma risk and quality of life. Health-related quality of life will be collected using the Australian Assessment of Quality of Life four domains (AQoL-4D) instrument.(15-17) Participants who have a history of skin cancer will also complete the Skin Cancer Quality of Life Impact Tool (SCQOLIT).(18)

Clinical data

Melanographers and/or dermatologically-trained medical practitioners will conduct a research skin examination. Eye colour and freckling density on the face, dorsum of right hand and shoulders will be recorded (none, mild, moderate, severe). Skin colour will be clinically assessed as being very fair, fair, medium, olive, brown or dark brown on the ventral upper arm (unexposed) and dorsal forearm (exposed), using a standard colour chart. Skin colour will also be assessed objectively using the 3D total body photography once validated algorithms for this purpose have been developed. Height and weight of participants will be measured. Information relating to any suspicious lesions will be recorded, including recent changes in size, shape, elevation, bleeding, itch, previous biopsy, previous cryotherapy or other ablative treatments.

3D total body photography and dermoscopy

Participants will undergo 3D total body photography (excluding skin beneath underwear, scalp and soles of feet) using a VECTRA whole-body scanner (VECTRA WB360 Serial Number WB00009, Canfield Scientific Inc, Parsippany, NJ, USA). The scanner consists of 92 cameras with white or cross-polarised lighting, which simultaneously capture images to construct a digital 3D avatar of the participant, providing a record of all pigmented and non-pigmented skin lesions.

Each participant will undress to their underwear (underwear that exposes the most skin that the participant is comfortable with) with hair tied up if applicable. Participants will be instructed on the correct stance and posture for scanning; the 3D image will then be captured in approximately 5 seconds and the 3D avatar digitally will be constructed in approximately 10 minutes. Participants may be offered their images on a password-protected Universal Serial Bus device, for their reference and to take to routine visits to their medical practitioner if required.

Dermoscopic images (non-polarised or polarised depending on site dermatologist's discretion) will be taken of any skin lesions that are of concern to the study participant or dermatologically-trained melanographer using a Visiomed D200e dermatoscope (Canfield Scientific Inc, Parsippany, NJ, USA) attached to the VECTRA. Any lesions 5mm or greater in diameter will also be dermoscopically imaged, with a maximum of 50 lesions per participant.

Collection of biological samples

A convenience sample of participants will be asked to provide a saliva sample. Saliva samples will be collected using an Oragene DNA self-collection kit (DNA Genotek) according to the standards recommended by the Royal College of Pathologists of Australasia for medical genetic testing (Position Statement 3/2007), adopting the guidelines for Specimen Labelling at Point of Collection (1/2006). Depending on the available study resources, some participants may also be asked to provide a blood, tissue or urine sample at the baseline visit, as approved by the ethics committee. Donation of biospecimens including saliva, blood, urine, and/or tissue samples is voluntary, and will not affect the participant's inclusion in the cohort study if they do not wish to donate biospecimens.

Collection of Healthcare use

Medicare claims data through linkage from Services Australia has been approved (Services Australia EREC approval RMS1199) for 4.5 years of data from the participant's baseline visit date. This will include Medicare item number and description, provider charge, schedule fee (AUD$), patient out-of-pocket cost and prescribed medicines, for the duration of the study period. These de-identified data will be used to analyse the type, volume and cost of healthcare used per participant and for the cohort. Consent for this data is optional and will be obtained via a separate consent form.

Follow-up study procedures

Participants will undergo repeat 3D total body imaging, dermoscopy and clinical examination every 24, 12 or 6 months based on if they are in the low/average risk, high risk or very high risk group, respectively (Figure 1). At the 12-monthly follow-up visits, a follow-up questionnaire will be administered to assess changes in sun behaviour, skin cancer diagnoses and quality of life. Participants in the low/average group will complete their 12-month and 36-month questionnaire online. For all risk groups, at the 24-month follow-up visit, a questionnaire on the acceptability of 3D total body photography will also be administered to obtain feedback on this technology.

Identification of suspicious lesions

During the study period, lesions identified by the melanographer or study dermatologist as suspicious for malignancy will be referred to the participant's clinician for management. A report including images of any lesions requiring management will be sent to the participant's nominated treating medical practitioner. Any referrals will be followed up and pathology reports requested.

Participants are encouraged to continue seeing their clinician for routine skin checks. At follow-up study visits, participants will be asked if they have had any skin lesions excised by their regular clinician outside of the study. Pathology reports of these excised skin lesions will be requested, and this information will be recorded.

As per routine clinical practice, skin biopsies and excisions will be sent to accredited pathology laboratories to be processed and diagnosed using standard histology practices. Pathology reports of all skin biopsies or excisions in study participants will be collected by the study team. Following the generation of a pathology report, some of the slides used for microscopic diagnosis may undergo digital scanning (all melanomas, borderline lesions and 10% of benign lesions will be randomly selected). Whole slide scans will be reviewed by 2-3 pathologists to confirm diagnoses.

Participant reimbursement

Monetary reimbursements will not be provided to participants in this study.

Standard Operating Procedure adherence checks

Adherence at sites to the Standard Operating Procedures of the study will be monitored on a quarterly basis to ensure standardised quality of data produced at each of the 15 sites. These checks will be conducted by the respective ACEMID managers in QLD, NSW and VIC.

Data collection and storage

Clinical and questionnaire data will be recorded on the REDCap system, a secure study database software built by Vanderbilt University and hosted by Monash University, Melbourne, Australia (https://redcap.helix.monash.edu).

Pathology reports will be obtained from each State's (Queensland, New South Wales, Victoria) cancer registry and pathology laboratories; redacted and uploaded onto the REDCap database. Claims and health service data will be collected by linkage from the Medicare Benefits Schedule (MBS) and the Pharmaceutical Benefits Scheme (PBS), via a separate consent form approved by Services Australia.

Cleansed image data (de-identified and/or without demographic data) will be stored in the national ACEMID research repository. Access to the research repository will be controlled and governed by the ACEMID Data Governance Working Group using secure software platforms, including Extensible Neuroimaging Archive Toolkit (XNAT) and relevant Universities' Secure eResearch Platforms (SeRP) and Keypoint.

Participant data will be handled with utmost confidentiality. A participant log will be kept where a coded ID number will be allocated to each participant, which will be kept securely and separately from other data. All images, questionnaires, forms, medical reports, samples and genetic data will only have the participant ID number to protect their privacy. Participants may withdraw from the study at any time and will be given the option for the study to either retain or destroy any collected data.

Data Processing and analysis

Sample size

The ACEMID Cohort Study aims to recruit 15,000 participants, with quota sampling employed to recruit 3000 participants (20%) in the low/average melanoma risk group, 9000 participants (60%) in the high risk group and 3000 participants (20%) in the very high risk group.

Based on previous studies, from baseline to 36 months we anticipate a participant dropout rate of up to 20%, 10% and 10% in the low/average, high and very high risk groups, respectively.

Based on the melanoma incidence in previous studies conducted in New South Wales and Queensland,(19, 20) we conservatively expect to observe a melanoma incidence rate over the 3-year study follow-up of 0.4% (n=8), 2% (n=162) and 5% (n=135) in the low/average, high and very high risk groups, respectively.(21)

Power calculations were conducted to ensure the sample size is sufficient to detect associations between new melanomas (yes/no) and potential risk factors in both the high risk and very high risk groups. Based on the numbers above, we will have at least 80% power to detect a relative risk of 2 comparing risk factor

presence and absence, for a risk factor that has prevalence 10% in each of the high and very high risk groups, assuming a two-sided alpha of 0.05. In analyses for which multiple comparisons may be of concern, for example broad-based genetic markers, a more stringent alpha may be appropriate. In this case with a lower alpha (0.001, two-sided) we will have at least 80% power to detect a relative risk of 2.3 in the high risk group, and 2.5 in the very high risk group, for a risk factor with prevalence of 10% in each group.

We expect a small number of new melanomas in the low/average melanoma risk group and therefore we examine power for associations between risk factors and new keratinocyte cancers in this group. Based on an expectation of approximately 67 keratinocyte cancers per 1 melanoma,(22) we anticipate 6.7% of the low/average risk group will develop a new keratinocyte cancer over 2 years of follow-up. Based on this, we will have 89% power to detect a relative risk of 2, for a risk factor that is prevalent in only 10% of the low/average risk group with 89% power and assuming a two-sided alpha of 0.05. As above, for analyses in which multiple comparisons may be of concern, with a two-sided alpha of 0.001, there is 91% power to detect a relative risk of 2.5, for a risk factor that is prevalent in only 10% of the low/average risk group.

Statistical analysis

Primary outcome

For the cross-sectional data, descriptive statistical analyses including counts and proportions will be used to describe the total number of in situ and advanced melanoma, keratinocyte cancers, and pigmented and non-pigmented skin lesions (≥ 2mm and ≥ 5mm). These skin lesions will be analysed and summarised according to melanoma risk group, sex, age and body site. Descriptive statistics will be used to summarise dermoscopic features of pigmented skin lesions by body site. Cross-sectional associations will be quantified by regression methods suited to the measurement scale of each outcome.

Secondary outcomes

To assess the unadjusted and adjusted strength of association between participants' phenotypic or genotypic characteristics and lesion outcomes, linear and log-linear (relative risk) regression models will be fitted, for continuous and binary/count outcomes respectively. Where multiple lesion outcomes per participant are included the model for mean outcome will be fit using generalised estimating equations with an exchangeable working correlation matrix and robust standard errors. The adjusted models will include explanatory factors (for example skin type) according to a causal diagram. Interaction terms will also be fitted where appropriate (for example phenotype and genotype) to explain lesion counts or distributions.

Additional longitudinal analysis will include spatio-temporal models to analyse lesion distribution patterns over time, and whether changes are associated with a naevus cluster, or a specific body site, in each of the risk groups. Age, sex, and residence-based geographical and socio-economic status related information are

available to assess response bias effects. To further assess effects of response bias, we will compare traits including naevus counts to those of other studies in well-characterised community and clinical populations.

Performance of melanoma and keratinocyte risk prediction models based on self-reported risk factors will be assessed throughout the study period, overall and in different population subgroups. Discrimination will be assessed using area under the receiver operating characteristic curve (AUC) at a single time-point and c-index with censored data, and net reclassification improvement. Calibration will be assessed using calibration plots. Objective measures of phenotypic risk from imaging, together with behavioural and genomic risk factors, will be assessed in their ability to further discriminate risk of developing melanoma and keratinocyte cancers.

Exploratory outcomes

Macroscopic, dermoscopic and histologic imaging data, lesion history and de-identified participant risk data will be stored in a national research repository for development of diagnostic algorithms. Machine learning, including convolutional neural networks and support vector machine algorithms will be applied to training data sets and evaluated in test sets. The impact of including metadata, including genomic data and other risk factors, on diagnostic accuracy will be assessed in these analyses. The relative benefit of including macroscopic and dermoscopic data with histology image data will also be assessed.

Genomic analysis

The saliva samples will be processed to extract DNA. Once extracted, the DNA will be quantified using either the Nanodrop spectrophotometer or the Qubit 2.0 fluorometer along with the Qubit dsDNA BR Assay kits (Thermo Scientific). The DNA will be stored at a temperature of -20°C. A minimum of 2 micrograms of the extracted DNA will be submitted for genotyping.

Economic analysis

Utility-based quality of life will be assessed using scores from the AQoL-4D instrument at baseline, 12 and 24 months for the cohort during the study period, and used to calculate quality-adjusted survival at 24 months. Data relating to treatment costs, hospitalisations, participant time and effort required to participate, convenience of location, acceptability of the technology, out-of-pocket expenses and changes in productivity associated with referrals will be collected. Total costs, including use of AI-based diagnosis, and total outcomes expressed as QALYs gained for this cohort, will be calculated and reported as mean values with standard deviations and 95% confidence intervals. A comparison of healthcare use 12 months prior and 48 months after enrolment in the cohort study will be undertaken using MBS and PBS data. Mean annual and total healthcare use, costs and QALYs will be quantified for the cohort, pre and post inception. A budget impact analysis (BIA) will be modelled using best practice methods(23-25) over a 5 year timeframe. In this BIA, several scenarios will be investigated for the provision of services in a staged implementation in which 50%

of eligible Australians will access 3D total body photography in year 1, subsequently rising to 60% in year 2, 70% in year 3, 80% in year 4 and 90% in year 5.

Ethics and dissemination

Ethics approval has been obtained by the Metro South Human Research Ethics Committee (approval number: HREC/2019/QMS/57206) and the University of Queensland Human Research Ethics Committee (Approval number: 2019003077). The trial is prospectively registered on the Australian New Zealand Clinical Trials Registry (ACTRN12619001706167). The protocol adheres to the Standard Protocol Items Recommendations for Interventional Trials (SPIRIT) statement.(26) The findings from this study will be circulated through peer-reviewed publications, conferences, policy documents and media outlets.

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Author contributions

UK, AEC, PFP, CH, GJM, VM, RLM, HPS, RW, MS, GK, EJP, RAM and MJ were all involved in developing the study protocol. AEC, PFP, GJM, VM, RLM, HPS, RW, MJ and others worked together on the funding proposal. RW provided support for the development of the statistical analysis plan. RLM and RAM provided the health economics analysis. All authors have reviewed, edited and approved the final version.

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Competing interests

HPS is a shareholder of MoleMap NZ Limited and e-derm consult GmbH and undertakes regular teledermatological reporting for both companies. HPS is a Medical Consultant for Canfield Scientific Inc, Blaze Bioscience Inc, and a Medical Advisor for First Derm.

VM has received speakers fees from Novartis, Bristol Myers Squibb, Merck, Janssen and conference sponsorship from L'Oreal.

PFP has consulted for Leo, Amgen, Abbvie, UCB, Sanofi, Janssen, Novartis, BMS, MSD, Pfizer and Lilly. PFP has received speakers fees from Janssen, Leo, Amgen, Sanofi, Lilly, Abbvie, UCB, Novartis, Merck and Pfizer.

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Figure Legend:

Figure 1: Overview of Study Procedures

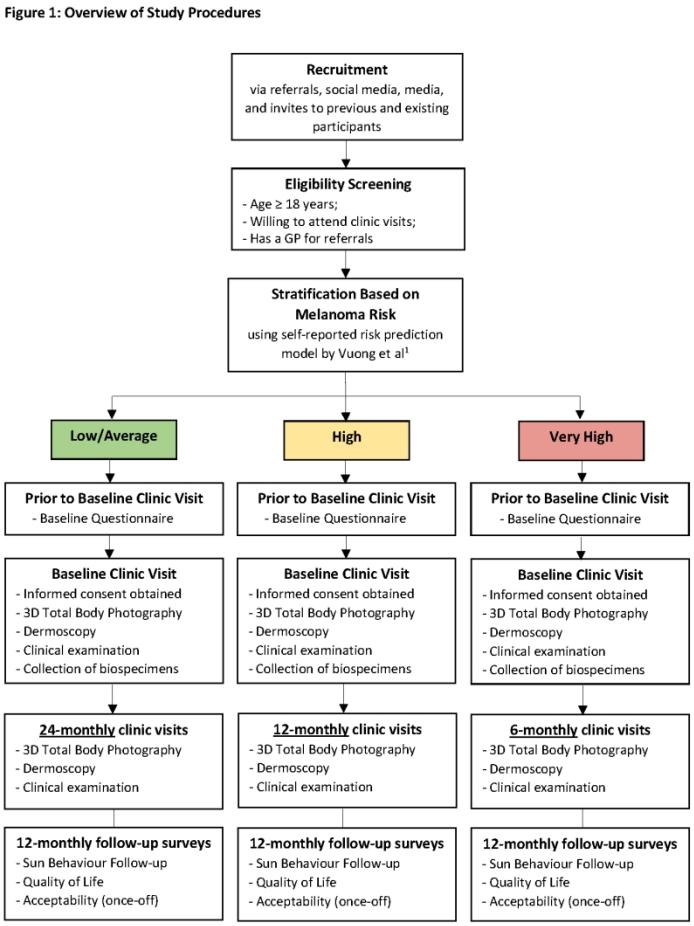

Figure 1: Overview of Study Procedures

531x752mm (79 x 79 DPI)

SPIRIT 2013 Checklist: Recommended items to address in a clinical trial protocol and related documents*

Section/item	Item No	Description
Administrative information		
Title	1	Descriptive title identifying the study design, population, interventions, and, if applicable, trial acronym
Trial registration	2a	Trial identifier and registry name. If not yet registered, name of intended registry
	2b	All items from the World Health Organization Trial Registration Data Set
Protocol version	3	Date and version identifier
Funding	4	Sources and types of financial, material, and other support
Roles and responsibilities	5a	Names, affiliations, and roles of protocol contributors
	5b	Name and contact information for the trial sponsor
	5c	Role of study sponsor and funders, if any, in study design; collection, management, analysis, and interpretation of data; writing of the report; and the decision to submit the report for publication, including whether they will have ultimate authority over any of these activities
	5d	Composition, roles, and responsibilities of the coordinating centre, steering committee, endpoint adjudication committee, data management team, and other individuals or groups overseeing the trial, if applicable (see Item 21a for data monitoring committee)
Introduction		
Background and rationale	6a	Description of research question and justification for undertaking the trial, including summary of relevant studies (published and unpublished) examining benefits and harms for each intervention
	6b	Explanation for choice of comparators
Objectives	7	Specific objectives or hypotheses
Trial design	8	Description of trial design including type of trial (eg, parallel group, crossover, factorial, single group), allocation ratio, and framework (eg, superiority, equivalence, noninferiority, exploratory)

Methods: Participants, interventions, and outcomes

Study setting	9	Description of study settings (eg, community clinic, academic hospital) and list of countries where data will be collected. Reference to where list of study sites can be obtained
Eligibility criteria	10	Inclusion and exclusion criteria for participants. If applicable, eligibility criteria for study centres and individuals who will perform the interventions (eg, surgeons, psychotherapists)
Interventions	11a	Interventions for each group with sufficient detail to allow replication, including how and when they will be administered
	11b	Criteria for discontinuing or modifying allocated interventions for a given trial participant (eg, drug dose change in response to harms, participant request, or improving/worsening disease)
	11c	Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence (eg, drug tablet return, laboratory tests)
	11d	Relevant concomitant care and interventions that are permitted or prohibited during the trial
Outcomes	12	Primary, secondary, and other outcomes, including the specific measurement variable (eg, systolic blood pressure), analysis metric (eg, change from baseline, final value, time to event), method of aggregation (eg, median, proportion), and time point for each outcome. Explanation of the clinical relevance of chosen efficacy and harm outcomes is strongly recommended
Participant timeline	13	Time schedule of enrolment, interventions (including any run-ins and washouts), assessments, and visits for participants. A schematic diagram is highly recommended (see Figure)
Sample size	14	Estimated number of participants needed to achieve study objectives and how it was determined, including clinical and statistical assumptions supporting any sample size calculations
Recruitment	15	Strategies for achieving adequate participant enrolment to reach target sample size

Methods: Assignment of interventions (for controlled trials)

Allocation:

Sequence generation	16a	Method of generating the allocation sequence (eg, computer-generated random numbers), and list of any factors for stratification. To reduce predictability of a random sequence, details of any planned restriction (eg, blocking) should be provided in a separate document that is unavailable to those who enrol participants or assign interventions

Allocation concealment mechanism	16b	Mechanism of implementing the allocation sequence (eg, central telephone; sequentially numbered, opaque, sealed envelopes), describing any steps to conceal the sequence until interventions are assigned
Implementation	16c	Who will generate the allocation sequence, who will enrol participants, and who will assign participants to interventions
Blinding (masking)	17a	Who will be blinded after assignment to interventions (eg, trial participants, care providers, outcome assessors, data analysts), and how
	17b	If blinded, circumstances under which unblinding is permissible, and procedure for revealing a participant's allocated intervention during the trial
Methods: Data collection, management, and analysis		
Data collection methods	18a	Plans for assessment and collection of outcome, baseline, and other trial data, including any related processes to promote data quality (eg, duplicate measurements, training of assessors) and a description of study instruments (eg, questionnaires, laboratory tests) along with their reliability and validity, if known. Reference to where data collection forms can be found, if not in the protocol
	18b	Plans to promote participant retention and complete follow-up, including list of any outcome data to be collected for participants who discontinue or deviate from intervention protocols
Data management	19	Plans for data entry, coding, security, and storage, including any related processes to promote data quality (eg, double data entry; range checks for data values). Reference to where details of data management procedures can be found, if not in the protocol
Statistical methods	20a	Statistical methods for analysing primary and secondary outcomes. Reference to where other details of the statistical analysis plan can be found, if not in the protocol
	20b	Methods for any additional analyses (eg, subgroup and adjusted analyses)
	20c	Definition of analysis population relating to protocol non-adherence (eg, as randomised analysis), and any statistical methods to handle missing data (eg, multiple imputation)
Methods: Monitoring		
Data monitoring	21a	Composition of data monitoring committee (DMC); summary of its role and reporting structure; statement of whether it is independent from the sponsor and competing interests; and reference to where further details about its charter can be found, if not in the protocol. Alternatively, an explanation of why a DMC is not needed

	21b	Description of any interim analyses and stopping guidelines, including who will have access to these interim results and make the final decision to terminate the trial
Harms	22	Plans for collecting, assessing, reporting, and managing solicited and spontaneously reported adverse events and other unintended effects of trial interventions or trial conduct
Auditing	23	Frequency and procedures for auditing trial conduct, if any, and whether the process will be independent from investigators and the sponsor

Ethics and dissemination

Research ethics approval	24	Plans for seeking research ethics committee/institutional review board (REC/IRB) approval
Protocol amendments	25	Plans for communicating important protocol modifications (eg, changes to eligibility criteria, outcomes, analyses) to relevant parties (eg, investigators, REC/IRBs, trial participants, trial registries, journals, regulators)
Consent or assent	26a	Who will obtain informed consent or assent from potential trial participants or authorised surrogates, and how (see Item 32)
	26b	Additional consent provisions for collection and use of participant data and biological specimens in ancillary studies, if applicable
Confidentiality	27	How personal information about potential and enrolled participants will be collected, shared, and maintained in order to protect confidentiality before, during, and after the trial
Declaration of interests	28	Financial and other competing interests for principal investigators for the overall trial and each study site
Access to data	29	Statement of who will have access to the final trial dataset, and disclosure of contractual agreements that limit such access for investigators
Ancillary and post-trial care	30	Provisions, if any, for ancillary and post-trial care, and for compensation to those who suffer harm from trial participation
Dissemination policy	31a	Plans for investigators and sponsor to communicate trial results to participants, healthcare professionals, the public, and other relevant groups (eg, via publication, reporting in results databases, or other data sharing arrangements), including any publication restrictions
	31b	Authorship eligibility guidelines and any intended use of professional writers
	31c	Plans, if any, for granting public access to the full protocol, participant-level dataset, and statistical code

Appendices

Informed consent materials	32	Model consent form and other related documentation given to participants and authorised surrogates
Biological specimens	33	Plans for collection, laboratory evaluation, and storage of biological specimens for genetic or molecular analysis in the current trial and for future use in ancillary studies, if applicable

*It is strongly recommended that this checklist be read in conjunction with the SPIRIT 2013 Explanation & Elaboration for important clarification on the items. Amendments to the protocol should be tracked and dated. The SPIRIT checklist is copyrighted by the SPIRIT Group under the Creative Commons "Attribution-NonCommercial-NoDerivs 3.0 Unported" license.

STROBE 2007 (v4) Statement—Checklist of items that should be included in reports of *cohort studies*

Section/Topic	Item #	Recommendation	Reported on page #
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract	1
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found	2
Introduction			
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	4-5
Objectives	3	State specific objectives, including any prespecified hypotheses	5
Methods			
Study design	4	Present key elements of study design early in the paper	5
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	5
Participants	6	(*a*) Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up	6-7
		(*b*) For matched studies, give matching criteria and number of exposed and unexposed	N/A
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	11-12
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	7-9
Bias	9	Describe any efforts to address potential sources of bias	11-12
Study size	10	Explain how the study size was arrived at	10-11
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	11-12
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding	11-12
		(*b*) Describe any methods used to examine subgroups and interactions	11-12
		(*c*) Explain how missing data were addressed	11-12
		(*d*) If applicable, explain how loss to follow-up was addressed	10-11
		(*e*) Describe any sensitivity analyses	N/A
Results			

Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed	N/A – protocol paper
		(b) Give reasons for non-participation at each stage	N/A – protocol paper
		(c) Consider use of a flow diagram	N/A – protocol paper
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders	N/A – protocol paper
		(b) Indicate number of participants with missing data for each variable of interest	N/A – protocol paper
		(c) Summarise follow-up time (eg, average and total amount)	N/A – protocol paper
Outcome data	15*	Report numbers of outcome events or summary measures over time	N/A – protocol paper
Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included	N/A – protocol paper
		(*b*) Report category boundaries when continuous variables were categorized	N/A – protocol paper
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	N/A – protocol paper
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	N/A – protocol paper
Discussion			
Key results	18	Summarise key results with reference to study objectives	N/A – protocol paper
Limitations			
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	N/A – protocol paper
Generalisability	21	Discuss the generalisability (external validity) of the study results	N/A – protocol paper
Other information			
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	13

*Give information separately for cases and controls in case-control studies and, if applicable, for exposed and unexposed groups in cohort and cross-sectional studies.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at www.strobe-statement.org.