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Protocol for a Randomised Controlled Trial to evaluate the efficacy of 3D Total Body Photography with sequential digital dermoscopy in a high risk melanoma cohort.

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ABSTRACT

Introduction: Melanoma is Australia's 4th most common cancer. Early detection is fundamental in maximising health outcomes and minimising treatment costs. To date, population based screening programs have not been justified in health economic studies. However, a skin surveillance approach targeting high-risk individuals could improve the cost-benefit ratio.

Methods and analysis: This paper describes a two year longitudinal randomised controlled trial (RCT) to compare routine clinical care (control) with an intensive skin surveillance program (intervention) consisting of novel three dimensional (3D) total body photography (TBP), sequential digital dermoscopy and melanoma risk stratification, in a high risk melanoma cohort. Primary outcomes will evaluate clinical, economic and consumer impact of the intervention. Clinical outcomes will evaluate differences in the rate of lesion excisions/biopsies per person, benign to malignant ratio for excisions, and thickness of melanomas diagnosed. A health economic analysis using government data repositories will capture healthcare utilisation and costs relating to skin surveillance. Consumer questionnaires will examine intervention acceptability, the psychological impact, and attitudes towards melanoma risk and sun protective behaviour. Secondary outcomes include the development of a holistic risk algorithm incorporating clinical, phenotypic and genetic factors to facilitate the identification of those most likely to benefit from this surveillance approach. Furthermore, the feasibility of integrating the intervention with teledermatology to enhance specialist care in remote locations will be evaluated. This will be the first RCT to compare a targeted surveillance program utilising new 3D TBP technology against current routine clinical care for individuals at high risk of melanoma.

Ethics and dissemination: This study has received Human Research Ethics Committee (HREC) approval from both Metro South Health HREC (HREC/17/QPAH/816) and The University of Queensland HREC (2018000074). The trial has been prospectively registered with the Australian New Zealand Clinical Trial Register (ANZCTR12618000267257).

Strengths and limitations of this study

- The first Randomised Controlled trial to compare three-dimensional (3D) total-body photography to standard-of-care for people who are high risk of melanoma.
- Large sample size, recruited from research volunteer registry and dermatologist referrals with a projected high retention rate.

- Collection of longitudinal data from government health repositories will allow a relatively complete, rich dataset on health care use and costs relevant to melanoma risk.
- Study will evaluate feasibility of using 3D total-body photography for tele-diagnosis.
- Limited outcomes assessment, with absence of gold-standard mortality as an endpoint.

INTRODUCTION

Australia, with a population of only 25 Million residents, has one of the highest rates of cutaneous melanoma incidence and mortality in the world, with over 13,000 new cases diagnosed in 2016, and over 1,700 deaths[1]. In 2014, the costs of advanced melanoma were estimated to be $422M nationally of which 39% was attributable to direct healthcare costs[2]. There is a clear correlation between melanoma stage at diagnosis and patient outcomes, both medically and fiscally[3-5]. Extensive research efforts have been undertaken to improve strategies for identifying and following those at greatest risk[6]. However, there is currently no consensus on the best risk assessment or surveillance strategies. As a result, recommendations vary and are inconsistently applied[7].

The most important markers of individual melanoma risk include: *CDKN2A* germline mutation, having > 100 naevi, > 5 atypical naevi, fair hair, eye and skin colour, a strong family history, or a personal history of melanoma[6, 8, 9]. Within Australia, dermatologists typically adhere to The Cancer Council Australia's (CCA) guidelines, that recommend high-risk individuals undergo clinical skin examinations every 6 months using total body photography (TBP) in combination with sequential digital dermoscopy imaging (SDDI)[10, 11]. This 'two step' process involving both TBP and dermoscopy for skin surveillance was initially described in 2002[12] and has been repeatedly shown to be associated with a lower benign to malignant excision ratio and decreased Breslow thickness of subsequently diagnosed melanomas[4, 13-15].

Surveillance strategies have evolved significantly over the past decade. One of the most promising approaches involves automated three-dimensional (3D) imaging of subjects, allowing objective documentation of all existing lesions and monitoring changes over time. The VECTRA WB360 system described previously[16, 17] allows fast 3D total-body photography and construction of a patient avatar, along with integrated dermoscopy. Consumer feedback indicates high acceptability and confidence in the technology for skin monitoring, and importantly, whole body imaging may reduce melanoma-related anxiety[16].

Melanoma patients in rural areas are often disadvantaged with unequitable access to dermatological care service and are reported to suffer 20% increased melanoma related mortality compared to urban

areas[18]. Already now, rural physicians are using teledermatology to obtain second opinions on suspicious lesions from specialist dermatologists[19]. Incorporating 3D TBP into a teledermatology service could facilitate remote full body skin examination by teledermatologists reflecting the service level that urban patients can access.

This study will recruit individuals that are at high risk of developing cutaneous melanoma to participate in a randomised trial comparing combined TBP and SDDI surveillance approach (3D TBP-SDDI), with routine clinical care. TBP and SDDI reportedly improves earlier detection rates[14, 20], however, the effect of 3D TBP is unknown. The feasibility of extending its use through a telehealth network will be explored. An evaluation of efficacy, costs, and consumer acceptability of the technology will determine long-term sustainability. Furthermore, a standardised, holistic approach to risk stratification for melanoma will be developed, optimising the identification of those who would most benefit from this high-risk surveillance program. This study is an integral step in guiding change in the way high-risk individuals may be managed in Australia.

OBJECTIVES

Primary objectives

- Compare clinical outcomes of the 3D TBP-SDDI approach with routine clinical care, including numbers of excisions or biopsies and histopathological findings.
- Compare health economic outcomes of the 3D TBP-SDDI approach with routine clinical care.
- Evaluate consumer acceptance of the intervention, psychological well-being, health behaviour and beliefs regarding sun protection and melanoma.

Secondary Objectives

- Assess feasibility of telehealth to deliver remotely captured 3D TBP-SDDI for teledermatologist review.
- Evaluate the degree of concordance between teledermatologist and in-person examination in terms of clinical assessment and management decisions.
- Identify rare and deleterious gene variants associated with melanoma risk.
- Refine a risk stratification model that combines medical history, family history, phenotypic risk factors, and genetic results to produce a melanoma-risk score.

METHODS AND ANALYSIS

Study design and setting

A two arm, single-site, parallel randomised control trial (RCT) will recruit 330 participants, with a 50:50 allocation ratio between intervention and control groups. The study site will be the Clinical Research Facility of the Translational Research Institute at the Princess Alexandra Hospital, Brisbane. The majority of study participants reside in South-East Queensland, Australia.

Participant and public involvement

Prior to applying for funding, we have conducted clinical research recruiting both average risk and high risk members of the public regarding skin surveillance since 2010, and have used questionnaires for participant feedback regarding skin cancer prevention which has contributed to the current study design. Since 2016, we have held biannual consumer forums to inform the public and our study participants of our research progress, and to give consumers the opportunities to discuss their priorities and concerns regarding skin cancer prevention with our group.

Eligibility criteria

Individuals that are at high risk of developing a primary or subsequent primary melanoma will be invited to participate. High risk will be defined as having one of the following:

- At least one melanoma (including *in situ*) diagnosed before the age of 40
- Two or more melanomas (including *in situ*) diagnosed before the age of 65
- A strong family history (2+ first-degree relatives) and/or known pathogenic genetic mutation and/or a diagnosis of dysplastic naevus syndrome.

Recruitment

Participants will be recruited from a registry of research volunteers with the University of Queensland, Dermatology Research Centre, and by referrals from dermatologists and medical practitioners from South-East Queensland, over a 12-18 month period. Potential participants will be emailed a short description of the study and a copy of the Participant Information and Consent Form (PICF), followed by a phone call approximately 2 weeks thereafter.

Randomisation and blinding

Once consented at the initial baseline visit, participants will be randomised to either the intervention or control group with simple random sampling using the randomisation function in REDCap (Research Electronic Data Capture). REDCap is a secure, online study database software developed by Vanderbilt University, and administrated by The Queensland Clinical Trials and Biostatistics Centre at the School of Public Health, The University of Queensland. An online random number generator[21] will create an allocation sequence table which will be uploaded to REDCap. Trial staff conducting patient visits will be blinded to the next allocation sequence. Due to the nature of the intervention once participants are randomised, allocation is unblinded.

To address the teledermatology objectives, a subset of participants will be evaluated two ways. Firstly by 3D-TBP SDDI and a face-to-face dermatologist, and secondly their images alone will be independently evaluated by another dermatologist.

Intervention

Participants randomised to the intervention group will receive clinical skin examinations, every 6 months for 2 years, supported by the 3D TBP imaging system (VECTRA WB360, Serial Number WB00009, Canfield Scientific, Parsipanny, NJ, USA). The VECTRA imaging system consists of a framework of 92 cameras, which simultaneously capture images of the participant holding one anatomical pose, to construct a 3D avatar. An attached dermoscopic camera (EOS Rebel T6i) enables imaging of individual naevi including anatomical localisation on the 3D avatar. Clinical skin examinations are performed at the time of imaging by dermatologically-trained medical practitioners, and images are reviewed and discussed fortnightly with an accredited dermatologist, simulating a teledermatology consultation to assess 3D-TBP avatars and corresponding dermoscopic images. Suspicious lesions will be discussed with the study participant by phone, and subsequently referred to their treating physician. Participants will be asked to continue attending their regular skin examination appointments.

Control

Participants randomised to the control group will be asked to continue attending their regular skin examination appointments (which may include 2D TBP), and to complete 6 monthly questionnaires. At the end of the study, all control participants will be offered a clinical skin examination including 3D-TBP imaging.

Participant timeline

Participants in both groups will be evaluated over a two year period from baseline, with the intervention group attending visits at baseline, 6, 12, 18 and 24 months. The control group will attend the clinic in person at baseline and at 24 months, and will complete an online questionnaire at months 6, 12 and 18. Refer to Figure 1 for an overview of participant timeline and assessments.

Primary outcomes

The primary outcome for this study is the number of excisions. The other main outcomes are defined in three categories, including clinical, economic and consumer outcomes. The assessment of these outcomes are described in Table 1.

Table 1: Primary outcomes and methods assessments

Outcome Category	Themes evaluated	Data source	Time points
Clinical	Number and thickness of melanomas (including *in situ*) found.	Clinical records and pathology reports.	0, 6, 12, 18 and 24 months
	Skin excisions/biopsies and the histopathological categorisations.		
Economic	Participant healthcare services utilisation relating to skin surveillance and management.	Participant claims through the Medicare Benefits Schedule (MBS) and Pharmaceutical Benefits Scheme (PBS).	24 months
		Queensland Hospital Admitted Patient Data Collection (QHAPDC) database, the Healthcare Purchasing and System Performance (HPSP) data and the Health Service Funding Models.	
Consumer	Satisfaction and acceptability	Self-administered, validated questionnaire [22] adapted from the Technology Acceptance Model [23, 24]. Additional questions will capture satisfaction with travel, waiting times, appointment length, convenience and perceived financial value of the surveillance program.	0 and 24 months

		Recruitment and retention will contribute to analysis	
	Health behaviours	Self-administered, validated questionnaire adapted from QSkin study to capture sun protective behaviours and relevant demographics [25].	0, 6, 12, 18 and 24 months
	Psychological well-being	Euro-QoL-5D [26], to capture quality of life index for the health economic assessment.	0, 6, 12, 18 and 24 months
	Health Beliefs	The validated Health Beliefs Survey [27, 28] to evaluate knowledge, perceived severity of melanoma, perceived personal risk and perceived worthiness of surveillance programs.	0, 6, 12, 18 and 24 months

Secondary outcomes

There are three secondary outcomes: the feasibility of viewing 3D TBP-SDDI images remotely using the telehealth network; the efficacy of performing skin examinations using 3D TBP-SDDI images using telehealth services; and lastly the identification of genetic mutations and their utility in melanoma risk stratification. The assessment of these outcomes are described in Table 2.

Table 2: Secondary outcomes and methods assessments

Outcome Category	Factors evaluated	Data source	Time points
Feasibility of telehealth approach	Technical feasibility of telehealth network for remote dermatological review of 3D TBP-SDDI images, and interoperability with hospital image repositories and integrated electronic medical records (iEMR).	• Investigate subsystems for image acquisition, storage and display by measuring network throughput (bandwidth) and latency between subsystems. • Measure data volume, and transmission time per 3D TBP-SDDI examination. • Assess the compression ratio of transmitted image files necessary to achieve adequate functionality. • Evaluate success of transmission and integrity of data.	24 months

Accuracy of telehealth skin examinations	Safety and accuracy of teledermatology review of 3D TBP-SDDI images.	• Review the concordance between provisional diagnosis and clinical management decisions of the teledermatologist to the gold standard of in-person dermatological assessment. • Assess comparative diagnostic accuracy between in-person clinical diagnosis, teledermatological diagnosis and histopathological diagnoses.	0-24 months
Melanoma risk stratification in a high risk population	Genetic Results	• Saliva samples collected using Oragene DNA self-collection kit. Methods for sample processing described previously [22].	Baseline
		• Whole Exome Sequencing (WES) or Sanger sequencing used to identify rare, pathogenic, germline variants in known melanoma genes. • Common variants associated with melanoma risk will be genotyped using Illumina CoreExomev24 chip array.	12-24 months
	Sun behaviour	• Self-administered, previously validated sun behaviour questionnaire to record sun protective behaviour, sun exposure, sunburn history, personal and family skin cancer history, and relevant demographic information [22, 25].	Baseline
	Deep phenotyping	• Documentation of eye, hair and skin colour. • Spectrophotometer readings for skin colour on the right arm including; the proximal anterior bicep, proximal anterior forearm, and proximal posterior forearm, using Spectrometer CM-600d (Konica Minolta inc., Osaka, Japan). • Digital photographs of participant's irises using a Nikon D3400 Digital Single-Lens Reflex (DSLR) camera (Nikon, Tokyo, Japan). • Freckling on the face, dorsum of right hand and shoulders are rated 0 to 4 (=none, mild,	Baseline

		moderate, severe) to produce an overall freckling score.	

Data collection and management

Baseline questionnaire and clinical data will be entered into the REDCap database. 3D-TBP-SDDI images will be captured using the VECTRA Imaging System and integrated software. Pathology reports will be requested from the Queensland Cancer Registry and medical records. One-off extractions of claims and health service data will occur at the end of follow-up from the Medicare Benefits Schedule (MBS) and Pharmaceutical Benefits Scheme (PBS), the Queensland Hospital admitted Patient Data Collection (QHAPDC) database, the Healthcare Purchasing and System Performance (HPSP) data, and the Hospital and Health Service Funding Models. By linking data, the whole journey of healthcare service contacts and patient skin cancer outcomes will be captured, to allow an estimate of related costs of skin cancers.

Saliva samples and subsequent sequencing results will be coded and linked using a re-identifiable Study ID. Data linking identifying information and Study ID will be stored in a password-controlled database, on a secure server, accessible to a limited subset of the study team to ensure privacy.

The REDCap management system, the VECTRA images and all remaining electronic data will be stored under The University of Queensland Research Data Management system on a secured network. Identifiers are removed from all participant data and replaced with a unique Study ID to further protect privacy. Regular quality assurance checks of image data and REDCap entries will be conducted.

Data monitoring

The study team determined that an independent data monitoring committee (iDMC) was not required as the risk to study participants was low, mainly relating to privacy and the possibility of unnecessary excision or biopsies. Privacy risks are mitigated as discussed above. An 'Issues Register' will be kept to record technical problems that occur during trial visits. Interviews with key stakeholders will identify problematic procedures. Any concerns with data quality or issues recorded will be discussed at regular team meetings. The study team will perform regular data monitoring and quality assurance tasks internally, and any protocol deviations or adverse events will be reported to the ethics committee.

STATISTICAL METHODS

Sample size

The study aims to recruit 330 high risk participants over a 12-18 month period, to be powered to compare excision rates between groups. This sample size is based on previously reported difference in excision rates in a high risk sample, between those monitored by TBP (mean=0.81, SD=0.75), and a standard care group (mean=2.55, SD=2.01)[4]. The definition of high risk is broader in this study, and approximately a third of participants are likely to be already monitored using TBP, therefore the difference between routine clinical care and monitoring with 3D TBP is likely to be smaller. Given this, the study was powered to observe a 50% smaller difference in excision rates than observed previously[4], including an increase in standard deviation of 50% within each group (mean intervention 0.81 (SD=1.13), mean control 1.68 (SD=3.02)). Given these estimates, with a power of 90% and a significance level of 5%, 153 participants will be required for each arm of the trial. Allowing for participant withdrawal, we will aim to recruit a total 330 participants.

Baseline demographic

Descriptive statistics will be used to summarise demographic and clinical characteristics for both the control and intervention groups. Chi-square tests will be used to estimate difference in proportions of categorical variables between the two groups, and t-tests will be used for continuous variables. Non-parametric equivalents will be used if the assumptions of the parametric tests are violated. Results will be considered statistically significant if $p < 0.05$.

Clinical outcomes

A non-parametric Mann-Whitney test will be used to assess the clinical primary outcome to test if there is a difference in mean annual rate of lesion excisions/biosies between the intervention and control groups, given the primary outcome is based on counts and therefore unlikely to follow a normal distribution. The primary outcome will be analysed as intention to treat, with a per protocol analysis as a secondary outcome. This outcome will also be re-evaluated on a subset excluding those from both the intervention and control groups who are receiving 2D TBP. The benign to malignant ratio for excisions of pigmented lesions and non-melanoma skin cancers will be calculated for both groups. Chi-square or fisher's exact test (as appropriate) will be used to compare the difference in proportions of pathology confirmed melanoma, melanoma in-situ, BCCs and SCCs dignosed between the two groups with diagnosis. Logistic regression analyses will be used to investigate the relationship between baseline demographic and phenotypic information, and past melanoma history. A subgroup analysis of participants diagnosed with melanoma excluding in-situ, and melanoma including in-situ will investigate the differences in staging, Breslow thickness and body site and other parameters of

interest, between the two groups, using linear, logistic and generalised regression models as appropriate. As above, results will be considered statistically significant if $p < 0.05$.

Economic outcomes

Data from Medicare and Queensland Health sources will be linked and aggregated for each patient covering the surveillance period of the study. Skin cancer related resource use will be identified and coded according to ICD-10, procedure and MBS/PBS items. Cost data are typically skewed so generalised linear models will be used with a gamma family and log link (if appropriate) to assess differences between the intervention and control groups. Non-parametric bootstrapping methods will also be applied for verification of differences in costs between groups. Subgroup cost analyses of hospital versus out-of-hospital, melanoma stage, age, phenotypes or other patient characteristics will be explored.

Telehealth review outcomes

The main telehealth outcome is the level of agreement in clinical decision between the teledermatologist and the dermatologist carrying out an in-person skin examination assessment. Four decision outcomes will be considered: No action (no suspicious lesion), follow up in 3-6 months, excision of lesion/s, and treatment of lesion. Weighted Cohen's kappa coefficient will be calculated to measure agreement.

Melanoma risk score development

Multivariable logistic regression will be used to assess what combinations of genetic, phenotypic and demographic risk factors are associates with an increased odds of melanoma within a high risk population. Variables with $p < 0.2$ in univariate regression will be included in the model, and backwards step-wise regression will be used, with variables in the model remaining statistically significant at the 5% level. Validation of the resulting risk stratification algorithms will be performed on larger collaborative cohorts.

Consumer perspectives

Data will be collected to determine the acceptability and feasibility of 3D imaging and any potential barriers and facilitators to implementation and adoption. This will include information related to

convenience, comfort, and reasons for participant retention/loss, and data on quality of life and fear of recurrence.

Questionnaire data will be prepared according to each scale's manual and standard procedures[22-28]. Total and subscale scores will be computed and tested for normality. If normally distributed, parametric tests will be used, otherwise non-parametric analytic procedures will be used as described above to assess differences between the two groups in the consumer self-reported outcomes.

ETHICS AND DISSEMINATION

The protocol has been prepared in concordance with the Standard Protocol Items Recommendations for Interventional Trials (SPIRIT) statement[29]. This study has received Human Research Ethics Committee (HREC) approval from Metro South Health HREC (HREC/17/QPAH/816) and The University of Queensland HREC (2018000074). The trial has been prospectively registered (ANZCTR12618000267257). Following national guidelines, if genetic sequencing reveals a high penetrance pathogenic mutation, clinical genetic testing will be offered to the participant. A reimbursement of $20 per visit will be paid to participants to assist in covering travel and/or parking costs. Study results will be disseminated through peer-reviewed publications, conferences and non-peer reviewed media outlets.

DISCUSSION

This will be the first RCT to assess the feasibility, efficacy and cost effectiveness of combining 3D TBP, with SDDI for clinical skin examinations of individuals at high-risk to melanoma in Australia. Consumer perceptions of the technology and its clinical utility will also be assessed. This study will enable us to determine whether excision rates and stage of melanoma detection are affected by the inclusion of 3D TBP-SDDI in a surveillance protocol. Exploring the societal and personal costs of the intervention will be invaluable in determining the feasibility of incorporating this technology in routine clinical care for this high-risk cohort. The study will determine whether remote administration of 3D TBP, with SDDI combined with teledermatologist evaluation will affect clinical management. For greater public benefit in the longer term, it is critical to be able to accurately identify high-risk individuals who might benefit from this more intensive surveillance approach and, therefore, this study aims to develop a holistic risk stratification algorithm.

Australia currently has three national population-based screening programs for early detection of breast, cervical and bowel cancers. However, there is no similar program for skin cancer, despite melanoma being Australia's 4th most common cancer[9]. The number needed to screen (NNS) in the

Australian general public to save one life from melanoma has been estimated at 25,000[30]. Therefore, population-based screening for melanoma may not be justified. However, by focusing on a high-risk population the probability of detecting a melanoma increases and the NNS decreases. Furthermore, the incorporation of TBP-SDDI enables a 'watch and wait' approach which would reduce the number needed to treat (NNT) based on the benign to malignant excision ratio, resulting in health cost savings[10]. Criteria for an effective screening program, outlined by the Australian Institute for Health and Welfare[31], stipulate that: the disease must be highly prevalent; the natural course of the disease is well understood including a recognisable latent or early symptomatic stage where disease can be detected; that there is available treatment which is effective and well accepted; the disease must cause considerable costs, both fiscally and clinically; and lastly, the screening program must be cost effective. With the criteria in mind, the current protocol is intended to build the evidence for a future targeted surveillance program for melanoma detection in high-risk individuals in Australia, including solutions for geographical challenges. Economic evaluation of resource use and associated costs collected through linkage of clinical and administrative healthcare data sources, will capture the whole journey of health service contacts and outcomes, to accurately estimate the related costs of screening and skin cancers within this high risk population.

CONCLUSION

This protocol will provide evidence as to whether pursuing the incorporation of 3D TBP-SDDI into a surveillance program for high-risk individuals can be cost effective and provide superior clinical outcomes over the current routine clinical care. Secondary outcomes will drive solutions in defining the population which would maximally benefit from this program, and determine the acceptability of this surveillance method. Furthermore, the study will determine if the 3D TBP-SDDI technology is suitable for review through telehealth services, supporting solutions for outreach to remote regions of the country.

AUTHOR CONTRIBUTIONS

CAP, AMM, BB-S, DCW, LGG, LJC, JFA, EE, SO, LG, BMS, MJ, HPS, AND AF were all involved in developing the study protocol. HPS, AF, MJ, BMS, LG, SO, EE, JFA, LJC, LGG, AND DCW worked together on the funding proposal. BB-S provided support for the development of the statistical analysis plan. All authors 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., a Medical Advisor for First Derm, and has a Medical Advisory Board Appointment with MoleMap NZ Limited.

Word count: 3097 (excluding figure/table, abstract and references), 2 tables, 1 figure.

Figure titles and legends

Figure 1: Overview of participant timeline and assessments (see attached PDF)

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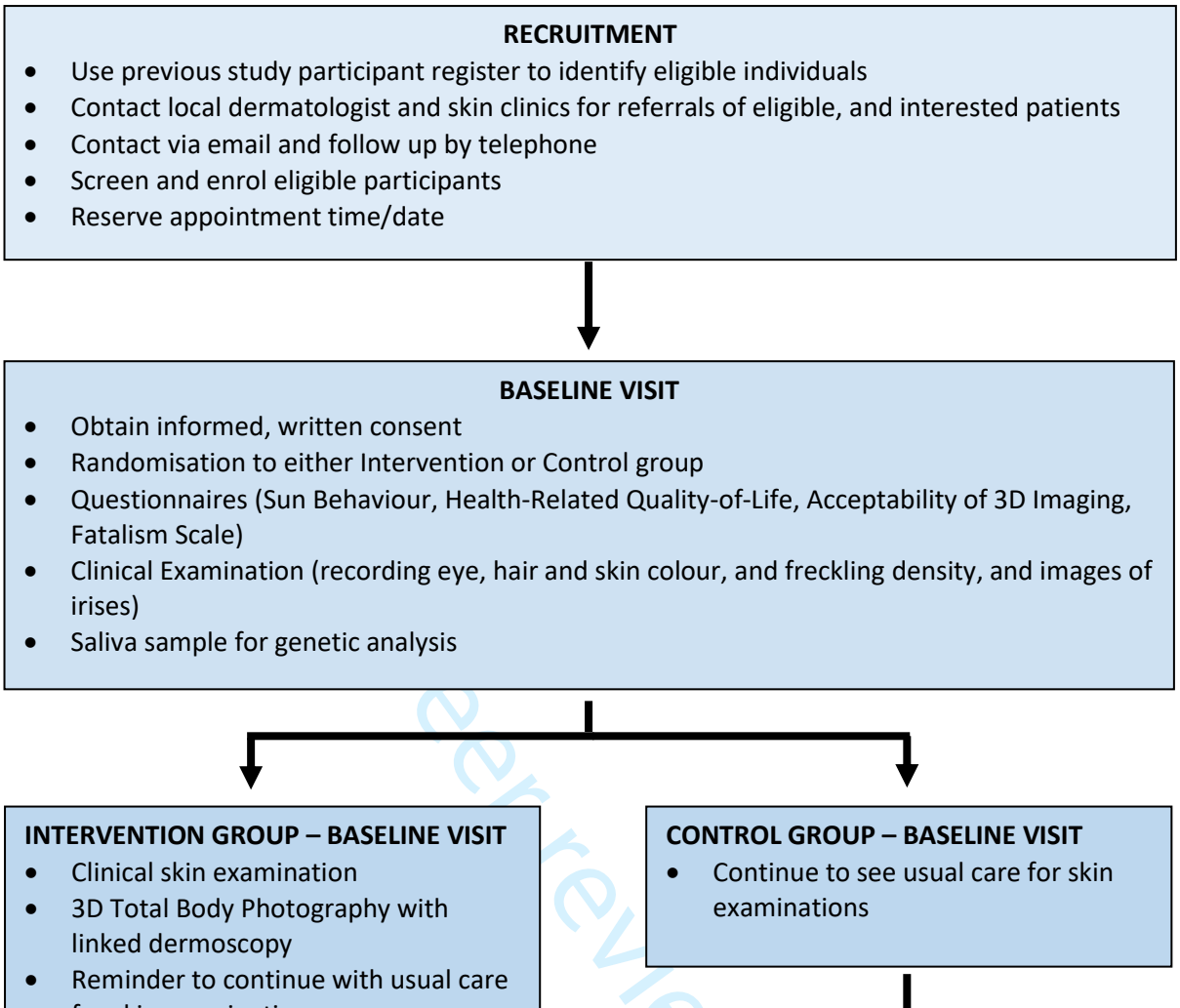

SPIRIT 2013 Checklist: Recommended items to address in a clinical trial protocol and related documents*

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.

BMJ Open

Protocol for a Randomised Controlled Trial to evaluate the efficacy of 3D Total Body Photography with sequential digital dermoscopy in a high risk melanoma cohort.

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Secondary Subject Heading:	Research methods
Keywords:	Melanoma, Early detection, Total body photography, RCT

TITLE: Protocol for a Randomised Controlled Trial to evaluate the efficacy of 3D Total Body Photography with sequential digital dermoscopy in a high risk melanoma cohort.

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ABSTRACT

Introduction: Melanoma is Australia's 4th most common cancer. Early detection is fundamental in maximising health outcomes and minimising treatment costs. To date, population based screening programs have not been justified in health economic studies. However, a skin surveillance approach targeting high-risk individuals could improve the cost-benefit ratio.

Methods and analysis: This paper describes a two year longitudinal randomised controlled trial (RCT) to compare routine clinical care (control) with an intensive skin surveillance program (intervention) consisting of novel three dimensional (3D) total body photography (TBP), sequential digital dermoscopy and melanoma risk stratification, in a high risk melanoma cohort. Primary outcomes will evaluate clinical, economic and consumer impact of the intervention. Clinical outcomes will evaluate differences in the rate of lesion excisions/biopsies per person, benign to malignant ratio for excisions, and thickness of melanomas diagnosed. A health economic analysis using government data repositories will capture healthcare utilisation and costs relating to skin surveillance. Consumer questionnaires will examine intervention acceptability, the psychological impact, and attitudes towards melanoma risk and sun protective behaviour. Secondary outcomes include the development of a holistic risk algorithm incorporating clinical, phenotypic and genetic factors to facilitate the identification of those most likely to benefit from this surveillance approach. Furthermore, the feasibility of integrating the intervention with teledermatology to enhance specialist care in remote locations will be evaluated. This will be the first RCT to compare a targeted surveillance program utilising new 3D TBP technology against current routine clinical care for individuals at high risk of melanoma.

Ethics and dissemination: This study has received Human Research Ethics Committee (HREC) approval from both Metro South Health HREC (HREC/17/QPAH/816) and The University of Queensland HREC (2018000074). The trial has been prospectively registered with the Australian New Zealand Clinical Trial Register (ANZCTR12618000267257).

Strengths and limitations of this study

- The first Randomised Controlled trial to compare three-dimensional (3D) total-body photography to standard-of-care for people who are high risk of melanoma.
- Large sample size, recruited from research volunteer registry and dermatologist referrals with a projected high retention rate.

- Collection of longitudinal data from government health repositories will allow a relatively complete, rich dataset on health care use and costs relevant to melanoma risk.
- Study will evaluate feasibility of using 3D total-body photography for tele-diagnosis.
- Limited outcomes assessment, with absence of gold-standard mortality as an endpoint.

INTRODUCTION

Australia, with a population of only 25 Million residents, has one of the highest rates of cutaneous melanoma incidence and mortality in the world, with over 13,000 new cases diagnosed in 2016, and over 1,700 deaths[1]. In 2014, the costs of advanced melanoma were estimated to be $422M nationally of which 39% was attributable to direct healthcare costs[2]. Early detection of melanoma is preferred because more advanced stage melanomas have poorer patient outcomes and are costly to manage[3-5]. While population based screening is not warranted, identifying people at high risk of melanoma could enable targeted screening, and be the most effective way of improving early detection. Extensive research efforts have been undertaken to improve strategies for identifying and following those at greatest risk[6]. However, there is currently no consensus on the best risk assessment or surveillance strategies. As a result, screening recommendations vary and are inconsistently applied[7].

Current approaches for identifying and screening those at greatest risk are imperfect[8]. Risk prediction tools have been developed, and involve weighting a subset of risk factors including phenotypic features, personal history and, more rarely, genetic test results. The most important markers of individual melanoma risk include: *CDKN2A* germline mutation, having > 100 naevi, > 5 atypical naevi, fair hair, eye and skin colour, a strong family history, or a personal history of melanoma[6, 9, 10]. Within Australia, dermatologists typically adhere to The Cancer Council Australia's (CCA) guidelines, that recommend high-risk individuals undergo clinical skin examinations every 6 months using total body photography (TBP) in combination with sequential digital dermoscopy imaging (SDDI)[11, 12].

TBP provides a comparative record of the skin surface assisting in identification of new lesions and to an extent, changes of existing naevi. Dermoscopy enables the visualisation of the surface morphology of pigmented skin lesions and reveals colours and structures that normally are not visible to the naked eye. Dermoscopy has consistently been shown to improve the diagnostic accuracy of melanomas[13], and when used across visits it is particularly useful for detection of incipient melanomas, which lack typical dermoscopy features[14]. This 'two step' process involving both TBP and dermoscopy for skin surveillance was initially described in 2002[15] and has been repeatedly shown to be associated with a lower benign to malignant excision ratio and decreased Breslow thickness of subsequently diagnosed

melanomas[4, 13, 16, 17]. More recently, surveillance of clinical patients at high risk of melanoma has demonstrated efficacy and cost-effectiveness. A large ten-year, retrospective review of a High Risk Clinic (HRC) in Sydney, Australia reported that patients were diagnosed with thinner melanomas, and underwent fewer excision compared to standard care[4]. A review of previous studies exploring targeted screening for melanoma using visual skin inspection reported mixed findings for cost-effectiveness depending on the baseline level of risk for the targeted population[18].

Surveillance strategies have evolved significantly over the past decade. One of the most promising approaches involves automated three-dimensional (3D) imaging of subjects, allowing objective documentation of all existing lesions and monitoring changes over time. The VECTRA WB360 system described previously[19, 20] allows fast 3D total-body photography and construction of a patient avatar, along with integrated dermoscopy. Consumer feedback indicates high acceptability and confidence in the technology for skin monitoring, and importantly, whole body imaging may reduce melanoma-related anxiety[19]. The advances in total body imaging in recent years were unprecedented, and now enable high resolution 3D imaging in minutes. The impact of these changes on health economic models of high risk screening warrants investigation. It is the objective of the current study to examine the use of 3D imaging technology for targeted surveillance for individuals at high risk to melanoma.

The geographical distribution of the population in Australia creates additional challenges to equitable health service delivery [21]. Melanoma patients in rural areas of Australia are often disadvantaged with unequitable access to dermatological care and are reported to suffer 20% increased melanoma related mortality compared to urban areas[21]. Already now, rural physicians are using teledermatology to obtain second opinions on suspicious lesions from specialist dermatologists[22]. Incorporating 3D TBP into a teledermatology service could facilitate remote full body skin examination by teledermatologists reflecting the service level that urban patients can access. The current study will evaluate the feasibility of using a telehealth network for transmission of 3D TBP-SDDI images, and the concordance of diagnostic decisions between in-person skin examinations and remote teledermatologist review.

This study will recruit individuals that are at high risk of developing cutaneous melanoma to participate in a randomised trial comparing combined TBP and SDDI surveillance approach (3D TBP-SDDI), with routine clinical care. TBP and SDDI reportedly improves earlier detection rates[13, 23], however, the effect of 3D TBP is unknown. The feasibility of extending its use through a telehealth network will be explored. An evaluation of efficacy, costs, and consumer acceptability of the technology will determine long-term sustainability. Furthermore, a standardised, holistic approach to risk stratification for melanoma will be developed, optimising the identification of those who would most

benefit from this high-risk surveillance program. This study is an integral step in guiding change in the way high-risk individuals may be managed in Australia.

OBJECTIVES

Primary objectives

- Compare clinical outcomes of the 3D TBP-SDDI approach with routine clinical care, including numbers of excisions or biopsies and histopathological findings.
- Compare health economic outcomes of the 3D TBP-SDDI approach with routine clinical care.
- Evaluate consumer acceptance of the intervention, psychological well-being, health behaviour and beliefs regarding sun protection and melanoma.

Secondary Objectives

- Assess feasibility of telehealth to deliver remotely captured 3D TBP-SDDI for teledermatologist review.
- Evaluate the degree of concordance between teledermatologist and in-person examination in terms of clinical assessment and management decisions.
- Identify rare and deleterious gene variants associated with melanoma risk.
- Refine a risk stratification model that combines medical history, family history, phenotypic risk factors, and genetic results to produce a melanoma-risk score.

METHODS AND ANALYSIS

Study design and setting

A two arm, single-site, parallel randomised control trial (RCT) will recruit 330 participants, with a 50:50 allocation ratio between intervention and control groups. Study visits commenced in April 2018, and are expected to be completed by August 2021. The study site will be the Clinical Research Facility of the Translational Research Institute at the Princess Alexandra Hospital, Brisbane. The majority of study participants reside in South-East Queensland, Australia.

Participant and public involvement

Prior to applying for funding, we have conducted clinical research recruiting both average risk and high risk members of the public regarding skin surveillance since 2010, and have used questionnaires for participant feedback regarding skin cancer prevention which has contributed to the current study

design. Since 2016, we have held biannual consumer forums to inform the public and our study participants of our research progress, and to give consumers the opportunities to discuss their priorities and concerns regarding skin cancer prevention with our group.

Eligibility criteria

Individuals that are at high risk of developing a primary or subsequent primary melanoma will be invited to participate. High risk will be defined as having one of the following:

- At least one melanoma (including *in situ*) diagnosed before the age of 40
- Two or more melanomas (including *in situ*) diagnosed before the age of 65
- A strong family history (2+ first-degree relatives) and/or known pathogenic genetic mutation and/or a diagnosis of dysplastic naevus syndrome.

Recruitment

Participants will be recruited from a registry of research volunteers with the University of Queensland, Dermatology Research Centre, and by referrals from dermatologists and medical practitioners from South-East Queensland, over a 12-18 month period. Potential participants will be emailed a short description of the study and a copy of the Participant Information and Consent Form (PICF), followed by a phone call approximately 2 weeks thereafter.

Randomisation and blinding

Once consented at the initial baseline visit, participants will be randomised to either the intervention or control group with simple random sampling using the randomisation function in REDCap (Research Electronic Data Capture). REDCap is a secure, online study database software developed by Vanderbilt University, and administrated by The Queensland Clinical Trials and Biostatistics Centre at the School of Public Health, The University of Queensland. Simple randomisation method is selected as it is an agnostic approach which is straightforward to implement. It is acknowledged that this approach is vulnerable to random sampling errors, however we will account for this in our secondary analysis. An online random number generator[24] will create an allocation sequence table which will be uploaded to REDCap. Trial staff conducting patient visits will be blinded to the next allocation sequence. Due to the nature of the intervention once participants are randomised, allocation is unblinded.

To address the teledermatology objectives, a subset of participants will be evaluated two ways. Firstly by 3D-TBP SDDI and a face-to-face dermatologist, and secondly their images alone will be independently evaluated by another dermatologist.

Intervention

Participants randomised to the intervention group will receive clinical skin examinations, every 6 months for 2 years, supported by the 3D TBP imaging system (VECTRA WB360, Serial Number WB00009, Canfield Scientific, Parsipanny, NJ, USA). The VECTRA imaging system consists of a framework of 92 cameras, which simultaneously capture images of the participant holding one anatomical pose, to construct a 3D avatar. An attached dermoscopic camera (EOS Rebel T6i) enables imaging of individual naevi including anatomical localisation on the 3D avatar. Clinical skin examinations are performed at the time of imaging by dermatologically-trained medical practitioners, and images are reviewed and discussed fortnightly with an accredited dermatologist, simulating a teledermatology consultation to assess 3D-TBP avatars and corresponding dermoscopic images. Suspicious lesions will be discussed with the study participant by phone, and subsequently referred to their treating physician. Participants will be asked to continue attending their regular skin examination appointments.

Control

Participants randomised to the control group will be asked to continue attending their regular skin examination appointments (which may include 2D TBP), and to complete 6 monthly questionnaires (as described in Table 1, and Figure 1). At the end of the study, all control participants will be offered a clinical skin examination including 3D-TBP imaging.

Participant timeline

Participants in both groups will be evaluated over a two year period from baseline, with the intervention group attending visits at baseline, 6, 12, 18 and 24 months. The control group will attend the clinic in person at baseline and at 24 months, and will complete an online questionnaire at months 6, 12 and 18. Refer to Figure 1 for an overview of participant timeline and assessments.

Primary outcomes

The primary outcome for this study is the number of excisions. The other main outcomes are defined in three categories, including clinical, economic and consumer outcomes. The assessment of these outcomes are described in Table 1.

Table 1: Primary outcomes and methods assessments

Outcome Category	Themes evaluated	Data source	Time points
Clinical	Number and thickness of melanomas (including *in situ*) found.	Clinical records and pathology reports.	0, 6, 12, 18 and 24 months
	Skin excisions/biopsies and the histopathological categorisations.		
Economic	Participant healthcare services utilisation relating to skin surveillance and management.	Participant claims through the Medicare Benefits Schedule (MBS) and Pharmaceutical Benefits Scheme (PBS).	One-off extraction capturing the entire study period of 0-24 months
		Queensland Hospital Admitted Patient Data Collection (QHAPDC) database, the Healthcare Purchasing and System Performance (HPSP) data and the Health Service Funding Models.	
Consumer	Satisfaction and acceptability	Self-administered, validated questionnaire [25] adapted from the Technology Acceptance Model [26, 27]. Additional questions will capture satisfaction with travel, waiting times, appointment length, convenience and perceived financial value of the surveillance program. Recruitment and retention will contribute to analysis	0 and 24 months
	Health behaviours	Self-administered, validated questionnaire adapted from QSkin study to capture sun protective behaviours and relevant demographics [28].	0, 6, 12, 18 and 24 months

	Psychological well-being	Euro-QoL-5D [29], to capture quality of life index for the health economic assessment.	0, 6, 12, 18 and 24 months
	Health Beliefs	The validated Health Beliefs Survey [30, 31] to evaluate knowledge, perceived severity of melanoma, perceived personal risk and perceived worthiness of surveillance programs.	0, 6, 12, 18 and 24 months

Secondary outcomes

There are three secondary outcomes: the feasibility of viewing 3D TBP-SDDI images remotely using the telehealth network; the efficacy of performing skin examinations using 3D TBP-SDDI images using telehealth services; and lastly the identification of genetic mutations and their utility in melanoma risk stratification. The assessment of these outcomes are described in Table 2.

Table 2: Secondary outcomes and methods assessments

Outcome Category	Factors evaluated	Data source	Time points
Feasibility of telehealth approach	Technical feasibility of telehealth network for remote dermatological review of 3D TBP-SDDI images, and interoperability with hospital image repositories and integrated electronic medical records (iEMR).	• Investigate subsystems for image acquisition, storage and display by measuring network throughput (bandwidth) and latency between subsystems. • Measure data volume, and transmission time per 3D TBP-SDDI examination. • Assess the compression ratio of transmitted image files necessary to achieve adequate functionality. • Evaluate success of transmission and integrity of data.	24 months
Accuracy of telehealth skin examinations	Safety and accuracy of teledermatology review of 3D TBP-SDDI images.	• Review the concordance between provisional diagnosis and clinical management decisions of the teledermatologist to the gold standard of in-person dermatological assessment. • Assess comparative diagnostic accuracy between in-person clinical diagnosis,	0-24 months

		teledermatological diagnosis and histopathological diagnoses.	
Melanoma risk stratification in a high risk population	Genetic Results	• Saliva samples collected using Oragene DNA self-collection kit. Methods for sample processing described previously [25].	Baseline
		• Whole Exome Sequencing (WES) or Sanger sequencing used to identify rare, pathogenic, germline variants in known melanoma genes. • Common variants associated with melanoma risk will be genotyped using Illumina CoreExomev24 chip array.	12-24 months
	Sun behaviour	• Self-administered, previously validated sun behaviour questionnaire to record sun protective behaviour, sun exposure, sunburn history, personal and family skin cancer history, and relevant demographic information [25, 28].	Baseline
	Deep phenotyping	• Documentation of eye, hair and skin colour. • Spectrophotometer readings for skin colour on the right arm including; the proximal anterior bicep, proximal anterior forearm, and proximal posterior forearm, using Spectrometer CM-600d (Konica Minolta inc., Osaka, Japan). • Digital photographs of participant's irises using a Nikon D3400 Digital Single-Lens Reflex (DSLR) camera (Nikon, Tokyo, Japan). • Freckling on the face, dorsum of right hand and shoulders are rated 0 to 4 (=none, mild, moderate, severe) to produce an overall freckling score.	Baseline

Data collection and management

Baseline questionnaire and clinical data will be entered into the REDCap database. 3D-TBP-SDDI images will be captured using the VECTRA Imaging System and integrated software. Pathology reports will be requested from the Queensland Cancer Registry and medical records. One-off extractions of claims and health service data will occur at the end of follow-up from the Medicare Benefits Schedule (MBS) and Pharmaceutical Benefits Scheme (PBS), the Queensland Hospital admitted Patient Data Collection (QHAPDC) database, the Healthcare Purchasing and System Performance (HPSP) data, and the Hospital and Health Service Funding Models. By linking data, the whole journey of healthcare service contacts and patient skin cancer outcomes will be captured, to allow an estimate of related costs of skin cancers. Costs will be analysed from the health provider (government) perspective. Intervention resources will be compiled and monitored by the project manager.

Saliva samples and subsequent sequencing results will be coded and linked using a re-identifiable Study ID. Data linking identifying information and Study ID will be stored in a password-controlled database, on a secure server, accessible to a limited subset of the study team to ensure privacy.

The REDCap management system, the VECTRA images and all remaining electronic data will be stored under The University of Queensland Research Data Management system on a secured network. Identifiers are removed from all participant data and replaced with a unique Study ID to further protect privacy. Regular quality assurance checks of image data and REDCap entries will be conducted.

Data monitoring

The study team determined that an independent data monitoring committee (iDMC) was not required as the risk to study participants was low, mainly relating to privacy and the possibility of unnecessary excision or biopsies. Privacy risks are mitigated as discussed above. An 'Issues Register' will be kept to record technical problems that occur during trial visits. Interviews with key stakeholders will identify problematic procedures. Any concerns with data quality or issues recorded will be discussed at regular team meetings. The study team will perform regular data monitoring and quality assurance tasks internally, and any protocol deviations or adverse events will be reported to the ethics committee.

STATISTICAL METHODS

Sample size

The study aims to recruit 330 high risk participants over a 12-18 month period, to be powered to compare excision rates between groups. This sample size is based on previously reported difference in excision rates in a high risk sample, between those monitored by TBP (mean=0.81, SD=0.75), and a

standard care group (mean=2.55, SD=2.01)[4]. The definition of high risk is broader in this study, and approximately a third of participants are likely to be already monitored using TBP, therefore the difference between routine clinical care and monitoring with 3D TBP is likely to be smaller. Given this, the study was powered to observe a 50% smaller difference in excision rates than observed previously[4], including an increase in standard deviation of 50% within each group (mean intervention 0.81 (SD=1.13), mean control 1.68 (SD=3.02)). Given these estimates, with a power of 90% and a significance level of 5%, 153 participants will be required for each arm of the trial. Allowing for participant withdrawal, we will aim to recruit a total 330 participants.

Baseline demographic

Descriptive statistics will be used to summarise demographic and clinical characteristics for both the control and intervention groups. Chi-square tests will be used to estimate difference in proportions of categorical variables between the two groups, and t-tests will be used for continuous variables. Non-parametric equivalents will be used if the assumptions of the parametric tests are violated. Results will be considered statistically significant if $p < 0.05$.

Clinical outcomes

A non-parametric Mann-Whitney test will be used to assess the clinical primary outcome to test if there is a difference in mean annual rate of lesion excisions/biosies between the intervention and control groups, given the primary outcome is based on counts and therefore unlikely to follow a normal distribution. The primary outcome will be analysed as intention to treat, with a per protocol analysis as a secondary outcome. This outcome will also be re-evaluated on a subset excluding those from both the intervention and control groups who are receiving 2D TBP. The benign to malignant ratio for excisions of pigmented lesions and non-melanoma skin cancers will be calculated for both groups. Chi-square or fisher's exact test (as appropriate) will be used to compare the difference in proportions of pathology confirmed melanoma, melanoma in-situ, BCCs and SCCs dignosed between the two groups with diagnosis. Logistic regression analyses will be used to investigate the relationship between baseline demographic and phenotypic information, and past melanoma history. A subgroup analysis of participants diagnosed with melanoma excluding in-situ, and melanoma including in-situ will investigate the differences in staging, Breslow thickness and body site and other parameters of interest, between the two groups, using linear, logistic and generalised regression models as appropriate. As above, results will be considered statistically significant if $p < 0.05$. As primary outcome data will be collected through Medicare information consented to at baseline, there will be no or very

minimal missing data. Therefore assuming the data is missing at random, we will remove participants with no outcome data from that analysis.

Economic outcomes

The economic analysis will assess the resource and cost differences between arms rather than a full economic evaluation due to the relatively short follow-up and small sample with which to detect health outcomes such as skin cancers. Data from Medicare and Queensland Health sources will be linked and aggregated for each patient covering the surveillance period of the study. Skin cancer related resource use will be identified and coded according to ICD-10, procedure and MBS/PBS items. Cost data are typically skewed so generalised linear models will be used with a gamma family and log link (if appropriate) to assess differences between the intervention and control groups. Non-parametric bootstrapping methods will also be applied for verification of differences in costs between groups. Subgroup cost analyses of hospital versus out-of-hospital, melanoma stage, age, phenotypes or other patient characteristics will be explored.

Telehealth review outcomes

The main telehealth outcome is the level of agreement in clinical decision between the teledermatologist and the dermatologist carrying out an in-person skin examination assessment. Four decision outcomes will be considered: No action (no suspicious lesion), follow up in 3-6 months, excision of lesion/s, and treatment of lesion. Weighted Cohen's kappa coefficient will be calculated to measure agreement across the four categories using R package irr[32]. A kappa between 0.6-079 will indicate substantial agreement, while a kappa of greater than 0.8 will indicate almost perfect agreement[33].

Melanoma risk score development

Multivariable logistic regression will be used to assess what combinations of genetic, phenotypic and demographic risk factors are associates with an increased odds of melanoma within a high risk population. Variables with $p < 0.2$ in univariate regression will be included in the model, and backwards step-wise regression will be used, with variables in the model remaining statistically significant at the 5% level. Validation of the resulting risk stratification algorithms will be performed on larger collaborative cohorts.

Consumer perspectives

Data will be collected to determine the acceptability and feasibility of 3D imaging and any potential barriers and facilitators to implementation and adoption. This will include information related to convenience, comfort, and reasons for participant retention/loss, and data on quality of life and fear of recurrence.

Questionnaire data will be prepared according to each scale's manual and standard procedures[25-31]. Total and subscale scores will be computed and tested for normality. If normally distributed, parametric tests will be used, otherwise non-parametric analytic procedures will be used as described above to assess differences between the two groups in the consumer self-reported outcomes.

ETHICS AND DISSEMINATION

The protocol has been prepared in concordance with the Standard Protocol Items Recommendations for Interventional Trials (SPIRIT) statement[34]. This study has received Human Research Ethics Committee (HREC) approval from Metro South Health HREC (HREC/17/QPAH/816) and The University of Queensland HREC (2018000074). The trial has been prospectively registered (ANZCTR12618000267257). Following national guidelines, if genetic sequencing reveals a high penetrance pathogenic mutation, clinical genetic testing will be offered to the participant. A reimbursement of $20 per visit will be paid to participants to assist in covering travel and/or parking costs. Study results will be disseminated through peer-reviewed publications, conferences and non-peer reviewed media outlets.

DISCUSSION

This will be the first RCT to assess the feasibility, efficacy and cost effectiveness of combining 3D TBP, with SDDI for clinical skin examinations of individuals at high-risk to melanoma in Australia. Consumer perceptions of the technology and its clinical utility will also be assessed. This study will enable us to determine whether excision rates and stage of melanoma detection are affected by the inclusion of 3D TBP-SDDI in a surveillance protocol. Exploring the societal and personal costs of the intervention will be invaluable in determining the feasibility of incorporating this technology in routine clinical care for this high-risk cohort. The study will determine whether remote administration of 3D TBP, with SDDI combined with teledermatologist evaluation will affect clinical management. For greater public benefit in the longer term, it is critical to be able to accurately identify high-risk individuals who might benefit from this more intensive surveillance approach and, therefore, this study aims to develop a holistic risk stratification algorithm.

Australia currently has three national population-based screening programs for early detection of breast, cervical and bowel cancers. However, there is no similar program for skin cancer, despite melanoma being Australia's 4th most common cancer[10]. The number needed to screen (NNS) in the Australian general public to save one life from melanoma has been estimated at 25,000[35]. Therefore, population-based screening for melanoma may not be justified. However, by focusing on a high-risk population the probability of detecting a melanoma increases and the NNS decreases. Furthermore, the incorporation of TBP-SDDI enables a 'watch and wait' approach which would reduce the number needed to treat (NNT) based on the benign to malignant excision ratio, resulting in health cost savings[11]. Criteria for an effective screening program, outlined by the Australian Institute for Health and Welfare[36], stipulate that: the disease must be highly prevalent; the natural course of the disease is well understood including a recognisable latent or early symptomatic stage where disease can be detected; that there is available treatment which is effective and well accepted; the disease must cause considerable costs, both fiscally and clinically; and lastly, the screening program must be cost effective. With the criteria in mind, the current protocol is intended to build the evidence for a future targeted surveillance program for melanoma detection in high-risk individuals in Australia, including solutions for geographical challenges. Economic evaluation of resource use and associated costs collected through linkage of clinical and administrative healthcare data sources, will capture the whole journey of health service contacts and outcomes, to accurately estimate the related costs of screening and skin cancers within this high risk population.

CONCLUSION

This protocol will provide evidence as to whether pursuing the incorporation of 3D TBP-SDDI into a surveillance program for high-risk individuals can be cost effective and provide superior clinical outcomes over the current routine clinical care. Secondary outcomes will drive solutions in defining the population which would maximally benefit from this program, and determine the acceptability of this surveillance method. Furthermore, the study will determine if the 3D TBP-SDDI technology is suitable for review through telehealth services, supporting solutions for outreach to remote regions of the country.

AUTHOR CONTRIBUTIONS

CAP, AMM, BB-S, DCW, LGG, LJC, JFA, EE, SO, LG, BMS, MJ, HPS, AND AF were all involved in developing the study protocol. HPS, AF, MJ, BMS, LG, SO, EE, JFA, LJC, LGG, AND DCW worked

together on the funding proposal. BB-S provided support for the development of the statistical analysis plan. All authors 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., a Medical Advisor for First Derm, and has a Medical Advisory Board Appointment with MoleMap NZ Limited.

Word count: 3723 (excluding figure/table, abstract and references), 2 tables, 1 figure.

Figure titles and legends

Figure 1: Overview of participant timeline and assessments (see attached PDF)

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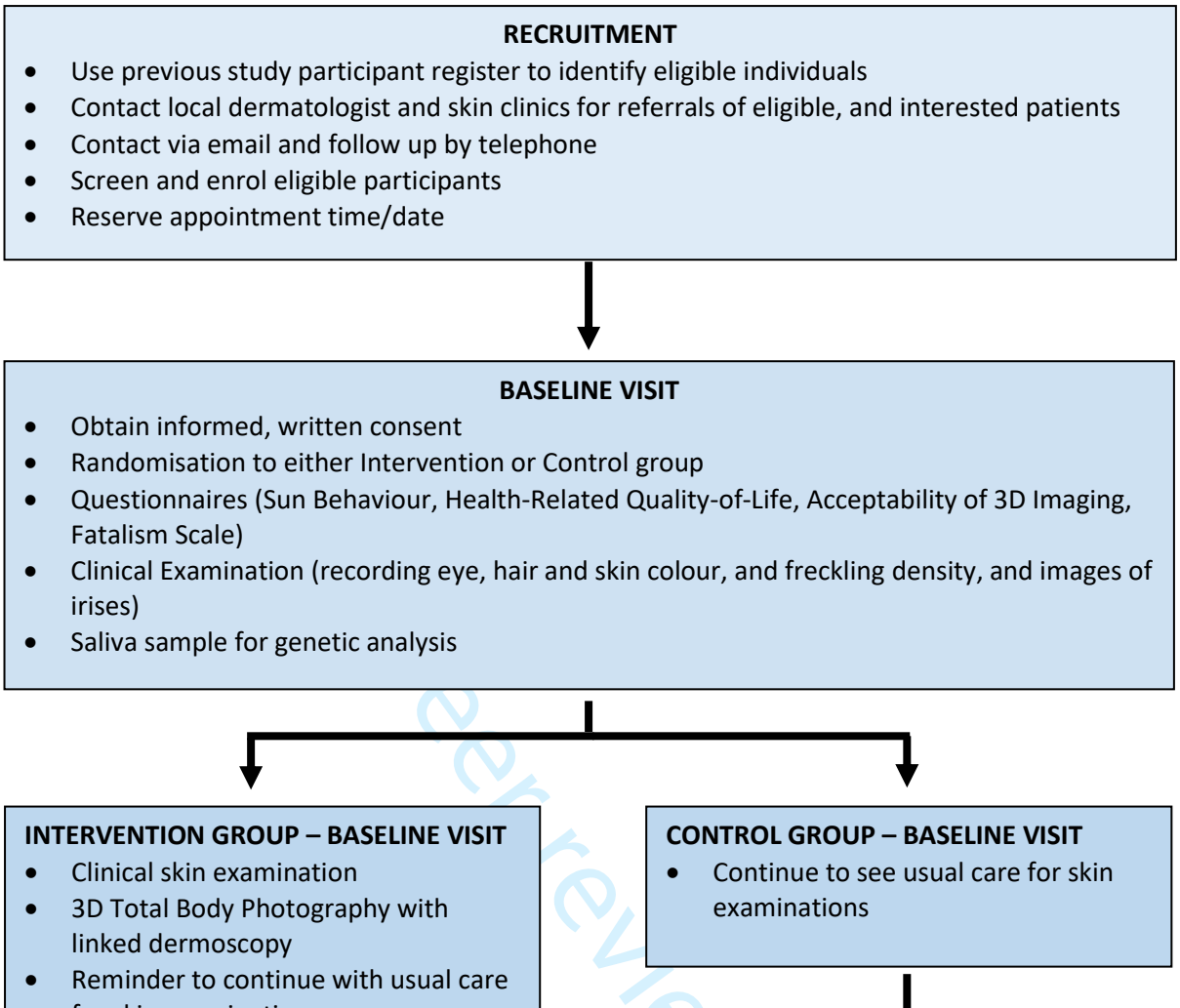

SPIRIT
STANDARD PROTOCOL ITEMS: RECOMMENDATIONS FOR INTERVENTIONAL TRIALS

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.