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Improving Skin cancer Management with ARTificial Intelligence (SMARTI): protocol for a Phase II pre-post intervention trial of an Artificial Intelligence system used as a diagnostic aid for skin cancer management in a specialist dermatology setting

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Abstract

Introduction

Convolutional neural networks (CNNs) have diagnosed skin cancers with impressive accuracy in experimental settings. However, these AI-diagnostic algorithms require further validation in prospective clinical trials.

Methods and analysis

Participants will be recruited from skin cancer assessment clinics at the Alfred Hospital and Skin Health Institute, Melbourne. Skin lesions will be imaged using a proprietary dermoscopic camera. The AI algorithm, a CNN developed by MoleMap Ltd and Monash eResearch, classifies lesions as benign, malignant or uncertain.

This is a pre-post-intervention study. In the pre-intervention period, treating doctors are blinded to AI lesion assessment. In the post-intervention period, treating doctors review the AI lesion assessment in real time, and have the opportunity to then change their diagnosis and management. Any skin lesions of concern and at least two benign lesions will be selected for imaging. Each participant's lesions will be examined by the registrar and consultant dermatologist, and later assessed by a teledermatologist.

At the conclusion of the pre-intervention period, the safety of the AI algorithm will be evaluated by measuring its agreement with the consultant dermatologists' classification and with histopathology for biopsied lesions.

Primary analysis will evaluate AI performance by assessing agreement between AI lesion classifications and those of the teledermatologist. AI classifications will also be compared with those of the registrar, treating dermatologist and histopathology. The impact of the AI algorithm on appropriateness of management decisions will be evaluated by: 1) comparing the initial management decision of the registrar with their AI-assisted management decision, using the consultant dermatologist's initial management decision as the reference standard; and 2) comparing the benign to malignant ratio (for lesions biopsied) between the pre-intervention and post-intervention periods.

Ethics and dissemination

Human Research Ethics Committee (HREC) approval received from the Alfred Health HREC on 14th February 2019 (HREC/48865/Alfred-2018).

Trial registration

ClinicalTrials.gov identifier: NCT04040114.

Strengths and limitations of this study

- The first prospective clinical trial to evaluate safety and performance of an Artificial Intelligence diagnostic aid for skin cancer detection and management in the real-world clinical setting.
- Participants are recruited on a consecutive basis from routine attendance at melanoma and skin cancer assessment clinics, forming a representative sample of patients and lesion phenotypes from which to evaluate AI algorithm performance.
- AI performance will be compared with Teledermatologist assessment, as well as to face-to-face assessors of varying clinical experience (registrar and consultant dermatologist), and with histopathology results for biopsied lesions.
- Longitudinal follow-up is not undertaken and the ultimate malignancy status of lesions will not be evaluated in this phase II study.
- Inherent differences in application of AI in the specialist setting may limit generalisability of study findings (regarding AI utility) to primary care settings, necessitating further research to establish feasibility for broader clinical implementation.

Introduction

Skin cancer, including melanoma and keratinocyte carcinoma, is the most common type of cancer in Caucasian populations, and its incidence is increasing worldwide[1-3]. The incidence of keratinocyte carcinoma is difficult to establish precisely due to a lack of nationwide cancer registry data, although Australia is thought to have the highest incidence worldwide, with over 1000 cases per 100,000 person-years[4]. Similarly, Australia has one of the highest incidence rates of melanoma in the world, with almost 14,000 Australians diagnosed with invasive and more than 20,000 with in-situ melanoma each year[5]. Melanoma is the third most commonly diagnosed invasive cancer irrespective of gender and is responsible for over 1600 deaths each year[5].

Early diagnosis of skin cancer reduces morbidity and, in the case of melanoma, is associated with significantly improved survival[3, 6]. More accurate and timely skin cancer diagnosis and management could be brought about by the use of new Artificial Intelligence (AI)-based diagnostic aids[7-9].

A subset of AI is machine learning. Machine learning refers to the ability of a computer system to write its own programming for a task, and to automatically learn and improve through training data. Deep learning is a branch of machine learning which is becoming increasingly utilised in medicine[10]. Convolutional neural networks (CNNs) are a class of artificial neural networks that are most often used to analyse visual imagery through deep learning. They are especially effective at automated image recognition.

CNNs have been tested with the task of diagnosing skin cancers in multiple studies, and have displayed impressive accuracy equal or superior to that of the dermatologists with whom they have been compared[11-20]. However, these studies have thus far been undertaken in experimental (in silica) settings, and the use of AI as a diagnostic aid has not been adequately evaluated in the real-world clinical setting and in the hands of clinician end-users[8, 21].

AI algorithms should be tested with datasets separate to those with which they are trained, in order to avoid over-fitting or prior dataset bias, which can lead to over-estimation of an algorithm's accuracy[22, 23]. In particular, AI algorithms should be tested on the end-target patients or lesions to ensure their reliability and safety in their intended setting.

Furthermore, in the real-world, dermatologists have additional clinical information (for example, patient demographics and skin cancer history), which improves their diagnostic accuracy[24]. Previous studies comparing AI and dermatologist diagnostic accuracy without provision of this clinical information have therefore disadvantaged dermatologists.

Additionally, these experimental studies positing AI and dermatologists as opponents have been unable to assess the impact of AI algorithms, when used by clinicians, on clinicians' diagnoses and management decisions.

There is a need for prospective clinical trials to validate performance and ensure generalisability of the algorithms, and to evaluate the safety, utility and feasibility of implementing an AI diagnostic aid for skin cancer detection in the clinical setting[8, 11, 12, 25].

This Phase II validation study will evaluate the utility of AI as a diagnostic aid for skin cancer detection and management in the specialist dermatology setting, prior to a larger Phase III trial of the intervention in the primary care setting.

If AI diagnostic aids for skin cancer management are proven safe, consistent and reliable in a specialist setting, implementation in primary care should be considered and when examined carefully may lead to earlier detection and improved management of malignant lesions, improved appropriateness of specialist referrals (and subsequently reduced waiting times and improved access), fewer biopsies of benign lesions, thereby reducing healthcare system costs without compromising patient outcomes[7, 9].

Objectives

Primary Objective:

Evaluate performance of the artificial intelligence diagnostic aid, using teledermatologist skin lesion assessment as reference-standard.

Secondary Objectives:

- Evaluate the impact of the AI device when used as a diagnostic aid on the appropriateness of skin cancer management decisions.
- Evaluate the safety of the AI device when used as a diagnostic aid for skin cancer detection.
- Assess the feasibility of implementing the AI device as a diagnostic aid for skin cancer detection and management.

Methods and analysis

Study design and setting

A Phase II pre-post intervention study of an AI diagnostic aid for skin cancer detection and management.

Participants will be recruited between October 2019 and May 2021 from the patient population attending specialist dermatology and melanoma clinics at two Australian tertiary centres: Skin Health Institute and the Alfred Hospital in Melbourne, Australia. Participants attending these clinics have a suspected or confirmed diagnosis of skin cancer, or are attending for routine skin surveillance.

Participant and public involvement

The study protocol is endorsed by the Melanoma and Skin Cancer (MASC) Trials group, a registered not-for-profit Australian Cancer Collaborative Trials Group member and affiliate of Monash University. All MASC Trials endorsed protocols are subject to review by consumer group representatives, including members of the Australian Melanoma Consumer Alliance.

Eligibility criteria

Patients aged 18 or over, with at least one skin lesion of concern (to either the patient or treating doctor, excluding acral or scalp lesions), who are able to provide written informed consent and are willing to have multiple lesions imaged are eligible to participate.

Recruitment

Participants are recruited on a consecutive basis via convenience sampling from routine attendance at specialist clinics. Those who meet eligibility criteria are invited to participate during their clinic consultation. The participant information and consent form (PICF) is completed, with a copy provided to the participant.

Randomisation and blinding

In this pre-post intervention study design, the pre-intervention period will provide an estimate of skin cancer management parameters as a comparator (control) for assessing the impact of AI in the post-intervention period. Participants are recruited on a consecutive basis during each of the pre-intervention and post-intervention periods; there is no randomisation. Data is collected on participant risk factors and potentially relevant confounders to be considered during analysis.

In the pre-intervention period, treating doctors remain blinded to each other's lesion assessment and are unexposed to the AI assessment. Teledermatologists are blinded to the treating doctors' diagnoses and management plans, and to the AI assessment.

In the post-intervention period, treating doctors record their initial diagnosis and management plan decision, and are then exposed to the AI assessment prior to recording a final AI-assisted diagnosis and management plan. The teledermatologists remain blinded to the treating doctors' diagnoses and management plans, and to the AI assessment.

Description of the Intervention: The SMARTI Artificial Intelligence System

The investigational device includes a proprietary MoleMap Ltd camera capable of taking dermoscopic and macroscopic images and uploading them to an adjacent conventional computer, and the artificial intelligence software that performs lesion assessments. The computer displays the participant's avatar and lesion images, along with diagnostic and management plan options from which the doctor chooses (Figures 1 and 2). Prior to the commencement of the study, research and medical staff working in the clinics receive training on use of the camera, uploading of images and use of the computer software for making diagnoses and management plans.

The SMARTI AI system is a convolutional neural network (CNN) trained to classify lesions using a three-point scale: benign, malignant or uncertain. Figures 1 and 2 demonstrate the SMARTI computer displays and participant avatar indicating the lesion location.

In a laboratory setting, when compared with teledermatologist lesion classification, the first version of the CNN demonstrated a sensitivity of 85%, specificity of 78%, and area under the receiver operating characteristic curve (AUROC) of 0.91 for detection of melanoma; and a sensitivity of 72%, specificity of 88%, and AUROC of 0.89 for distinguishing a "cancer" from a benign lesion in a binary decision task. These results are comparable to those in pre-existing literature[11-13]. The AUROC is a statistical measure used to assess the discrimination ability of a diagnostic test when there is a dichotomous outcome[26]. An AUROC of 1.00 would mean that the test can discriminate perfectly between the two outcomes. The algorithm was tested with different images to those with which it was trained, however they were derived from the same dataset of images from MoleMap Ltd. Both macroscopic and dermoscopic images were used to train the algorithm.

The CNN has since been updated to improve its sensitivity and specificity. The algorithm used in the post-intervention period will be the algorithm which classifies the lesions imaged during the pre-intervention period with the greatest accuracy, as assessed by the interim quality assurance analysis.

Pre-intervention period

In the pre-intervention period, lesion assessments made by the AI algorithm are not visible to the treating doctors and therefore do not contribute to diagnostic or management decisions applicable to each lesion.

Participants receive standard of care according to Australian Guidelines [27, 28], including a full skin examination. The participant is first examined by a registrar who selects all skin lesions of concern for imaging, along with two or more non-suspicious lesions. These randomly selected non-suspicious lesions are included to enable analysis of the AI algorithm's specificity. Macroscopic and polarised dermoscopic images are obtained for each lesion, and are uploaded to the participant's electronic Case Report Form (eCRF), with the location of each lesion recorded on a digital avatar. The registrar records their initial favoured diagnosis and management plan for each lesion in the eCRF. Once entered, the diagnostic classification and management plan is locked and cannot be altered.

The consultant dermatologist then assesses the participant, recording their favoured diagnosis and management plan for each lesion in the eCRF. If the consultant identifies

additional lesions of concern, these are imaged and uploaded to the eCRF and are assessed by the consultant only.

The participant receives recommended management advice from the consultant dermatologist for each lesion, and the final patient-agreed management plan is recorded in the eCRF.

All lesion images are reviewed remotely by one of three experienced teledermatologists. The teledermatologist records their favoured diagnosis and management plan in the eCRF for each lesion. This information is not visible to the treating doctors.

At the conclusion of the pre-intervention period, the AI algorithm will be applied to generate assessment of all lesions for an interim Quality Assurance analysis to evaluate safety of the AI algorithm prior to its use in the post-intervention period.

Post-intervention period

Following the same procedure described above for the pre-intervention period, participants will be examined by the registrar. Lesions of concern and non-suspicious lesions will be selected, photographed, and uploaded to the eCRF. The registrar will record their initial favoured diagnosis and management plan for each lesion and will then submit the images to be analysed by the AI algorithm. The AI assessment will be visible to the registrar in the form of a benign, malignant or uncertain classification for each lesion. Upon review of the AI assessment, if they choose to, the registrar can update their diagnosis and management plan

for each lesion, which will be recorded as an additional AI-assisted diagnosis and management plan in the eCRF.

The consultant dermatologist will then assess the participant and record their favoured diagnosis and management plan for each lesion in the eCRF. The consultant dermatologist will also submit the same images to be analysed by the AI algorithm. The AI assessment will then become visible to the consultant. Upon review of the AI assessment, if they choose to, the consultant dermatologist may update their diagnosis and management plan for each lesion, which will be recorded as an additional AI-assisted diagnosis and management plan in the eCRF.

The participant will then receive recommended management advice from the consultant dermatologist, which will be recorded on the eCRF. The final plan agreed upon between the participant and treating doctors will be recorded. If either the consultant dermatologist initial or AI-assisted management plan included the decision to biopsy, the biopsy will be undertaken. This is to ensure that standard of care is provided.

The teledermatologists will assess all lesion images remotely following the patient visit and record their favoured diagnosis and management plan in the eCRF, maintaining blinding to the AI assessments. The teldermatologists' diagnoses and plans will not be visible to the treating doctors during either period. The teledermatologists' diagnoses and plans will therefore not influence management decisions in the clinic. Rather, they will be collected for the purpose of comparing and evaluating the accuracy of the AI assessments. All management

decisions will ultimately be determined by the treating consultant dermatologist in the clinic (after discussion and agreement with the participant), in line with the standard of care.

Participant timeline and follow-up procedures

The participant will exit the study after the single study visit is completed if the participant's lesions have all been managed by either: 1) reassurance that no action is required; or 2) non-surgical treatment, such as cryotherapy or imiquimod cream.

If a participant has lesions which have been biopsied or surgically treated, and has no lesions to be monitored, they will exit the study at the time of receipt of the histopathology result.

If any lesions are to be monitored, participants will exit the study when either: 1) the monitored lesion(s) progress to biopsy at the three- or six-month follow-up, and the histopathology results are received; 2) the monitored lesion(s) are classified as benign at the three- or six-month follow-up; or 3) the participant is lost to follow-up (Figure 3).

Upon study completion, participants will continue to undergo routine surveillance depending on their level of risk and will receive treatment for all lesions as per Australian Guidelines (Figure 3).

Primary outcomes

The primary outcome measure for this study is lesion classification, using a three-point scale: benign, uncertain, or malignant. Definitions and examples for these classifications are given in Table 1. The intention of the 'uncertain' classification option for clinicians is to highlight

lesions for which a diagnostic tool is most likely to be called upon. The aim of the 'uncertain' class for the algorithm is to enable AI categorisation of lesions which are not definitely benign or malignant (for example, severely dysplastic naevi or low grade actinic keratoses), without misleading the clinician.

The primary analysis to evaluate AI performance will compare lesion classification determined by the AI algorithm to lesion classification according to teledermatologist assessment (as the reference standard).

The primary safety measures include: 1) for all lesions, the proportion of false positive lesion classifications of the AI algorithm that lead to inappropriate registrar management decisions; and 2) for all biopsied lesions, the proportion of false negative lesion classifications of the AI algorithm, using histopathology as the reference standard.

Secondary outcomes

The secondary outcome is the management decision made by treating doctors, per lesion using the five categories: leave; manage – monitor; manage – biopsy; treat – elective; or treat – essential. Table 2 describes management decision outcome categories.

There are seven secondary endpoints: 1) lesion classification of the AI algorithm compared with dermatologist classification; 2) lesion classification of the AI algorithm compared with registrar classification; 3) lesion classification of the AI algorithm compared with histopathology results of any lesions biopsied; 4) initial management decision of the registrar compared with their AI-assisted management decision, using the consultant dermatologist's

initial management decision as the reference standard; 5) discordance in the initial and AI-assisted dermatologist management decision during the post-intervention period; 6) management decision of the teledermatologist compared with the AI-assisted registrar, using the initial consult dermatologist management decision as the reference standard; and 7) the benign to malignant ratio for lesions biopsied in the post-intervention period compared with the pre-intervention period.

Data collection and management

Participant demographic and risk factor data, including personal and family history of melanoma and keratinocyte carcinoma, ascertained by participant recall will be collected during interview by study staff, recorded directly to paper Case Report Forms (pCRFs) and transcribed to the eCRF at study visit completion.

Pathology reports will be obtained from participants' medical records and relevant histopathology data will be transcribed directly to the eCRF.

Data entered to the custom eCRF platform by study site staff will be automatically synchronised to the electronic database tables built in Microsoft Access. The database will contain only de-identified, re-identifiable data appended to the participant's unique numerical study identifier. The database will be securely stored and backed-up within an approved data-sharing platform with infrastructure enabling at rest encryption using 256-bit Advanced Encryption Standard and Secure Sockets Layer /Transport Layer Security to protect data in transit with 128-bit or higher Advanced Encryption Standard encryption.

Data Monitoring

Routine risk-based monitoring will be undertaken by MASC Trials Ltd for the purpose of source data verification at regular intervals throughout the trial. Data management is centralised to MASC Trials Research Centre at Monash University, who will be responsible for ongoing surveillance of data quality and integrity.

An independent Data Safety Monitoring Committee will be established to monitor study accrual rates and ethical conduct, to review accumulating data with respect to device safety and performance, and to make recommendations to the Trial Management Committee with respect to study continuation.

The Trial Management Committee will conduct regular meetings to review all aspects of study conduct, compliance and progress, in addition to data quality assurance, protocol deviation and adverse event review activities. Adverse events and protocol violations will be reported to the approving HREC according to HREC-specific guidelines.

Statistical methods

Sample size

The study aims to recruit 220 participants, providing a minimum of three lesions per participant to the final analysis, thus providing sufficient power to estimate, with reasonable precision, the AI algorithm lesion classification accuracy using teledermatologist assessment as the reference standard. Sample calculations are based on the assumption that 20% of lesions will be categorised as malignant and 10% will be categorised as uncertain; therefore, approximately 30% of lesions will be categorised as 'not benign' by teledermatologist assessment. If a kappa statistic of 0.8 signifies 'almost perfect' agreement[29], we will require

approximately 220 participants in order to achieve a 95% confidence interval of +/- 0.05 (i.e. 95% CI 0.75 to 0.85).

Statistical analysis

AI algorithm lesion classification accuracy

The AI algorithm lesion classification accuracy will be compared to relevant physician assessors and histopathology results (for lesions biopsied) as reference standards using Kappa statistics to evaluate agreement between benign/uncertain/malignant lesion classification, with quadratic weights used for kappa calculation. Standard validity indices will be used to evaluate discriminatory ability of the AI algorithm for malignant lesions, including sensitivity, specificity, and positive and negative predictive values.

Performance errors of the CNN will be examined closely. Specifically, all lesions which are classified as benign by the CNN and malignant by the consultant dermatologist or histopathology, and all which are classified as malignant by the CNN and benign by the consultant dermatologist or histopathology, will be reviewed by a dermatologist to determine the nature of these errors.

Appropriateness of AI-assisted management

The impact of the AI diagnostic aid on appropriateness of the registrar's management decision will be evaluated by measuring the proportion of false positive lesion classifications of the AI algorithm that lead to inappropriate registrar management decisions; comparing the initial registrar management decision with the AI-assisted registrar management decision; and comparing the management decision of the teledermatologist with the AI-assisted

registrar decision (all using the dermatologist's initial management decision as the reference standard). The appropriateness of the AI-assisted management will be further assessed by measuring discordance between the initial and AI-assisted management decisions of the dermatologist; and by comparing the benign to malignant ratio (for lesions biopsied) between the pre-intervention and post-intervention periods.

Interim quality assurance analysis

Following the conclusion of the pre-intervention period, an interim Quality Assurance analysis will be conducted to evaluate safety of the AI algorithm to be implemented in the clinical setting during the post-intervention period. The safety of the AI algorithm will be evaluated by its agreement with the consultant dermatologists' classification (as benign, malignant or uncertain) for all lesions, and with the histopathology classification for biopsied or excised lesions. Kappa statistics and standard validity indices will be used to assess agreement, evaluating safety of the AI diagnostic aid with reference to gold-standard clinical care provided by consultant dermatologists. The focus of this analysis will be to ensure that the accuracy of the AI algorithm is on par with that of previously produced algorithms[30].

Ethics and dissemination

The protocol has been developed to comply with international standards of Good Clinical Practice (ICH-GCP E6(R2) and TGA Annotation 2016), NHMRC *National Statement* (2018) and *The Code* (2018), and all relevant national, state and local legislative requirements governing data privacy and handling. Study conduct will adhere to principles set out in Declaration of Helsinki 1962 (rev. 2000) and the aforementioned standards.

The findings from this study will be disseminated through peer-reviewed publications, non-peer reviewed media outlets, and conferences.

In the Patient Information Sheet and Consent Form, participants are asked whether they consent for their de-identified skin lesion images to be used freely for other research studies. There is an additional tick box on the form for participants to indicate consent for this.

The CNN and its code, which is currently an unapproved tool, cannot yet be accessed by the public.

Conclusion

This will be the first study to evaluate the accuracy, safety and feasibility of implementing an AI-driven diagnostic aid for skin cancer detection and management in a clinical setting. The study will provide an understanding of the AI device performance in comparison to highly relevant real-world clinical reference standards, representing varying degrees of experience and, therefore, accuracy in skin cancer detection. Additionally, we will gain appreciation for the potential impact of the AI diagnostic aid on the appropriateness of clinician management decisions. The study will provide unique insights into the utility and feasibility of implementing an AI-driven diagnostic aid for skin cancer in a specialist dermatology setting, prior to a Phase III trial of the intervention in primary care.

Contributors:

All authors were involved in developing the study protocol. VM, RW, MH and ZG worked together on the funding proposal. ZG developed the Artificial Intelligence algorithm to be

used in the study. RW provided support for the development of the statistical analysis plan. AB and AS provided technical support with the MoleMap computer software. All authors reviewed, edited and approved the final version.

Competing Interests:

VM is supported by an NHMRC Early Career Fellowship. VM reports personal fees from Novartis, personal fees from Bristol-Myers-Squibb, personal fees from Merck, outside the submitted work.

MH reports personal fees from MoleMap Ltd, during the conduct of the study; and is a shareholder in MoleMap Ltd.

AB reports personal fees from MoleMap Ltd, during the conduct of the study; personal fees from Molemap Ltd, outside the submitted work; and is a shareholder in Molemap Ltd.

AS reports personal fees from MoleMap Ltd, during the conduct of the study; personal fees from Molemap Ltd, outside the submitted work.

NW and SM are former employees of the Cancer Collaborative Trials Group contracted to implement the SMARTI Study - Melanoma and Skin Cancer (MASC) Trials Ltd.

CF is supported by a Monash University Research Training Program Scholarship.

RW, ZG, NA, WC and MW have nothing to disclose.

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Tables

Table 1. Classification definitions

Classification	Definition/situation	Examples

Benign	When the clinician is confident that the lesion is benign	Benign naevus, or seborrheic keratosis
Uncertain	When the clinician is unsure and would like a second opinion	Any skin lesion about which the clinician is not confident with regards to its benign/ malignant status
Malignant	When the clinician is confident that the lesion is malignant	Melanoma, basal cell carcinoma, squamous cell carcinoma, actinic keratosis*

* The malignant classification includes pre-malignant conditions, such as actinic keratosis.

Table 2. Management decision definitions

Management decision	Definition	Example
Leave	Reassure patient and take no further action.	Benign lesion requiring no further monitoring or medical management.
Manage - monitor	Reassessment of lesion at later time point according to Australian Guidelines.	Patient advised to self-monitor for period of 3 months prior to follow-up monitoring visit.

Manage - biopsy	Partial or complete biopsy of the lesion required to confirm diagnosis.	Shave or excisional biopsy of suspected malignancy.
Treat - elective	Benign or pre-cancerous lesion where treatment is not essential.	Patient requesting cryotherapy of a benign seborrheic keratosis
Treat - essential	Malignancy requiring non-surgical intervention.	Cryotherapy, pharmacotherapy or non-surgical intervention to treat malignancy.

Figures

Figure 1. The SMARTI computer display: Participant avatar indicating the lesion location.

Figure 2. The SMARTI computer display: Clinician diagnosis and management plan entry, where: 'Diagnosis 1' is the clinician's initial assessment; 'Assessment' is the AI algorithm's classification; 'Diagnosis 2' is the clinician's AI-assisted assessment; and 'Action Plans' detail the recommended and final agreed-upon plan.

Figure 3. Participant flow chart.

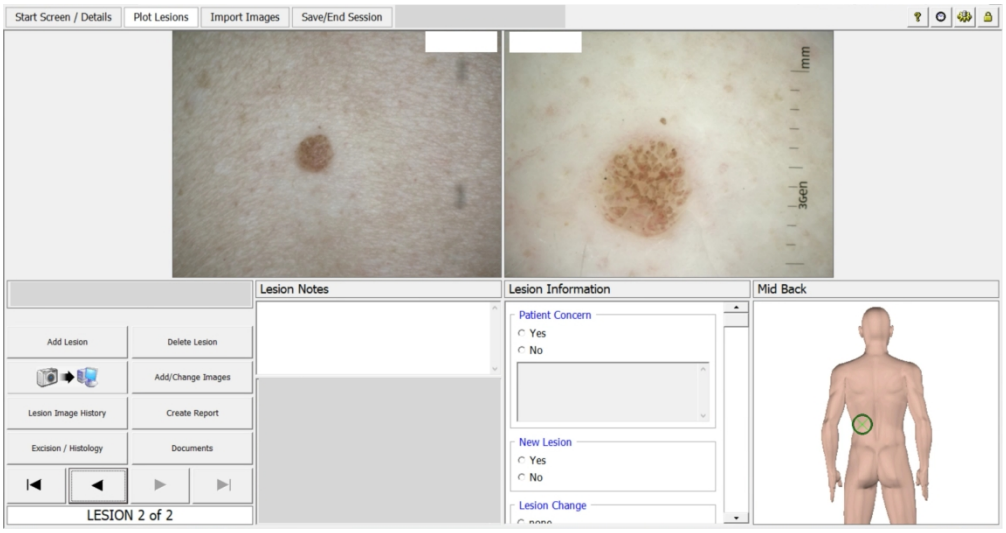

Figure 1. The SMARTI computer display: Participant avatar indicating the lesion location.

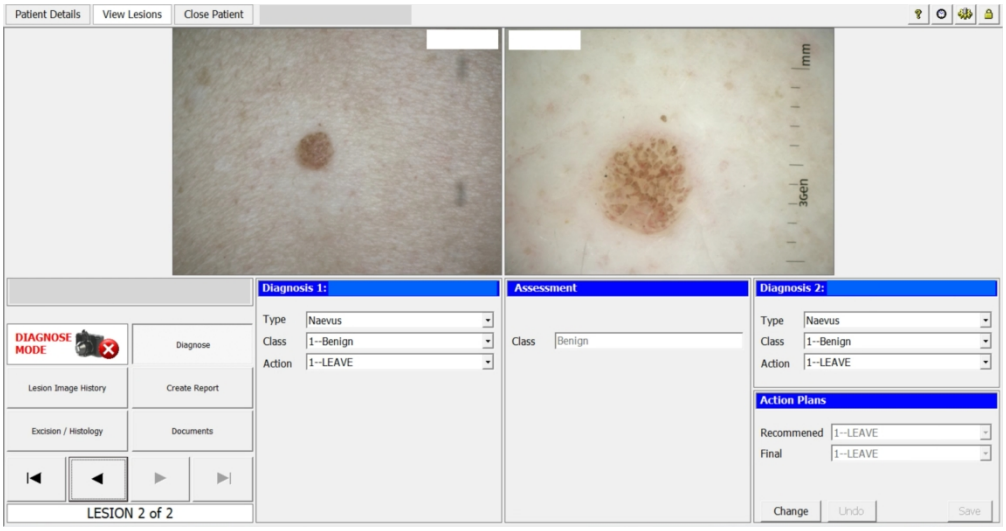

Figure 2. The SMARTI computer display: Clinician diagnosis and management plan entry, where: 'Diagnosis 1' is the clinician's initial assessment; 'Assessment' is the AI algorithm's classification; 'Diagnosis 2' is the clinician's AI-assisted assessment; and 'Action Plans' detail the recommended and final agreed-upon plan.

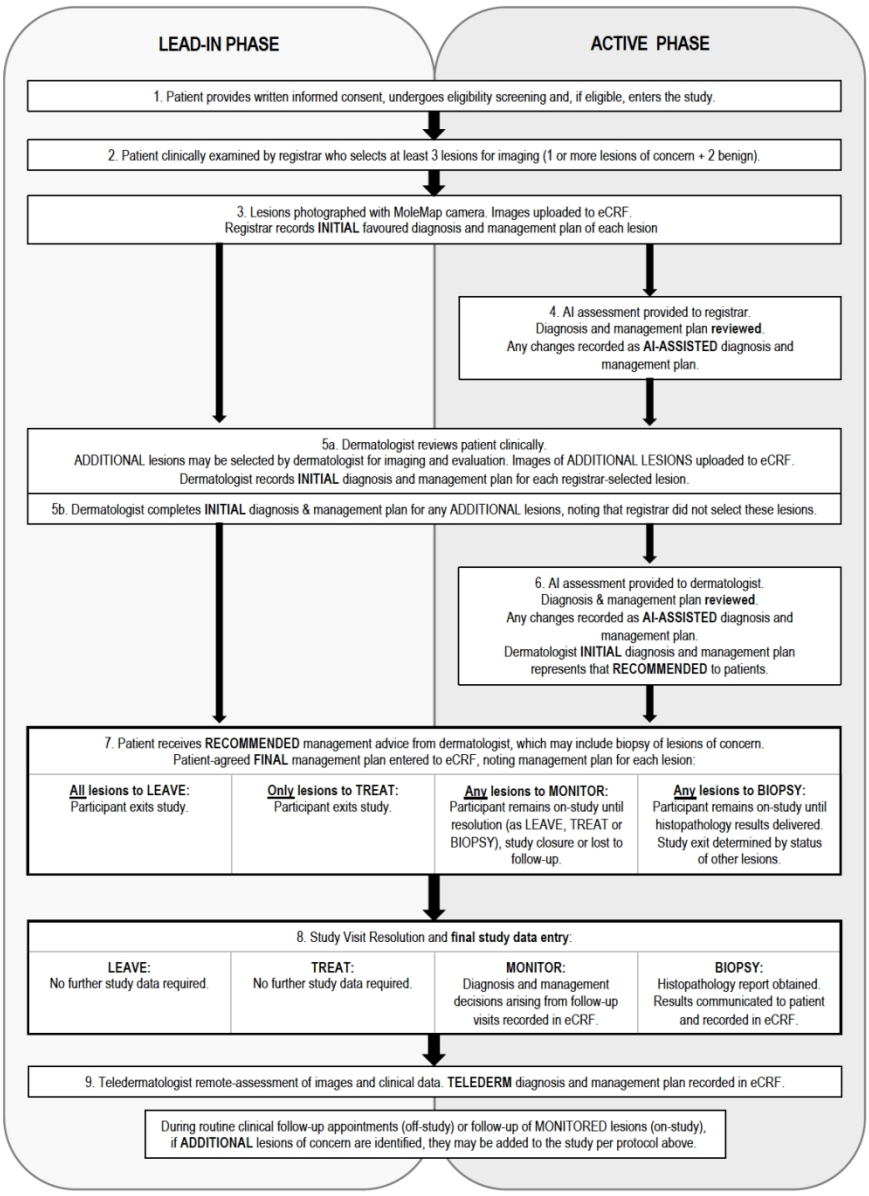

Figure 3. Participant flow chart.

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.

RESEARCH METHODS AND REPORTING

Guidelines for clinical trial protocols for interventions involving artificial intelligence: the SPIRIT-AI Extension

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The SPIRIT 2013 (The Standard Protocol Items: Recommendations for Interventional Trials) statement aims to improve the completeness of clinical trial protocol reporting, by providing evidence-based recommendations for the minimum set of items to be addressed. This guidance has been instrumental in promoting transparent evaluation of new interventions. More recently, there is a growing recognition that interventions involving artificial intelligence need to undergo rigorous, prospective evaluation to demonstrate their impact on health outcomes.

The SPIRIT-AI extension is a new reporting guideline for clinical trials protocols evaluating interventions with an AI component. It was developed in parallel with its companion statement for trial reports: CONSORT-AI. Both guidelines were developed using a staged consensus process, involving a literature review and expert consultation to generate 26 candidate items, which were consulted on by an international multi-stakeholder group in a 2-stage Delphi survey (103 stakeholders), agreed on in a consensus meeting (31 stakeholders) and refined through a checklist pilot (34 participants).

The SPIRIT-AI extension includes 15 new items, which were considered sufficiently important for clinical trial protocols of AI interventions. These new items should be routinely reported in addition to the core SPIRIT 2013 items. SPIRIT-AI recommends that investigators provide clear descriptions of the AI intervention, including instructions and skills required for use, the setting in which the AI intervention will be integrated, considerations around the handling of input and output data, the human-AI interaction and analysis of error cases.

SPIRIT-AI will help promote transparency and completeness for clinical trial protocols for AI interventions. Its use will assist editors and peer-reviewers, as well as the general readership, to understand, interpret and critically appraise the design and risk of bias for a planned clinical trial.

Introduction

A clinical trial protocol is an essential document produced by study investigators detailing a priori the rationale, proposed methods and plans for how a clinical trial will be conducted.[1 2] This key document is used by external reviewers (funding agencies, regulatory bodies, research ethics committees, journal editors, peer reviewers and institutional review boards, and increasingly the wider public) to understand and interpret the rationale, methodological rigor and ethical considerations of the trial. Additionally, trial protocols provide a shared reference point to support the research team in conducting a high-quality study.

Despite their importance, the quality and completeness of published trial protocols are variable.[1 2] The Standard Protocol Items: Recommendations for Interventional Trials (SPIRIT) statement was published in 2013 to provide guidance for the minimum reporting content of a clinical trial protocol and has been widely endorsed as an international standard.[3-5] The SPIRIT statement published in 2013 provides minimum guidance applicable for all clinical trial interventions, but recognises that certain interventions may require extension or elaboration of these items.[1 2] Artificial intelligence (AI) is an area of enormous interest, with strong drivers to accelerate new interventions through to publication, implementation and market.[6] While AI systems have been researched for some

time, recent advances in deep learning and neural networks have gained significant interest for their potential in health applications. Examples of such applications of these are wide-ranging and include AI systems for screening and triage,[7 8] diagnosis,[9-12] prognostication,[13 14] decision-support[15] and treatment recommendation.[16] However, in most recent cases, the majority of published evidence consists of *in silico*, early-phase validation. It has been recognised that most recent AI studies are inadequately reported and existing reporting guidelines do not fully cover potential sources of bias specific to AI systems.[17] The welcome emergence of randomised controlled trials (RCTs) seeking to evaluate clinical efficacy of newer interventions based on, or including, an AI component (hereafter 'AI interventions') [15 18-23] has similarly been met with concerns about design and reporting.[17 24-26] This has highlighted the need to provide reporting guidance that is 'fit-for-purpose' in this domain.

SPIRIT-AI (as part of the SPIRIT-AI and CONSORT-AI initiative) is an international initiative supported by SPIRIT and the EQUATOR (Enhancing Quality and Transparency of Health Research) Network to extend or elaborate the existing SPIRIT 2013 statement where necessary, to develop consensus-based AI-specific protocol guidance.[27 28] It is complementary to the CONSORT-AI statement, which aims to promote high quality reporting of AI trials. This article describes the methods used to identify and evaluate candidate items and gain consensus. In addition, it also provides the full SPIRIT-AI checklist including new items and their accompanying explanations.

Methods

The SPIRIT-AI and CONSORT-AI extensions were simultaneously developed for clinical trial protocols and trial reports. An announcement for the SPIRIT-AI and CONSORT-AI initiative was published in October 2019,[27] and the two guidelines were registered as reporting guidelines under development on the EQUATOR library of reporting guidelines in May 2019. Both guidelines were developed in accordance with the EQUATOR Network's methodological framework.[29] The SPIRIT-AI and CONSORT-AI steering group, consisting of 15 international experts, was formed to oversee the conduct and methodology of the study. Definitions of key terms are contained in the glossary box 1.

Ethical approval

This study was approved by the ethical review committee at the University of Birmingham, UK (ERN_19-1100). Participant information was provided to Delphi participants electronically before survey completion and before the consensus meeting. Delphi participants provided electronic informed consent, and written consent was obtained from consensus meeting participants.

Literature review and candidate item generation

An initial list of candidate items for the SPIRIT-AI and CONSORT-AI checklists was generated through review of the published literature and consultation with the steering group and known international experts. A search was performed on 13 May 2019 using the terms "artificial intelligence," "machine learning," and "deep learning" to identify existing clinical trials for AI interventions listed within the US National Library of Medicine's clinical trial registry, ClinicalTrials.gov. There were 316 registered trials on ClinicalTrials.gov, of which 62 were completed and seven had published results.[22 30-35] Two studies were reported with reference to the CONSORT statement,[22 34] and one study provided an unpublished trial protocol.[34] The Operations Team (XL, SCR, MJC, and AKD) identified AI-specific considerations from these studies and reframed them as candidate reporting items. The candidate items were also informed by findings from a previous systematic review which evaluated the diagnostic accuracy of deep learning systems for medical imaging.[17] After consultation with the steering group and additional international experts (n=19), 29 candidate items were generated: 26 of which were relevant for both SPIRIT-AI and CONSORT-AI and three of which were relevant only for CONSORT-AI. The Operations Team mapped these items to the corresponding SPIRIT and CONSORT items, revising the wording and providing explanatory text as required to contextualise the items. These items were included in subsequent Delphi surveys.

Delphi consensus process

In September 2019, 169 key international experts were invited to participate in the online Delphi survey to vote on the candidate items and suggest additional items. Experts were identified and contacted via the steering group and were allowed one round of snowball recruitment, where contacted experts could suggest additional experts. In addition, individuals who made contact following publication of the announcement were included.[27] The steering group agreed that individuals with expertise in clinical trials and AI/ML, as well as key users of the technology should be well represented in the consultation. Stakeholders included healthcare professionals, methodologists, statisticians, computer scientists, industry representatives, journal editors, policy makers, health informaticists, law and ethicists, regulators, patients, and funders. Participant characteristics are described in the appendix (page 2: supplementary table 1). Two online Delphi surveys were conducted. DelphiManager software (version 4.0), developed and maintained by the COMET (Core Outcome Measures in Effectiveness Trials) initiative, was used to undertake the e-Delphi surveys. Participants were given written information about the study and asked to provide their level of expertise within the fields of (i) AI/ML, and (ii) clinical trials. Each item was presented for consideration (26 for SPIRIT-AI and 29 for CONSORT-AI). Participants were asked to vote on each item using a 9-point scale: (1-3) not important, (4-6) important but not critical, and (7-9) important and critical. Respondents provided separate ratings for SPIRIT-AI and CONSORT-AI. There was an option to opt out of voting for each item, and

Box 1: Glossary

- *Artificial intelligence (AI)*—The science of developing computer systems which can perform tasks normally requiring human intelligence.
- *AI intervention*—A health intervention which relies on an artificial intelligence/machine learning component to serve its purpose.
- *CONSORT*—Consolidated Standards of Reporting Trials.
- *CONSORT-AI extension item*—An additional checklist item to address AI-specific content that is not adequately covered by CONSORT 2010.
- *Class activation map*—Class activation maps are particularly relevant to image classification AI interventions. Class activation maps are visualizations of the pixels that had the greatest influence on predicted class, by displaying the gradient of the predicted outcome from the model with respect to the input. They are also referred to as saliency maps or heatmaps.
- *Health outcome*—Measured variables in the trial which are used to assess the effects of an intervention.
- *Human-AI interaction*—The process of how users/humans interact with the AI intervention, for the AI intervention to function as intended.
- *Clinical outcome*—Measured variables in the trial which are used to assess the effects of an intervention.
- *Delphi study*—A research method which derives the collective opinions of a group through a staged consultation of surveys, questionnaires, or interviews, with an aim to reach consensus at the end.
- *Development environment*—The clinical and operational settings from which the data used for training the model is generated. This includes all aspects of the physical setting (such as geographical location, physical environment), operational setting (such as integration with an electronic record system, installation on a physical device) and clinical setting (such as primary/secondary/tertiary care, patient disease spectrum).
- *Fine-tuning*—Modifications or additional training performed on the AI intervention model, done with the intention of improving its performance.
- *Input data*—The data that need to be presented to the AI intervention to allow it to serve its purpose.
- *Machine learning (ML)*—A field of computer science concerned with the development of models/algorithms which can solve specific tasks by learning patterns from data, rather than by following explicit rules. It is seen as an approach within the field of artificial intelligence.
- *Operational environment*—The environment in which the AI intervention will be deployed, including the infrastructure required to enable the AI intervention to function.
- *Output data*—The predicted outcome given by the AI intervention based on modelling of the input data. The output data can be presented in different forms, including a classification (including diagnosis, disease severity or stage, or recommendation such as referability), a probability, a class activation map, etc. The output data typically provides additional clinical information and/or triggers a clinical decision.
- *Performance error*—Instances where the AI intervention fails to perform as expected. This term can describe different types of failures and it is up to the investigator to specify what should be considered a performance error, preferably based on prior evidence. This can range from small decreases in accuracy (compared to expected accuracy), to erroneous predictions, or the inability to produce an output in certain cases.
- *SPIRIT*—Standard Protocol Items: Recommendations for Interventional Trials.
- *SPIRIT-AI*—An additional checklist item to address AI-specific content that is not adequately covered by SPIRIT 2013.
- *SPIRIT-AI elaboration item*—Additional considerations to an existing SPIRIT 2013 item when applied to AI interventions.

each item included space for free text comments. At the end of the Delphi survey, participants had the opportunity to suggest new items. One hundred and three responses were received for the first Delphi round, and 91 (88% of participants from round one) responses received for the second round. The results of the Delphi surveys informed the subsequent international consensus meeting. Twelve new items were proposed by the Delphi study participants and were added for discussion at the consensus meeting. Data collected during the Delphi survey were anonymised and item-level results were presented at the consensus meeting for discussion and voting.

The two-day consensus meeting took place in January 2020 and was hosted by the University of Birmingham, UK, to seek consensus on the content of SPIRIT-AI and CONSORT-AI. Thirty one international stakeholders were invited from the Delphi survey participants to discuss the items and vote for their inclusion. Participants were selected to achieve adequate representation from all the stakeholder groups. Thirty eight items were discussed in turn, comprising the 26 items generated in the initial literature review and item generation phase (these 26 items were relevant to both SPIRIT-AI and CONSORT-AI; 3 extra items relevant to CONSORT-AI only were also discussed) and the 12 new items proposed by participants during the Delphi surveys. Each item was presented to the consensus group, alongside its score from the Delphi exercise (median and interquartile ranges) and any comments made by Delphi participants related to that item. Consensus meeting participants were invited to comment on the importance of each item and whether the item should be included in the AI extension. In

addition, participants were invited to comment on the wording of the explanatory text accompanying each item and the position of each item relative to the SPIRIT 2013 and CONSORT 2010 checklists. After open discussion of each item and the option to adjust wording, an electronic vote took place with the option to include or exclude the item. An 80% threshold for inclusion was pre-specified and deemed reasonable by the steering group to demonstrate majority consensus. Each stakeholder voted anonymously using Turning Point voting pads (Turning Technologies LLC, Ohio, USA; version 8.7.2.14).

Checklist pilot

Following the consensus meeting, attendees were given the opportunity to make final comments on the wording and agree that the updated SPIRIT-AI and CONSORT-AI items reflected discussions from the meeting. The Operations Team assigned each item as extension or elaboration item based on a decision tree and produced a penultimate draft of the SPIRIT-AI and CONSORT-AI checklist (supplementary fig 1). A pilot of the penultimate checklist was conducted with 34 participants to ensure clarity of wording. Experts participating in the pilot included: a) Delphi participants who did not attend the consensus meeting and b) external experts, who had not taken part in the development process but who had reached out to the steering committee after the Delphi study commenced. Final changes were made on wording only to improve clarity for readers, by the Operations Team (supplementary fig 2).

Results

SPIRIT-AI checklist items and explanations

The SPIRIT-AI Extension recommends that, in conjunction with existing SPIRIT 2013 items, 15 items (12 extensions and 3 elaborations) should be addressed for trial protocols of AI-interventions. These items were considered sufficiently important for clinical trial protocols for AI interventions that should be routinely reported in addition to the core SPIRIT 2013 checklist items. Table 1 lists the SPIRIT-AI items.

All 15 items included in the SPIRIT-AI Extension passed the threshold of 80% for inclusion at the consensus meeting. SPIRIT-AI 6a (i), SPIRIT-AI 11a (v) and SPIRIT-AI 22 each resulted from the merging of two items after discussion. SPIRIT-AI 11a (iii) did not fulfil the criteria for inclusion based on its initial wording (73% vote to include); however, after extensive discussion and rewording, the consensus group unanimously supported a re-vote at which point it passed the inclusion threshold (97% to include).

Administrative information

SPIRIT-AI 1 (i) Elaboration: Indicate that the intervention involves artificial intelligence/machine learning and specify the type of model.

Explanation: Indicating in the protocol title and/or abstract that the intervention involves a form of AI is encouraged, as it immediately identifies the intervention as an artificial intelligence/machine learning intervention, and also serves to facilitate indexing and searching of the trial protocol in bibliographic databases, registries, and other online resources. The title should be understandable by a wide audience; therefore, a broader umbrella term such as "artificial intelligence" or "machine learning" is encouraged. More precise terms should be used in the abstract, rather than the title, unless broadly recognised as being a form of artificial intelligence/machine learning. Specific terminology relating to the model type and architecture should be detailed in the abstract.

SPIRIT-AI 1 (ii) Elaboration: State the intended use of the AI intervention.

Explanation: The intended use of the AI intervention should be made clear in the protocol's title and/or abstract. This should describe the purpose of the AI intervention and the disease context.[19 36] Some AI interventions may have multiple intended uses, or the intended use may evolve over time. Therefore, documenting this allows readers to understand the intended use of the algorithm at the time of the trial.

Introduction

SPIRIT-AI 6a (i) Extension: Explain the intended use of the AI intervention in the context of the clinical pathway, including its purpose and its intended users (such as healthcare professionals, patients, public).

Explanation: In order to understand how the AI intervention will fit into a clinical pathway, a detailed description of its role should be included in the protocol background. AI interventions may be designed to interact with different users including healthcare professionals, patients, and the public, and their roles can be wide-ranging (for example, the same AI intervention could theoretically be replacing, augmenting or adjudicating components of clinical decision-making). Clarifying the intended use of the AI intervention and its intended user helps readers understand the purpose for which the AI intervention will be evaluated in the trial.

SPIRIT-AI 6a (ii) Extension: Describe any pre-existing evidence for the AI intervention.

Explanation: Authors should describe in the protocol any pre-existing published (with supporting references) or unpublished evidence relating to validation of the AI intervention, or lack thereof. Consideration should be given to whether the evidence was for a similar use, setting and target population as the planned trial. This may include previous development of the AI model, internal and external validations, and any modifications made before the trial.

Participants, interventions, and outcomes

SPIRIT-AI 9 Extension: Describe the onsite and offsite requirements needed to integrate the AI intervention into the trial setting.

Explanation: There are limitations to the generalisability of AI algorithms, one of which is when they are

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used outside of their development environment.[37 38] AI systems are dependent on their operational environment, and the protocol should provide details of the hardware and software requirements to allow technical integration of the AI intervention at each study site. For example, it should be stated if the AI intervention requires vendor-specific devices, if there is a need for specialised computing hardware at each site, or if the sites must support cloud integration, particularly if this is vendor-specific. If any changes to the algorithm are required at each study site as part of the implementation procedure (such as fine-tuning the algorithm on local data), then this process should also be clearly described.

SPIRIT-AI 10 (i) Elaboration: State the inclusion and exclusion criteria at the level of participants.

Explanation: The inclusion and exclusion criteria should be defined at the participant level as per usual practice in protocols of non-AI interventional trials. This is distinct from the inclusion and exclusion criteria made at the input data level, which is addressed in item 10 (ii).

SPIRIT-AI 10 (ii) Extension: State the inclusion and exclusion criteria at the level of the input data.

Explanation: Input data refer to the data required by the AI intervention to serve its purpose (for example, for a breast cancer diagnostic system, the input data could be the unprocessed or vendor-specific post-processing mammography scan on which a diagnosis is being made; for an early warning system, the input data could be physiological measurements or laboratory results from the electronic health record). The trial protocol should pre-specify if there are minimum requirements for the input data (such as image resolution, quality metrics, or data format), which would determine pre-randomisation eligibility. It should specify when, how, and by whom this will be assessed. For example, if a participant met the eligibility criteria for lying flat for a CT scan as per item 10 (i), but the scan quality was compromised (for any given reason) to such a level that it is no longer fit for use by the AI system, this should be considered as an exclusion criterion at the input data level. Note that where input data are acquired after randomisation (addressed by SPIRIT-20c), any exclusion is considered to be from the analysis, not from enrolment (fig 1).

SPIRIT-AI 11a (i) Extension: State which version of the AI algorithm will be used.

Explanation: Similar to other forms of software as a medical device, AI systems are likely to undergo multiple iterations and updates in their lifespan. The protocol should state which version of the AI system will be used in the clinical trial, and whether this is the same version that had been used in previous studies to justify the study rationale. If applicable, the protocol should describe what has changed between the relevant versions and the rationale for the changes. Where available, the protocol should include a regulatory marking reference, such as a unique device identifier (UDI) which requires a new identifier for updated versions of the device.[39]

SPIRIT-AI 11a (ii) Extension: Specify the procedure for acquiring and selecting the input data for the AI intervention.

Explanation: The measured performance of any AI system may be critically dependent on the nature and quality of the input data.[40] The procedure for how input data will be handled—including data acquisition, selection, and pre-processing before analysis by the AI system—should be provided. Completeness and transparency of this process is integral to feasibility assessment and to future replication of the intervention beyond the clinical trial. It will also help to identify whether input data handling procedures will be standardised across trial sites.

SPIRIT-AI 11a (iii) Extension: Specify the procedure for assessing and handling poor quality or unavailable input data.

Explanation: As with 10 (ii), input data refer to the data required by the AI intervention to serve its purpose. As noted in item SPIRIT-AI 10 (ii), the performance of AI systems may be compromised as a result of poor quality or missing input data[41] (for example, excessive movement artefact on an electrocardiogram). The study protocol should specify if and how poor quality or unavailable input data will be identified and handled. The protocol should also specify a minimum standard required for the input data, and the procedure for when the minimum standard is not met (including the impact on, or any changes to, the participant care pathway).

Poor quality or unavailable data can also affect non-AI interventions. For example, suboptimal quality of a scan could impact a radiologist's ability to interpret it and make a diagnosis. It is therefore important that this information is reported equally for the control intervention, where relevant. If this minimum quality standard is different from the inclusion criteria for input data used to assess eligibility pre-randomisation, this should be stated.

SPIRIT-AI 11a (iv) Extension: Specify whether there is human-AI interaction in the handling of the input data, and what level of expertise is required for users.

Explanation: A description of the human-AI interface and the requirements for successful interaction when handling input data should be described. Examples include clinician-led selection of regions of interest from a histology slide which is then interpreted by an AI diagnostic system,[42] or endoscopist selection of a colonoscopy video clip as input data for an algorithm designed to detect polyps.[21] A description of any planned user training and instructions for how users will handle the input data provides transparency and replicability of trial procedures. Poor clarity on the human-AI interface may lead to a lack of a standard

RESEARCH METHODS AND REPORTING

Table 1 | SPIRIT-AI checklist

Section	Item	SPIRIT 2013 Item*	SPIRIT-AI item		Addressed on page No†
Administrative information					
Title	1	Descriptive title identifying the study design, population, interventions, and, if applicable, trial acronym	SPIRIT-AI 1(i) Elaboration	Indicate that the intervention involves artificial intelligence/machine learning and specify the type of model.	
			SPIRIT-AI 1(ii) Elaboration	Specify the intended use of the AI intervention.	
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	SPIRIT-AI 6a (i) Extension	Explain the intended use of the AI intervention in the context of the clinical pathway, including its purpose and its intended users (e.g. healthcare professionals, patients, public).	
			SPIRIT-AI 6a (ii) Extension	Describe any pre-existing evidence for the AI 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, non-inferiority, 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	SPIRIT-AI 9 Extension	Describe the onsite and offsite requirements needed to integrate the AI intervention into the trial setting.	
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)	SPIRIT-AI 10 (i) Elaboration	State the inclusion and exclusion criteria at the level of participants.	
			SPIRIT-AI 10 (ii) Extension	State the inclusion and exclusion criteria at the level of the input data.	
Interventions	11a	Interventions for each group with sufficient detail to allow replication, including how and when they will be administered	SPIRIT-AI 11a (i) Extension	State which version of the AI algorithm will be used.	
			SPIRIT-AI 11a (ii) Extension	Specify the procedure for acquiring and selecting the input data for the AI intervention.	
			SPIRIT-AI 11a (iii) Extension	Specify the procedure for assessing and handling poor quality or unavailable input data.	
			SPIRIT-AI 11a (iv) Extension	Specify whether there is human-AI interaction in the handling of the input data, and what level of expertise is required for users.	
			SPIRIT-AI 11a (v) Extension	Specify the output of the AI intervention.	
			SPIRIT-AI 11a (vi) Extension	Explain the procedure for how the AI intervention's output will contribute to decision-making or other elements of clinical practice.	
	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			

Table 1 | Continued

Section	Item	SPIRIT 2013 Item*	SPIRIT-AI item		Addressed on page No†
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 fig 1)			
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)					
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	SPIRIT-AI 22 Extension	Specify any plans to identify and analyse performance errors. If there are no plans for this, justify why not.	
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 ascent	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			

(*Continued*)

Table 1 | Continued

Section	Item	SPIRIT 2013 Item*	SPIRIT-AI item		Addressed on page No†
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	SPIRIT-AI 29 Extension	State whether and how the AI intervention and/or its code can be accessed, including any restrictions to access or re-use.	
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 and Elaboration for important clarification on the items.
†Indicates page numbers to be completed by authors during protocol development.

approach and carry ethical implications, particularly in the event of harm.[43 44] For example, it may become unclear whether an error case occurred due to human deviation from the instructed procedure or if it was an error made by the AI system.

SPIRIT-AI 11a (v) Extension: Specify the output of the AI intervention.

Explanation: The output of the AI intervention should be clearly defined in the protocol. For example, an AI system may output a diagnostic classification or probability, a recommended action, an alarm alerting to an event, an instigated action in a closed loop system (such as titration of drug infusions), or other. The nature of the AI intervention's output has direct implications on its usability and how it may lead to downstream actions and outcomes.

SPIRIT-AI 11a (vi) Extension: Explain the procedure for how the AI intervention's outputs will contribute to decision-making or other elements of clinical practice.

Explanation: Since health outcomes may also critically depend on how humans interact with the AI intervention, the trial protocol should explain how the outputs of the AI system are used to contribute to decision-making or other elements of clinical practice. This should include adequate description of downstream interventions which can impact outcomes. As with SPIRIT-AI 11a (iv), any elements of human-AI interaction on the outputs should be described in detail. Including the level of expertise required to understand the outputs and any training/instructions provided for this purpose. For example, a skin cancer detection system that produces a percentage likelihood as output should be accompanied by an explanation of how this output should be interpreted and acted on by the user, specifying both the intended pathways (such as skin lesion excision if the diagnosis is positive) and the thresholds for entry to these pathways (such as skin lesion excision if the diagnosis is positive and the probability is >80%). The information produced by comparator interventions should be similarly described, alongside an explanation of how such information was used to arrive at clinical decisions for patient management, where relevant.

Monitoring

SPIRIT-AI 22 Extension: Specify any plans to identify and analyse performance errors. If there are no plans for this, explain why not.

Explanation: Reporting performance errors and failure case analysis is especially important for AI interventions. AI systems can make errors which may be hard to foresee but which, if allowed to be deployed at scale, could have catastrophic consequences.[45] Therefore, identifying cases of error and defining risk mitigation strategies are important for informing when the intervention can be safely implemented and for which populations. The protocol should specify whether there are any plans to analyse performance errors. If there are no plans for this, a justification should be included in the protocol.

Ethics and dissemination

SPIRIT-AI 29 Extension: State whether and how the AI intervention and/or its code can be accessed, including any restrictions to access or re-use.

Explanation: The protocol should make clear whether and how the AI intervention and/or its code can be

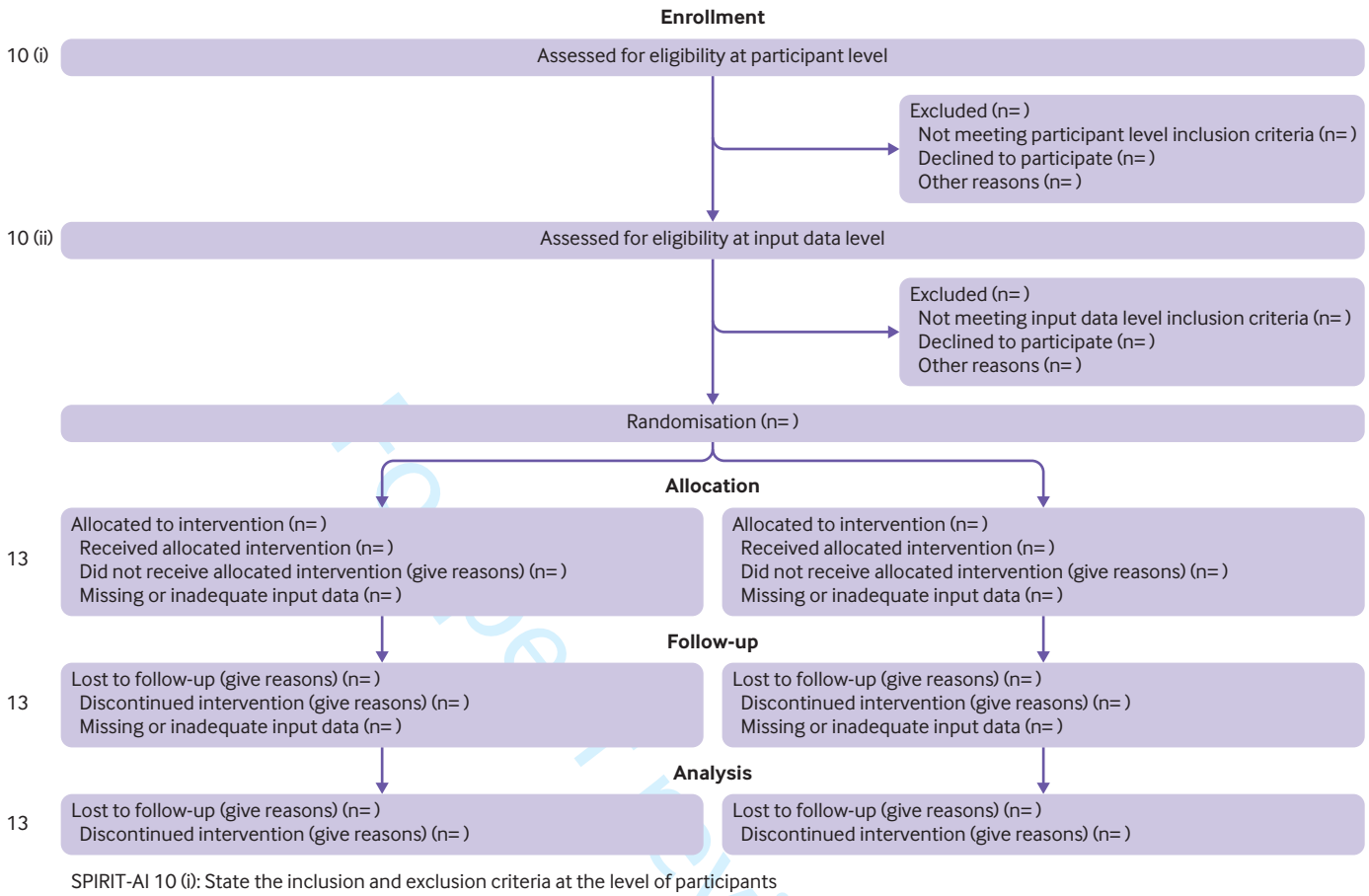

Fig 1 | CONSORT 2010 flow diagram - adapted for AI clinical trials

accessed or re-used. This should include details regarding the license and any restrictions to access.

Discussion

The SPIRIT-AI extension provides international consensus-based guidance on AI-specific information that should be reported in clinical trial protocols alongside SPIRIT 2013 and other relevant SPIRIT extensions.[4 46] It comprises 15 items: three elaborations to the existing SPIRIT 2013 guidance in the context of AI trials and 12 new extensions. The guidance does not aim to be prescriptive regarding the methodological approach to AI trials; rather it aims to promote transparency in reporting the design and methods of a clinical trial to facilitate understanding, interpretation, and peer review.

A number of extension items relate to the intervention (items 11(i-vi)), its setting (item 9), and intended role (item 6a (i)). Specific recommendations were made pertinent to AI systems relating to algorithm version, input and output data, integration into trial settings, expertise of the users, and protocol for acting on the AI system's recommendations. It was agreed that these details are critical for independent evaluation of the study protocol. Journal editors reported that, despite the importance of these items, they are currently often missing from trial protocols and reports at the time of submission for publication, providing further weight to their inclusion as specifically listed extension items.

A recurrent focus of the Delphi comments and consensus group discussion was around safety of AI systems. This is in recognition that these systems, unlike other health interventions, can unpredictably yield errors which are not easily detectable or explainable by human judgment. For example, changes to medical imaging which are invisible, or appear random, to the human eye may change the likelihood of the resultant diagnostic output entirely.[47 48] The concern is, given the theoretical ease at which AI systems could be deployed at scale, any unintended harmful consequences could be catastrophic. Two extension items were added to address this. SPIRIT-AI item 6a (ii) requires specification of the prior level of evidence for validation of the AI intervention. SPIRIT-AI item 22 requires specification of any plans to analyse performance errors, to emphasise the importance of anticipating systematic errors made by the algorithm and their consequences.

One topic which was raised in the Delphi survey responses and consensus meeting, which is not

included in the final guidelines, is "continuously evolving" AI systems (also known as "continuously adapting" or "continuously learning"). These are AI systems with the ability to continuously train on new data, which may cause changes in performance over time. The group noted that, while of interest, this field is relatively early in its development without tangible examples in healthcare applications, and that it would not be appropriate for it to be addressed by SPIRIT-AI at this stage.[49] This topic will be monitored and revisited in future iterations of SPIRIT-AI. It is worth noting that incremental software changes, whether continuous or iterative, intentional or unintentional, could have serious consequences on safety performance after deployment. It is therefore of vital importance that such changes are documented and identified by software version and a robust post-deployment surveillance plan is in place.

This study is set in the current context of AI in health; therefore, several limitations should be noted. First, at the time of SPIRIT-AI development there were only seven published trials and no published trial protocols in the field of AI for healthcare. Thus, the discussion and decisions made during the development of SPIRIT-AI are not always supported by existing real-world examples. This arises from our stated aim to address the issues of poor protocol development in this field as early as possible, recognising the strong drivers in the field and the specific challenges of study design and reporting for AI. As the science and study of AI evolves, we welcome collaboration with investigators to co-evolve these reporting standards to ensure their continued relevance. Second, the literature search of AI RCTs used terminology such as "artificial intelligence," "machine learning," and "deep learning" but not terms such as "clinical decision support systems" and "expert systems," which were more commonly used in the 1990s for technologies underpinned by AI systems and share similar risks with recent examples.[50] It is likely that such systems, if published today, would be indexed under "AI" or "machine learning"; however, clinical decision support systems were not actively discussed during this consensus process. Third, the initial candidate items list was generated by a relatively small group of experts consisting of steering group members and additional international experts. However, additional items from the wider Delphi group were taken forward for consideration by the consensus group, and no new items were suggested during the consensus meeting or post-meeting evaluation.

As with the SPIRIT statement, the SPIRIT-AI extension is intended as a minimum reporting guidance, and there are additional AI-specific considerations for trial protocols which may warrant consideration (see appendix, page 2: supplementary table 2). This extension is particularly aimed at investigators planning or conducting clinical trials; however, it may also serve as useful guidance for developers of AI interventions in earlier validation stages of an AI system. Investigators seeking to report studies developing and validating the diagnostic and predictive properties of AI models should refer to TRIPOD-ML (Transparent Reporting of a Multivariable Prediction Model for Individual Prognosis or Diagnosis - Machine Learning)[24] and STARD-AI (Standards for Reporting Diagnostic accuracy studies - Artificial Intelligence),[51] both of which are currently under development. Other potentially relevant guidelines are registered with the EQUATOR network which are agnostic to study design.[52] The SPIRIT-AI extension is expected to encourage careful early planning of AI interventions for clinical trials, and this, in conjunction with CONSORT-AI, should help to improve the quality of trials for AI interventions.

There is widespread recognition that AI is a rapidly evolving field and there will be the need to update SPIRIT-AI as the technology, and newer applications for it, develop. Currently, most applications of AI/ML involve disease detection, diagnosis, and triage, and this is likely to have influenced the nature and prioritisation of items within SPIRIT-AI. As wider applications that utilise "AI as therapy" emerge, it will be important to re-evaluate SPIRIT-AI in the light of such studies. Additionally, advances in computational techniques and the ability to integrate them into clinical workflows will bring new opportunities for innovation that benefits patients. However, they may be accompanied by new challenges of study design and reporting to ensure transparency, minimise potential biases and ensure that the findings of such a study are trustworthy and the extent to which they may be generalisable. The SPIRIT-AI and CONSORT-AI Steering Group will continue to monitor the need for updates.

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Appendix: Supplementary table 1 (details of Delphi survey and consensus meeting participants) and table 2 (details of Delphi survey and consensus meeting decisions)
Supplementary fig 1: Decision tree for inclusion/exclusion and extension/elaboration
Supplementary fig 2: Checklist development process

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Improving Skin cancer Management with ARTificial Intelligence (SMARTI): protocol for a pre-post intervention trial of an Artificial Intelligence system used as a diagnostic aid for skin cancer management in a specialist dermatology setting

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Improving Skin cancer Management with ARTificial Intelligence (SMARTI): protocol for a pre-post intervention trial of an Artificial Intelligence system used as a diagnostic aid for skin cancer management in a specialist dermatology setting

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Abstract

Introduction

Convolutional neural networks (CNNs) can diagnose skin cancers with impressive accuracy in experimental settings, however their performance in the real-world clinical setting, including comparison to teledermatology services, has not been validated in prospective clinical studies.

Methods and analysis

Participants will be recruited from dermatology clinics at the Alfred Hospital and Skin Health Institute, Melbourne. Skin lesions will be imaged using a proprietary dermoscopic camera. The Artificial Intelligence (AI) algorithm, a CNN developed by MoleMap Ltd and Monash eResearch, classifies lesions as benign, malignant or uncertain.

This is a pre-post-intervention study. In the pre-intervention period, treating doctors are blinded to AI lesion assessment. In the post-intervention period, treating doctors review the AI lesion assessment in real time, and have the opportunity to then change their diagnosis and management. Any skin lesions of concern and at least two benign lesions will be selected for imaging. Each participant's lesions will be examined by a registrar, the treating consultant dermatologist, and later by a teledermatologist.

At the conclusion of the pre-intervention period, the safety of the AI algorithm will be evaluated in a primary analysis by measuring its sensitivity, specificity and agreement with histopathology where available, or the treating consultant dermatologists' classification.

At trial completion, AI classifications will be compared with those of the teledermatologist, registrar, treating dermatologist and histopathology. The impact of the AI algorithm on diagnostic and management decisions will be evaluated by: 1) comparing the initial management decision of the registrar with their AI-assisted decision; and 2) comparing the benign to malignant ratio (for lesions biopsied) between the pre and post-intervention periods.

Ethics and dissemination

Human Research Ethics Committee (HREC) approval received from the Alfred Hospital Ethics Committee on 14th February 2019 (HREC/48865/Alfred-2018). Findings from this study will be disseminated through peer-reviewed publications, non-peer reviewed media, and conferences.

Trial registration

ClinicalTrials.gov identifier: NCT04040114.

Strengths and limitations of this study

- The first prospective clinical trial to evaluate safety and performance of an Artificial Intelligence diagnostic aid for skin cancer detection and management in the real-world clinical setting.
- Participants are recruited on a consecutive basis from routine attendance at melanoma and skin cancer assessment clinics, forming a representative sample of patients and lesion phenotypes from which to evaluate AI algorithm performance.
- AI performance will be compared with teledermatologists' assessment, as well as to face-to-face assessors of varying clinical experience (registrars and consultant dermatologists), and with histopathology results for biopsied lesions.
- Longitudinal follow-up is not undertaken for lesions labelled 'benign' and not actively 'monitored', hence the ultimate malignancy status of these lesions will not be evaluated in this study.
- Inherent differences in application of AI in the specialist setting may limit generalisability of study findings (regarding AI utility) to primary care settings, necessitating further research to establish feasibility for broader clinical implementation.

Introduction

Skin cancer, including melanoma and keratinocyte carcinoma, is the most common type of cancer in Caucasian populations, and its incidence is increasing worldwide[1-3]. The incidence of keratinocyte carcinoma is difficult to establish precisely due to a lack of nationwide cancer registry data, although Australia is thought to have the highest incidence worldwide, with over 1000 cases per 100,000 person-years[4]. Similarly, Australia has one of the highest incidence rates of melanoma in the world, with almost 14,000 Australians diagnosed with invasive and more than 20,000 with in-situ melanoma each year[5].

In Australia there is a shortage of dermatology services in rural and remote areas, where there are consequently long wait times to see a dermatologist. Travel to urban centres can be logistically challenging and expensive for patients. The MoleMap model of care involves total body and dermoscopic imaging by a melanographer. Images are sent to a teledermatologist for reporting. If a lesion is suspicious for malignancy, or if there is diagnostic uncertainty, a recommendation is made to monitor or biopsy the lesion and the patient is advised to consult their doctor. This teledermatology model is particularly useful for people living in areas poorly serviced by dermatologists[6]. It is, however, labour intensive, and it is hoped that AI may reduce workload for teledermatologists in the future.

Melanoma is the third most commonly diagnosed invasive cancer irrespective of gender and is responsible for over 1600 deaths in Australia each year[5]. Early diagnosis of skin cancer reduces morbidity and, in the case of melanoma, is associated with significantly improved survival[3, 7]. More accurate and timely skin cancer diagnosis and management could be brought about by the use of new AI-based diagnostic aids[8-10].

A subset of AI is machine learning. Machine learning refers to the ability of a computer system to write its own programming for a task, and to automatically learn and improve through training data. Deep learning is a branch of machine learning which is becoming increasingly utilised in medicine[11]. CNNs are a class of artificial neural networks that are most often used to analyse visual imagery through deep learning. They are especially effective at automated image recognition.

CNNs have been tested with the task of diagnosing skin cancers in multiple studies, and have displayed impressive accuracy equal or superior to that of the dermatologists with whom they have been compared[12-21]. However, these studies have thus far been undertaken in experimental (in silica) settings, and the use of AI as a diagnostic aid has not been adequately evaluated in the real-world clinical setting and in the hands of clinician end-users[9, 22].

AI algorithms should be tested with datasets separate to those with which they are trained, in order to avoid over-fitting or prior dataset bias, which can lead to over-estimation of an algorithm's accuracy[23, 24]. In particular, AI algorithms should be tested on the end-target patients or lesions to ensure their reliability and safety in their intended setting.

Furthermore, in the real-world, dermatologists have additional clinical information (for example, patient demographics and skin cancer history), which improves their diagnostic accuracy[25]. Previous studies comparing AI and dermatologist diagnostic accuracy without provision of this clinical information have therefore disadvantaged dermatologists.

Additionally, these experimental studies positing AI and dermatologists as opponents have been unable to assess the impact of AI algorithms, when used by clinicians, on clinicians' diagnoses and management decisions.

There is a need for prospective clinical trials to validate performance and ensure generalisability of the algorithms, and to evaluate the safety, utility and feasibility of implementing an AI diagnostic aid for skin cancer detection in the clinical setting[9, 12, 13, 26].

This validation study will evaluate the utility of AI as a diagnostic aid for skin cancer detection and management in the specialist dermatology setting, prior to a larger trial of the intervention in the primary care setting.

If this diagnostic aid for skin cancer management is proven safe, consistent and reliable in a specialist setting, and comparable to a teledermatologist diagnostic assessment, AI-assistance may be appropriate for use in specialist clinics including teledermatology-based services. Further research will be required to determine safety in a primary care setting prior to more widespread implementation, because there will be inherent differences in disease prevalence and clinician experience in this setting when compared to a specialist dermatology setting.

Objectives

Primary Objective:

Assess accuracy of the AI diagnostic aid compared with teledermatologist skin lesion assessment.

Secondary Objectives:

- Evaluate the impact of the AI device when used as a diagnostic aid on the appropriateness of skin cancer management decisions.
- Evaluate the accuracy and safety of the AI device when used as a diagnostic aid for skin cancer detection in specialist clinics.
- Assess the feasibility of implementing the AI device as a diagnostic aid for skin cancer detection and management in specialist settings, including teledermatology services.

Methods and analysis

Study design and setting

A pre-post intervention study of an AI diagnostic aid for skin cancer detection and management.

Participants will be recruited between October 2019 and May 2021 from the patient population attending specialist dermatology and melanoma clinics at two Australian tertiary centres: Skin Health Institute and the Alfred Hospital in Melbourne, Australia. Participants attending these clinics have a suspected or confirmed diagnosis of skin cancer, or are attending for routine skin surveillance.

Testing the algorithm in specialist dermatology settings allows for comparison of AI lesion classifications with the classifications of both experts (consultant dermatologists) and less-expert clinicians (dermatology registrars). The impact of the AI on less-expert (dermatology registrar) classification and management decisions can be assessed using the expert

(consultant dermatologist's) management decision and histopathology as the reference standard. Having established this knowledge, the AI algorithm could subsequently be applied and studied in a primary care setting more safely.

Participant and public involvement

The study protocol is endorsed by the Melanoma and Skin Cancer Trials Ltd (MASC Trials), a registered not-for-profit Australian and New Zealand's Cancer Collaborative Trials Group member and affiliate of Monash University. All MASC Trials endorsed protocols are subject to review by consumer group representatives, including members of the Australian Melanoma Consumer Alliance.

Eligibility criteria

Patients aged 18 or over, who are able to provide written informed consent, with at least one skin lesion of concern (to either the patient or treating doctor, excluding acral or scalp lesions), and are willing to have multiple lesions imaged are eligible to participate.

Recruitment

Willing patients who meet eligibility criteria are provided with a copy of the Participant Information and Consent Form (PICF) and guided through informed consent by their treating dermatology registrar during their clinic consultation. Participants are recruited on a consecutive basis via convenience sampling from routine attendance at specialist clinics.

Randomisation and blinding

In this pre-post intervention study design, the pre-intervention period will provide an estimate of skin cancer management parameters as a comparator (control) for assessing the impact of AI in the post-intervention period. Participants are recruited on a consecutive basis during each of the pre-intervention and post-intervention periods; there is no randomisation. Data is collected on participant risk factors and potentially relevant confounders to be considered during analysis.

In the pre-intervention period, treating doctors remain blinded to each other's lesion assessment and are unexposed to the AI assessment. Teledermatologists are blinded to the treating doctors' diagnoses and management plans, and to the AI assessment.

In the post-intervention period, treating doctors record their initial diagnosis and management plan decision, and are then exposed to the AI assessment prior to recording a final AI-assisted diagnosis and management plan. The teledermatologists remain blinded to the treating doctors' diagnoses and management plans, and to the AI assessment.

Description of the Intervention: The SMARTI Artificial Intelligence System

The investigational device includes a proprietary MoleMap Ltd camera capable of taking dermoscopic and macroscopic images and uploading them to an adjacent conventional computer, and the AI software that performs lesion assessments. The computer displays the participant's avatar and lesion images, along with diagnostic and management plan options from which the doctor chooses (Figures 1 and 2). Prior to the commencement of the study, research and medical staff working in the clinics receive training on use of the camera,

uploading of images and use of the computer software for making diagnoses and management plans.

The SMARTI AI system is a convolutional neural network (CNN) trained to classify lesions using a three-point scale: benign, malignant or uncertain. Figures 1 and 2 demonstrate the SMARTI computer displays and participant avatar indicating the lesion location.

In a laboratory setting, when compared with teledermatologist lesion classification, the first version of the CNN demonstrated a sensitivity of 85%, specificity of 78%, and area under the receiver operating characteristic curve (AUROC) of 0.91 for detection of melanoma; and a sensitivity of 72%, specificity of 88%, and AUROC of 0.89 for distinguishing a “cancer” from a benign lesion in a binary decision task. These results are comparable to those in pre-existing literature[12-14]. The AUROC is a statistical measure used to assess the discrimination ability of a diagnostic test when there is a dichotomous outcome[27]. An AUROC of 1.00 would mean that the test can discriminate perfectly between the two outcomes. The algorithm was tested with different images to those with which it was trained, however they were derived from the same dataset of images from MoleMap Ltd. Both macroscopic and dermoscopic images were used to train the algorithm.

The CNN has since been updated to improve its sensitivity and specificity. The algorithm used in the post-intervention period will be the algorithm which classifies the lesions imaged during the pre-intervention period with the greatest accuracy, as assessed by the interim quality assurance analysis.

Pre-intervention period

In the pre-intervention period, lesion assessments made by the AI algorithm are not visible to the treating doctors and therefore do not contribute to diagnostic or management decisions applicable to each lesion.

Participants receive standard of care according to Australian Guidelines [28, 29], including a full skin examination. The participant is first examined by a registrar who selects all skin lesions of concern for imaging, along with two or more non-suspicious lesions. These randomly selected non-suspicious lesions are included to enable analysis of the AI algorithm's specificity.

Acral and scalp lesions are excluded as these are inherently difficult areas to image, affecting reliability of diagnostic assessment. If approved for use, the algorithm would therefore not be appropriate to use for assessment of lesions at these sites in practice (unless further studies were undertaken) and this would need to be made clear to clinicians.

Macroscopic and polarised dermoscopic images are obtained for each lesion, and are uploaded to an electronic Case Report Form (eCRF) containing the participant's unique numerical study identifier, with the location of each lesion recorded on a digital avatar. The registrar records their initial favoured diagnosis and management plan for each lesion in the eCRF. Once entered, the diagnostic classification and management plan is locked and cannot be altered.

The treating consultant dermatologist then assesses the participant, recording their favoured diagnosis and management plan for each lesion in the eCRF. If the consultant identifies additional lesions of concern, these are imaged and uploaded to the eCRF and are assessed by the consultant only.

The participant receives recommended management advice from the consultant dermatologist for each lesion, and the final patient-agreed management plan is recorded in the eCRF.

All lesion images are reviewed remotely by one of three experienced teledermatologists. The teledermatologist records their favoured diagnosis and management plan in the eCRF for each lesion. This information is not visible to the treating doctors.

At the conclusion of the pre-intervention period, the AI algorithm will be applied to generate assessment of all lesions for an interim Quality Assurance analysis to evaluate safety of the AI algorithm prior to its use in the post-intervention period. The algorithm's sensitivity, specificity and agreement (using Kappa statistics) will be calculated, using histopathology as gold standard for biopsied lesions, and treating dermatologists' classifications as gold standard for lesions which are not biopsied to ensure acceptable accuracy prior to proceeding to the intervention phase. That is, whether the algorithm performs with a similar accuracy to the laboratory setting (sensitivity of 72%, specificity of 88%); and with a similar accuracy to that of other AI algorithms which have been shown to classify skin cancer with a sensitivity (ranging 76 – 96.3%) and specificity (ranging 53.5 – 92%) equal or superior to that of

dermatologists[30]. Images collected during the pre-intervention period will not be used for algorithm retraining.

Post-intervention period

Following the same procedure described above for the pre-intervention period, participants will be examined by the registrar. Lesions of concern and non-suspicious lesions will be selected, photographed, and uploaded to the eCRF. The registrar will record their initial favoured diagnosis and management plan for each lesion and will then submit the images to be analysed by the AI algorithm. The AI assessment will be visible to the registrar in the form of a benign, malignant or uncertain classification for each lesion. Upon review of the AI assessment, if they choose to, the registrar can update their diagnosis and management plan for each lesion, which will be recorded as an additional AI-assisted diagnosis and management plan in the eCRF.

The consultant dermatologist will then assess the participant and record their favoured diagnosis and management plan for each lesion in the eCRF. The consultant dermatologist will also submit the same images to be analysed by the AI algorithm. The AI assessment will then become visible to the consultant. Upon review of the AI assessment, if they choose to, the consultant dermatologist may update their diagnosis and management plan for each lesion, which will be recorded as an additional AI-assisted diagnosis and management plan in the eCRF.

The participant will then receive recommended management advice from the consultant dermatologist, which will be recorded on the eCRF. The final plan agreed upon between the

participant and treating doctors will be recorded. If either the consultant dermatologist initial or AI-assisted management plan included the decision to biopsy, the biopsy will be undertaken. This is to ensure that standard of care is provided.

The teledermatologists will assess all lesion images remotely following the patient visit and record their favoured diagnosis and management plan in the eCRF, maintaining blinding to the AI assessments. The teldermatologists' diagnoses and plans will not be visible to the treating doctors during either period. The teledermatologists' diagnoses and plans will therefore not influence management decisions in the clinic. Rather, they will be collected for the purpose of comparing and evaluating the accuracy of the AI assessments. All management decisions will ultimately be determined by the treating consultant dermatologist in the clinic (after discussion and agreement with the participant), in line with the standard of care.

Participant timeline and follow-up procedures

The participant will exit the study after the single study visit is completed if the participant's lesions have all been managed by either: 1) reassurance that no action is required; or 2) non-surgical treatment, such as cryotherapy or imiquimod cream.

If a participant has lesions which have been biopsied or surgically treated, and has no lesions to be monitored, they will exit the study at the time of receipt of the histopathology result.

If any lesions are to be monitored, participants will exit the study when either: 1) the monitored lesion(s) progress to biopsy at the three- or six-month follow-up, and the

histopathology results are received; 2) the monitored lesion(s) are classified as benign at the three- or six-month follow-up; or 3) the participant is lost to follow-up (Figure 3).

Upon study completion, participants will continue to undergo routine surveillance depending on their level of risk and will receive treatment for all lesions as per Australian Guidelines (Figure 3).

Primary outcomes

The primary outcome measure for this study is lesion classification, using a three-point scale: benign, uncertain, or malignant. Definitions and examples for these classifications are given in Table 1. The intention of the 'uncertain' classification option for clinicians is to highlight lesions for which a diagnostic tool is most likely to be called upon. The aim of the 'uncertain' class for the algorithm is to enable AI categorisation of lesions which are not definitely benign or malignant (for example, severely dysplastic naevi or low grade actinic keratoses), without misleading the clinician.

The primary analysis to evaluate AI performance will compare lesion classification accuracy determined by the AI algorithm to lesion classification accuracy according to teledermatologist assessment, using histopathology as reference standard where available, and the treating dermatologist's assessment as reference standard where histopathology is not available. The rationale behind this comparison of AI and teledermatologist accuracy is that: 1) AI and teledermatologists have the same available information (lesion images are available, although they cannot feel the lesion and cannot assess the rest of the patient's skin and non-imaged lesions); and 2) an AI diagnostic aid could serve a function similar to a

teledermatologist in the future, reducing workload for specialists and improving access to people living in areas poorly serviced by dermatologists.

The primary safety measures include: 1) for all lesions, the proportion of false positive lesion classifications of the AI algorithm that lead to inappropriate registrar management decisions; and 2) for all biopsied lesions, the proportion of false negative lesion classifications of the AI algorithm, using histopathology as the reference standard.

Secondary outcomes

The secondary outcome is the management decision made by treating doctors, per lesion using the five categories: leave; manage – monitor; manage – biopsy; treat – elective; or treat – essential. Table 2 describes management decision outcome categories.

There are seven secondary endpoints: 1) lesion classification of the AI algorithm compared with dermatologist classification; 2) lesion classification of the AI algorithm compared with registrar classification; 3) lesion classification of the AI algorithm compared with histopathology results of any lesions biopsied; 4) initial management decision of the registrar compared with their AI-assisted management decision, using the consultant dermatologist's initial management decision as the reference standard; 5) discordance in the initial and AI-assisted dermatologist management decision during the post-intervention period; 6) management decision of the teledermatologist compared with the AI-assisted registrar, using the initial consult dermatologist management decision as the reference standard; and 7) the benign to malignant ratio for lesions biopsied in the post-intervention period compared with the pre-intervention period.

Data collection and management

Participant demographic and risk factor data, including personal and family history of melanoma and keratinocyte carcinoma, ascertained by participant recall will be collected during interview by study staff, recorded directly to paper CRFs and transcribed to the electronic CRFs at study visit completion.

Pathology reports will be obtained from participants' medical records and relevant histopathology data will be transcribed directly to the eCRF.

Data entered to the custom eCRF platform by study site staff will be automatically synchronised to the electronic database tables built in Microsoft Access. The database will contain only de-identified, re-identifiable data appended to the participant's unique numerical study identifier. The database will be securely stored and backed-up within an approved data-sharing platform with infrastructure enabling at rest encryption using 256-bit Advanced Encryption Standard and Secure Sockets Layer /Transport Layer Security to protect data in transit with 128-bit or higher Advanced Encryption Standard encryption.

Data Monitoring

Routine risk-based monitoring will be undertaken by MASC Research Centre at Monash University for the purpose of source data verification at regular intervals throughout the trial. Data management is also centralised to MASC Research Centre at Monash University, who will be responsible for ongoing surveillance of data quality and integrity.

The Trial Management Committee will conduct regular meetings to review all aspects of study conduct, compliance and progress, in addition to data quality assurance, protocol deviation and monitoring of adverse events and device safety where relevant. Adverse events and protocol violations will be reported to the approving HREC according to HREC-specific guidelines.

Statistical methods

Sample size

The study aims to recruit 220 participants, providing a minimum of three lesions per participant to the final analysis, thus providing sufficient power to estimate, with reasonable precision, the AI algorithm lesion classification accuracy using teledermatologist assessment as the reference standard. Sample calculations are based on the assumption that 20% of lesions will be categorised as malignant and 10% will be categorised as uncertain; therefore, approximately 30% of lesions will be categorised as 'not benign' by teledermatologist assessment. If a kappa statistic of 0.8 signifies 'almost perfect' agreement[31], we will require approximately 220 participants in order to achieve a 95% confidence interval of +/- 0.05 (i.e. 95% CI 0.75 to 0.85).

Statistical analysis

AI algorithm lesion classification accuracy

The AI algorithm lesion classification accuracy will be compared to relevant physician assessors and histopathology results (for lesions biopsied). Kappa statistics will be used to evaluate agreement between benign/uncertain/malignant lesion classification, with quadratic weights used for kappa calculation. Standard validity indices will be used to

evaluate discriminatory ability of the AI algorithm for malignant lesions, including sensitivity, specificity, and positive and negative predictive values.

Performance errors of the CNN will be examined closely. Specifically, all lesions which are classified as benign by the CNN and malignant by the consultant dermatologist or histopathology, and all which are classified as malignant by the CNN and benign by the consultant dermatologist or histopathology, will be reviewed by a dermatologist to determine the nature of these errors.

Appropriateness of AI-assisted management

The impact of the AI diagnostic aid on appropriateness of the registrar's management decision will be evaluated by measuring the proportion of false positive lesion classifications of the AI algorithm that lead to inappropriate registrar management decisions; comparing the initial registrar management decision with the AI-assisted registrar management decision; and comparing the management decision of the teledermatologist with the AI-assisted registrar decision (all using the dermatologist's initial management decision as the reference standard). The appropriateness of the AI-assisted management will be further assessed by measuring discordance between the initial and AI-assisted management decisions of the dermatologist; and by comparing the benign to malignant ratio (for lesions biopsied) between the pre-intervention and post-intervention periods. Appropriate management of a malignant lesion may be to biopsy, excise or treat non-surgically. Therefore, a lesion will be considered treated appropriately with any of these options.

Where a lesion's follow up is unavailable the lesion will be included in analysis according to the treatment path (for example, a lesion that was planned for biopsy will be considered malignant if histopathology is not available). This approach will be supplemented by sensitivity analyses in which the opposite status is assumed (i.e. a lesion that was planned for biopsy will be considered benign if histopathology is not available).

Interim quality assurance analysis

Following the conclusion of the pre-intervention period, an interim Quality Assurance analysis will be conducted to evaluate safety of the AI algorithm to be implemented in the clinical setting during the post-intervention period. The safety of the AI algorithm will be evaluated by its agreement with the consultant dermatologists' classification (as benign, malignant or uncertain) for all lesions, and with the histopathology classification for biopsied or excised lesions. Kappa statistics and standard validity indices will be used to assess agreement, evaluating safety of the AI diagnostic aid with reference to gold-standard clinical care provided by consultant dermatologists. The focus of this analysis will be to ensure that the accuracy of the AI algorithm is on par with that of previously produced algorithms[30].

Ethics and dissemination

Ethics approval was obtained from the Alfred Hospital Ethics Committee. The protocol has been developed to comply with international standards of Good Clinical Practice (ICH-GCP E6(R2) and TGA Annotation 2016), NHMRC *National Statement* (2018) and *The Code* (2018), and all relevant national, state and local legislative requirements governing data privacy and handling. Study conduct will adhere to principles set out in Declaration of Helsinki 1962 (rev. 2000) and the aforementioned standards.

The findings from this study will be disseminated through peer-reviewed publications, non-peer reviewed media outlets, and conferences.

The Participant Information Sheet and Consent Form (PICF) requests participants indicate whether they consent for their de-identified skin lesion images to be used freely for other research studies. Participants can indicate their consent by completing an additional check box on the PICF.

Protocol Version:

Protocol No. 04.17 SMARTI Version 2.1, 16th June 2020.

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Contributors:

CF, SM, WC, NW, MW, NA, ZG, AS, AB, MH, RW and VM were all involved in developing the study protocol. VM, RW, MH and ZG worked together on the funding proposal. ZG developed the AI algorithm to be used in the study. RW provided support for the development of the statistical analysis plan. AB and AS provided technical support with the MoleMap computer software. All authors reviewed, edited and approved the final version.

Competing Interests:

VM is supported by an NHMRC Early Career Fellowship. VM reports personal fees from Novartis, personal fees from Bristol-Myers-Squibb, personal fees from Merck, outside the submitted work.

MH reports personal fees from MoleMap Ltd, during the conduct of the study; and is a shareholder in MoleMap Ltd.

AB reports personal fees from MoleMap Ltd, during the conduct of the study; personal fees from Molemap Ltd, outside the submitted work; and is a shareholder in Molemap Ltd.

AS reports personal fees from MoleMap Ltd, during the conduct of the study; personal fees from Molemap Ltd, outside the submitted work.

ZG reports personal fees from MoleMap Ltd.

NW and SM are former employees of the Cancer Collaborative Trials Group contracted to implement the SMARTI Study - Melanoma and Skin Cancer Trials (MASC Trials) Ltd.

CF is supported by a Monash University Research Training Program Scholarship.

RW, NA, WC and MW have nothing to disclose.

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Tables

Table 1. Classification definitions

Classification	Definition/situation	Examples
Benign	When the clinician is confident that the lesion is benign	Benign naevus, or seborrheic keratosis
Uncertain	When the clinician is unsure and would like a second opinion	Any skin lesion about which the clinician is not confident with regards to its benign/ malignant status
Malignant	When the clinician is confident that the lesion is malignant	Melanoma, basal cell carcinoma, squamous cell carcinoma, actinic keratosis*

* The malignant classification includes pre-malignant conditions, such as actinic keratosis.

Table 2. Management decision definitions

Management decision	Definition	Example
Leave	Reassure patient and take no further action.	Benign lesion requiring no further monitoring or medical management.

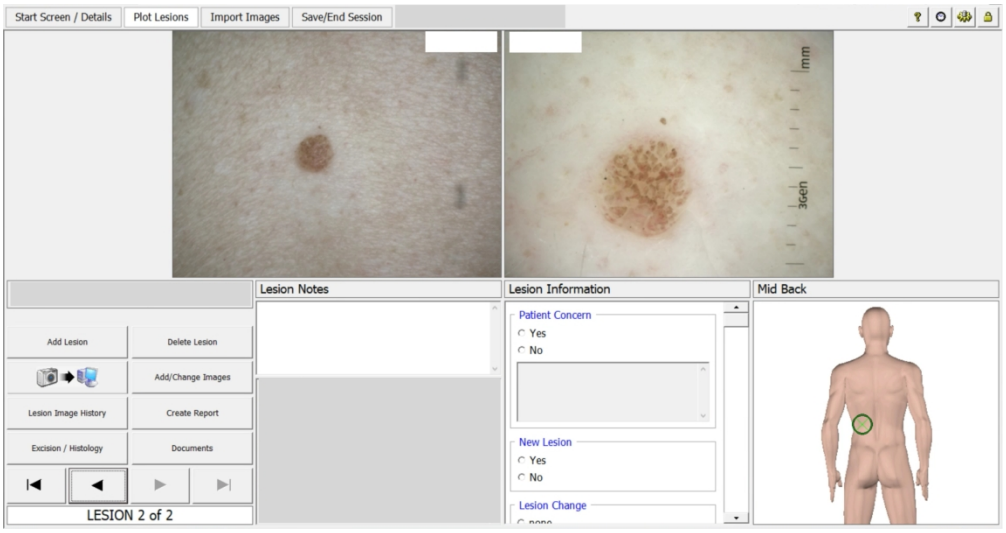
Manage - monitor	Reassessment of lesion at later time point according to Australian Guidelines.	Patient advised to self-monitor for period of 3 months prior to follow-up monitoring visit.
Manage - biopsy	Partial or complete biopsy of the lesion required to confirm diagnosis.	Shave or excisional biopsy of suspected malignancy.
Treat - elective	Benign or pre-cancerous lesion where treatment is not essential.	Patient requesting cryotherapy of a benign seborrheic keratosis
Treat - essential	Malignancy requiring non-surgical intervention.	Cryotherapy, pharmacotherapy or non-surgical intervention to treat malignancy.

Figures

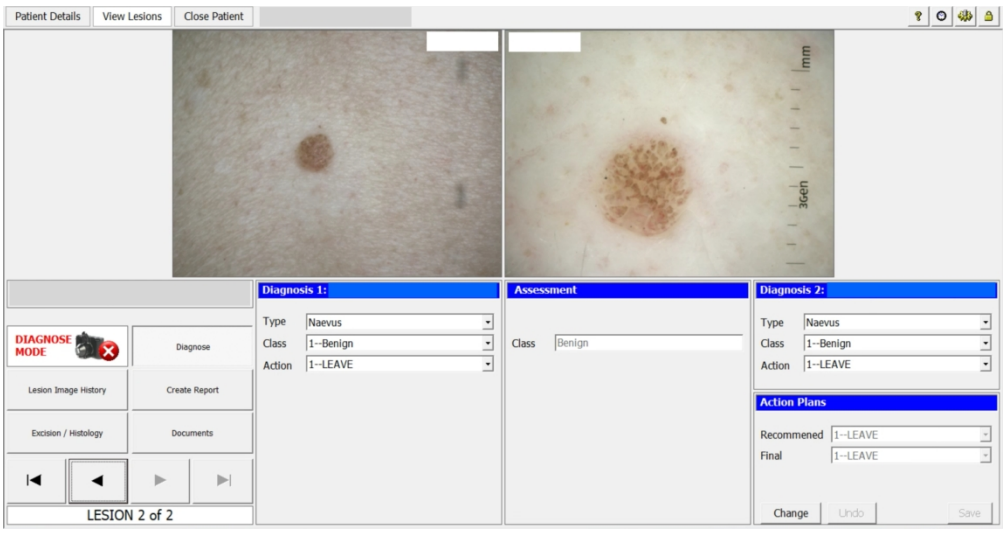
Figure 1. The SMARTI computer display: Participant avatar indicating the lesion location.

Figure 2. The SMARTI computer display: Clinician diagnosis and management plan entry, where: 'Diagnosis 1' is the clinician's initial assessment; 'Assessment' is the AI algorithm's classification; 'Diagnosis 2' is the clinician's AI-assisted assessment; and 'Action Plans' detail the recommended and final agreed-upon plan.

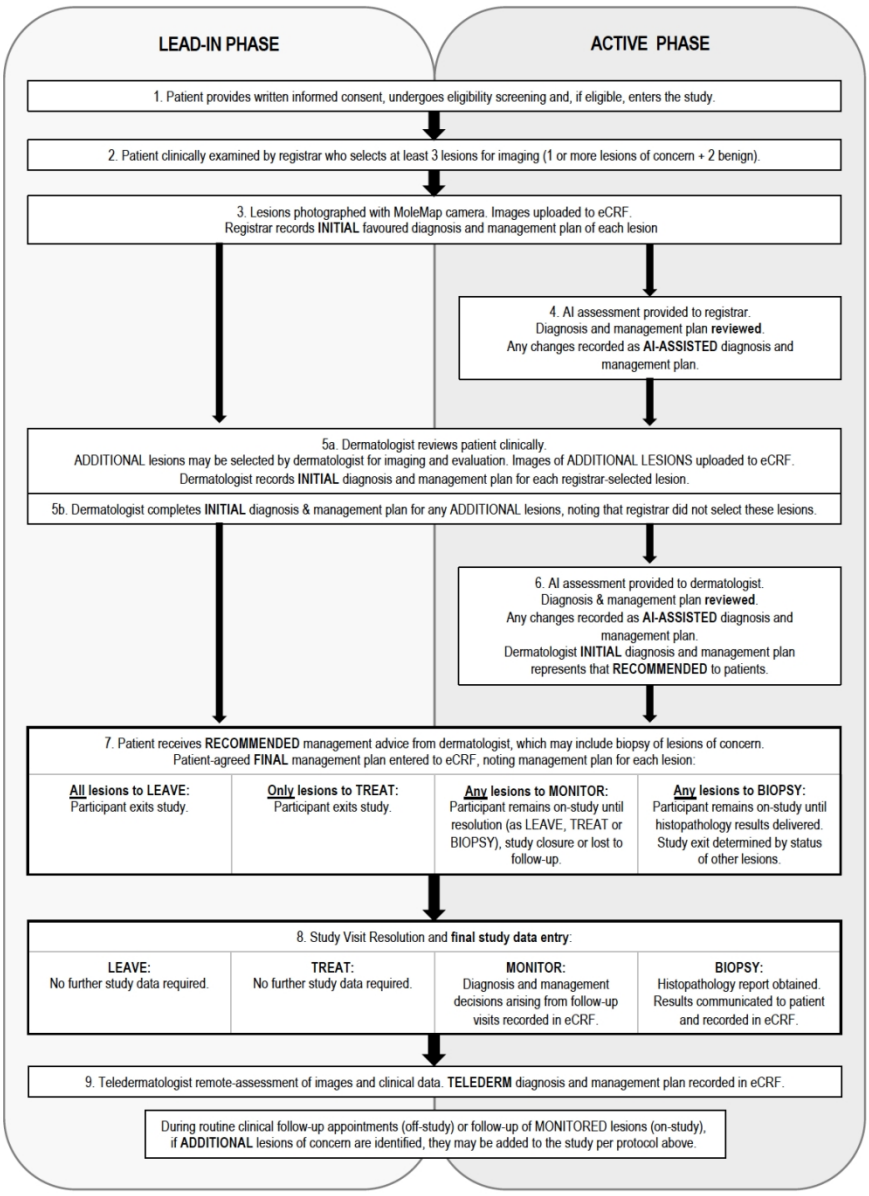
Figure 3. Participant flow chart.



The SMARTI computer display: Participant avatar indicating the lesion location.



The SMARTI computer display: Clinician diagnosis and management plan entry, where: 'Diagnosis 1' is the clinician's initial assessment; 'Assessment' is the AI algorithm's classification; 'Diagnosis 2' is the clinician's AI-assisted assessment; and 'Action Plans' detail the recommended and final agreed-upon plan.



Participant flow chart

SPIRIT Checklist

SECTION	ITEM	PAGE NUMBERS
#1 TITLE	Descriptive title identifying the study design, population, interventions, and, if applicable, trial acronym	1
#2A+B TRIAL REGISTRATION	Trial identifier and registry name. All items from the World Health Organization Trial Registration Data Set	4
#3 PROTOCOL VERSION	Date and version identifier	23
#4 FUNDING	Sources and types of financial, material, and other support	24-25
#5A ROLES AND RESPONSIBILITIES	Names, affiliations, and roles of protocol contributors	1, 23-24
# 5B ROLES AND RESPONSIBILITIES	Name and contact information for the trial sponsor	See Appendix
#5C ROLES AND RESPONSIBILITIES	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	See Appendix
#5D ROLES AND RESPONSIBILITIES	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)	19-20 and See Appendix
#6A BACKGROUND AND RATIONALE	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	6-8
#6B BACKGROUND AND RATIONALE	Explanation for choice of comparators	6-10, 17-18
#7 OBJECTIVES	Specific objectives or hypotheses	8-9
#8 TRIAL DESIGN	Description of trial design including type of trial (e.g. parallel group, crossover, factorial, single group), allocation ratio, and framework (e.g. superiority, equivalence, noninferiority, exploratory)	9-11

#9 STUDY SETTING	Description of study settings (e.g. community clinic, academic hospital) and list of countries where data will be collected	9
#10 ELIGIBILITY CRITERIA	Inclusion and exclusion criteria for participants. If applicable, eligibility criteria for study centres and individuals who will perform the interventions	10
#11A INTERVENTIONS	Interventions for each group with sufficient detail to allow replication, including how and when they will be administered	11-17
#11B INTEVRENTIONS	Criteria for discontinuing or modifying allocated interventions for a given trial participant (e.g. drug dose change in response to harms, participant request, or improving/worsening disease)	Not Applicable
#11C INTEVRENTIONS	Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence (e.g. drug tablet return; laboratory tests)	13
#11D INTEVRENTIONS	Relevant concomitant care and interventions that are permitted or prohibited during the trial	13-14
#12 OUTCOMES	Primary, secondary, and other outcomes, including the specific measurement variable (e.g. systolic blood pressure), analysis metric (e.g. change from baseline, final value, time to event), method of aggregation (e.g. median, proportion), and time point for each outcome	17-19; Tables 1 and 2
#13 PARTICIPANT TIMELINE	Time schedule of enrolment, interventions (including any run-ins and washouts), assessments, and visits for participants	16-17; Figure 3
#14 SAMPLE SIZE	Estimated number of participants needed to achieve study objectives and how it was determined, including clinical and statistical assumptions supporting any sample size calculations	20
#15 RECRUITMENT	Strategies for achieving adequate participant enrolment to reach target sample size	10-11
#16A-C ALLOCATION	Method of generating the allocation sequence; mechanism of implementing the allocation sequence; who will generate the allocation sequence, who will enrol	Not Applicable

	participants, and who will assign participants to interventions	
#17A BLINDING	Who will be blinded after assignment to interventions (eg, trial participants, care providers, outcome assessors, data analysts), and how	11
#17A BLINDING	If blinded, circumstances under which unblinding is permissible, and procedure for revealing a participant's allocated intervention during the trial	Not Applicable
#18A DATA COLLECTION PLAN	Plans for assessment and collection of outcome, baseline, and other trial data, including any related processes to promote data quality (e.g. duplicate measurements, training of assessors) and a description of study instruments (e.g. questionnaires, laboratory tests) along with their reliability and validity, if known	11-19; Figures 1 and 2
#18B DATA COLLECTION PLAN	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	Not Applicable
#19 DATA MANAGEMENT	Plans for data entry, coding, security, and storage, including any related processes to promote data quality (e.g. double data entry; range checks for data values)	19-20
#20A STATISTICS	Statistical methods for analysing primary and secondary outcomes	20-21
#20B STATISTICS	Methods for any additional analyses	Not Applicable
#20C STATISTICS	Definition of analysis population relating to protocol nonadherence and any statistical methods to handle missing data	21-22
#21A DATA MONITORING	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	19-20
#21B DATA MONITORING	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	14-15, 22
#22 HARMS	Plans for collecting, assessing, reporting, and managing solicited and spontaneously reported adverse events and other unintended effects of trial interventions or trial conduct	See Appendix

#23 AUDITING	Frequency and procedures for auditing trial conduct, if any, and whether the process will be independent from investigators and the sponsor	See Appendix
#24 RESEARCH ETHICS APPROVAL	Plans for seeking research ethics committee / institutional review board (REC / IRB) approval	4, 22-23
#25 PROTOCOL AMENDMENTS	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)	See Appendix
#26A CONSENT OR ASSENT	Who will obtain informed consent or assent from potential trial participants or authorised surrogates, and how	10-11
#26B CONSENT OR ASSENT	Additional consent provisions for collection and use of participant data and biological specimens in ancillary studies, if applicable	23
#27 CONFIDENTIALITY	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	19
#28 DECLARATION OF INTERESTS	Financial and other competing interests for principal investigators for the overall trial and each study site	23-25
#29 DATA ACCESS	Statement of who will have access to the final trial dataset, and disclosure of contractual agreements that limit such access for investigators	See Appendix
#30 ANCILLARY AND POST TRIAL CARE	Provisions, if any, for ancillary and post-trial care, and for compensation to those who suffer harm from trial participation	Not Applicable
#31A DISSEMINATION	Plans for investigators and sponsor to communicate trial results to participants, healthcare professionals, the public, and other relevant groups (e.g. via publication, reporting in results databases, or other data sharing arrangements), including any publication restrictions	4, 22-23
#31B DISSEMINATION	Authorship eligibility guidelines and any intended use of professional writers	23-24 and See Appendix
#31C DISSEMINATION	Plans, if any, for granting public access to the full protocol, participant-level dataset, and statistical code	See Appendix

#32 INFORMED CONSENT MATERIALS	Model consent form and other related documentation given to participants and authorised surrogates	See Attachment
#33 BIOLOGICAL SPECIMENS	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	Not Applicable

BMJ Open

Improving Skin cancer Management with ARTificial Intelligence (SMARTI): protocol for a pre-post intervention trial of an Artificial Intelligence system used as a diagnostic aid for skin cancer management in a specialist dermatology setting

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Improving Skin cancer Management with ARTificial Intelligence (SMARTI): protocol for a pre-post intervention trial of an Artificial Intelligence system used as a diagnostic aid for skin cancer management in a specialist dermatology setting

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Abstract

Introduction

Convolutional neural networks (CNNs) can diagnose skin cancers with impressive accuracy in experimental settings, however their performance in the real-world clinical setting, including comparison to teledermatology services, has not been validated in prospective clinical studies.

Methods and analysis

Participants will be recruited from dermatology clinics at the Alfred Hospital and Skin Health Institute, Melbourne. Skin lesions will be imaged using a proprietary dermoscopic camera. The Artificial Intelligence (AI) algorithm, a CNN developed by MoleMap Ltd and Monash eResearch, classifies lesions as benign, malignant or uncertain.

This is a pre-post-intervention study. In the pre-intervention period, treating doctors are blinded to AI lesion assessment. In the post-intervention period, treating doctors review the AI lesion assessment in real time, and have the opportunity to then change their diagnosis and management. Any skin lesions of concern and at least two benign lesions will be selected for imaging. Each participant's lesions will be examined by a registrar, the treating consultant dermatologist, and later by a teledermatologist.

At the conclusion of the pre-intervention period, the safety of the AI algorithm will be evaluated in a primary analysis by measuring its sensitivity, specificity and agreement with histopathology where available, or the treating consultant dermatologists' classification.

At trial completion, AI classifications will be compared with those of the teledermatologist, registrar, treating dermatologist and histopathology. The impact of the AI algorithm on diagnostic and management decisions will be evaluated by: 1) comparing the initial management decision of the registrar with their AI-assisted decision; and 2) comparing the benign to malignant ratio (for lesions biopsied) between the pre and post-intervention periods.

Ethics and dissemination

Human Research Ethics Committee (HREC) approval received from the Alfred Hospital Ethics Committee on 14th February 2019 (HREC/48865/Alfred-2018). Findings from this study will be disseminated through peer-reviewed publications, non-peer reviewed media, and conferences.

Trial registration

ClinicalTrials.gov identifier: NCT04040114.

Strengths and limitations of this study

- The first prospective clinical trial to evaluate safety and performance of an Artificial Intelligence diagnostic aid for skin cancer detection and management in the real-world clinical setting.
- Participants are recruited on a consecutive basis from routine attendance at melanoma and skin cancer assessment clinics, forming a representative sample of patients and lesion phenotypes from which to evaluate AI algorithm performance.
- AI performance will be compared with teledermatologists' assessment, as well as to face-to-face assessors of varying clinical experience (registrars and consultant dermatologists), and with histopathology results for biopsied lesions.
- Longitudinal follow-up is not undertaken for lesions labelled 'benign' and not actively 'monitored', hence the ultimate malignancy status of these lesions will not be evaluated in this study.
- Inherent differences in application of AI in the specialist setting may limit generalisability of study findings (regarding AI utility) to primary care settings, necessitating further research to establish feasibility for broader clinical implementation.

Introduction

Skin cancer, including melanoma and keratinocyte carcinoma, is the most common type of cancer in Caucasian populations, and its incidence is increasing worldwide[1-3]. The incidence of keratinocyte carcinoma is difficult to establish precisely due to a lack of nationwide cancer registry data, although Australia is thought to have the highest incidence worldwide, with over 1000 cases per 100,000 person-years[4]. Similarly, Australia has one of the highest incidence rates of melanoma in the world, with almost 14,000 Australians diagnosed with invasive and more than 20,000 with in-situ melanoma each year[5].

In Australia there is a shortage of dermatology services in rural and remote areas, where there are consequently long wait times to see a dermatologist. Travel to urban centres can be logistically challenging and expensive for patients. The MoleMap model of care involves total body and dermoscopic imaging by a melanographer. Images are sent to a teledermatologist for reporting. If a lesion is suspicious for malignancy, or if there is diagnostic uncertainty, a recommendation is made to monitor or biopsy the lesion and the patient is advised to consult their doctor. This teledermatology model is particularly useful for people living in areas poorly serviced by dermatologists[6]. It is, however, labour intensive, and it is hoped that AI may reduce workload for teledermatologists in the future.

Melanoma is the third most commonly diagnosed invasive cancer irrespective of gender and is responsible for over 1600 deaths in Australia each year[5]. Early diagnosis of skin cancer reduces morbidity and, in the case of melanoma, is associated with significantly improved survival[3, 7]. More accurate and timely skin cancer diagnosis and management could be brought about by the use of new AI-based diagnostic aids[8-10].

A subset of AI is machine learning. Machine learning refers to the ability of a computer system to write its own programming for a task, and to automatically learn and improve through training data. Deep learning is a branch of machine learning which is becoming increasingly utilised in medicine[11]. CNNs are a class of artificial neural networks that are most often used to analyse visual imagery through deep learning. They are especially effective at automated image recognition.

CNNs have been tested with the task of diagnosing skin cancers in multiple studies, and have displayed impressive accuracy equal or superior to that of the dermatologists with whom they have been compared[12-21]. However, these studies have thus far been undertaken in experimental (in silica) settings, and the use of AI as a diagnostic aid has not been adequately evaluated in the real-world clinical setting and in the hands of clinician end-users[9, 22].

AI algorithms should be tested with datasets separate to those with which they are trained, in order to avoid over-fitting or prior dataset bias, which can lead to over-estimation of an algorithm's accuracy[23, 24]. In particular, AI algorithms should be tested on the end-target patients or lesions to ensure their reliability and safety in their intended setting.

Furthermore, in the real-world, dermatologists have additional clinical information (for example, patient demographics and skin cancer history), which improves their diagnostic accuracy[25]. Previous studies comparing AI and dermatologist diagnostic accuracy without provision of this clinical information have therefore disadvantaged dermatologists.

Additionally, these experimental studies positing AI and dermatologists as opponents have been unable to assess the impact of AI algorithms, when used by clinicians, on clinicians' diagnoses and management decisions.

There is a need for prospective clinical trials to validate performance and ensure generalisability of the algorithms, and to evaluate the safety, utility and feasibility of implementing an AI diagnostic aid for skin cancer detection in the clinical setting[9, 12, 13, 26].

This validation study will evaluate the utility of AI as a diagnostic aid for skin cancer detection and management in the specialist dermatology setting, prior to a larger trial of the intervention in the primary care setting.

If this diagnostic aid for skin cancer management is proven safe, consistent and reliable in a specialist setting, and comparable to a teledermatologist diagnostic assessment, AI-assistance may be appropriate for use in specialist clinics including teledermatology-based services. Further research will be required to determine safety in a primary care setting prior to more widespread implementation, because there will be inherent differences in disease prevalence and clinician experience in this setting when compared to a specialist dermatology setting.

Objectives

Primary Objective:

Assess accuracy of the AI diagnostic aid compared with teledermatologist skin lesion assessment.

Secondary Objectives:

- Evaluate the impact of the AI device when used as a diagnostic aid on the appropriateness of skin cancer management decisions.
- Evaluate the accuracy and safety of the AI device when used as a diagnostic aid for skin cancer detection in specialist clinics.
- Assess the feasibility of implementing the AI device as a diagnostic aid for skin cancer detection and management in specialist settings, including teledermatology services.

Methods and analysis

Study design and setting

A pre-post intervention study of an AI diagnostic aid for skin cancer detection and management.

Participants will be recruited between October 2019 and May 2021 from the patient population attending specialist dermatology and melanoma clinics at two Australian tertiary centres: Skin Health Institute and the Alfred Hospital in Melbourne, Australia. Participants attending these clinics have a suspected or confirmed diagnosis of skin cancer, or are attending for routine skin surveillance.

Testing the algorithm in specialist dermatology settings allows for comparison of AI lesion classifications with the classifications of both experts (consultant dermatologists) and less-expert clinicians (dermatology registrars). The impact of the AI on less-expert (dermatology registrar) classification and management decisions can be assessed using the expert

(consultant dermatologist's) management decision and histopathology as the reference standard. Having established this knowledge, the AI algorithm could subsequently be applied and studied in a primary care setting more safely.

Participant and public involvement

The study protocol is endorsed by the Melanoma and Skin Cancer Trials Ltd (MASC Trials), a registered not-for-profit Australian and New Zealand's Cancer Collaborative Trials Group member and affiliate of Monash University. All MASC Trials endorsed protocols are subject to review by consumer group representatives, including members of the Australian Melanoma Consumer Alliance.

Eligibility criteria

Patients aged 18 or over, who are able to provide written informed consent, with at least one skin lesion of concern (to either the patient or treating doctor, excluding acral or scalp lesions), and are willing to have multiple lesions imaged are eligible to participate.

Recruitment

Willing patients who meet eligibility criteria are provided with a copy of the Participant Information and Consent Form (PICF) and guided through informed consent by their treating dermatology registrar during their clinic consultation. Participants are recruited on a consecutive basis via convenience sampling from routine attendance at specialist clinics.

Randomisation and blinding

In this pre-post intervention study design, the pre-intervention period will provide an estimate of skin cancer management parameters as a comparator (control) for assessing the impact of AI in the post-intervention period. Participants are recruited on a consecutive basis during each of the pre-intervention and post-intervention periods; there is no randomisation. Data is collected on participant risk factors and potentially relevant confounders to be considered during analysis.

In the pre-intervention period, treating doctors remain blinded to each other's lesion assessment and are unexposed to the AI assessment. Teledermatologists are blinded to the treating doctors' diagnoses and management plans, and to the AI assessment.

In the post-intervention period, treating doctors record their initial diagnosis and management plan decision, and are then exposed to the AI assessment prior to recording a final AI-assisted diagnosis and management plan. The teledermatologists remain blinded to the treating doctors' diagnoses and management plans, and to the AI assessment.

Description of the Intervention: The SMARTI Artificial Intelligence System

The investigational device includes a proprietary MoleMap Ltd camera capable of taking dermoscopic and macroscopic images and uploading them to an adjacent conventional computer, and the AI software that performs lesion assessments. The computer displays the participant's avatar and lesion images, along with diagnostic and management plan options from which the doctor chooses (Figures 1 and 2). Prior to the commencement of the study, research and medical staff working in the clinics receive training on use of the camera,

uploading of images and use of the computer software for making diagnoses and management plans.

The SMARTI AI system is a convolutional neural network (CNN) trained to classify lesions using a three-point scale: benign, malignant or uncertain. Figures 1 and 2 demonstrate the SMARTI computer displays and participant avatar indicating the lesion location.

In a laboratory setting, when compared with teledermatologist lesion classification, the first version of the CNN demonstrated a sensitivity of 85%, specificity of 78%, and area under the receiver operating characteristic curve (AUROC) of 0.91 for detection of melanoma; and a sensitivity of 72%, specificity of 88%, and AUROC of 0.89 for distinguishing a “cancer” from a benign lesion in a binary decision task. These results are comparable to those in pre-existing literature[12-14]. The AUROC is a statistical measure used to assess the discrimination ability of a diagnostic test when there is a dichotomous outcome[27]. An AUROC of 1.00 would mean that the test can discriminate perfectly between the two outcomes. The algorithm was tested with different images to those with which it was trained, however they were derived from the same dataset of images from MoleMap Ltd. Both macroscopic and dermoscopic images were used to train the algorithm.

The CNN has since been updated to improve its sensitivity and specificity. The algorithm used in the post-intervention period will be the algorithm which classifies the lesions imaged during the pre-intervention period with the greatest accuracy, as assessed by the interim quality assurance analysis.

Pre-intervention period

In the pre-intervention period, lesion assessments made by the AI algorithm are not visible to the treating doctors and therefore do not contribute to diagnostic or management decisions applicable to each lesion.

Participants receive standard of care according to Australian Guidelines [28, 29], including a full skin examination. The participant is first examined by a registrar who selects all skin lesions of concern for imaging, along with two or more non-suspicious lesions. These randomly selected non-suspicious lesions are included to enable analysis of the AI algorithm's specificity.

Acral and scalp lesions are excluded as these are inherently difficult areas to image, affecting reliability of diagnostic assessment. If approved for use, the algorithm would therefore not be appropriate to use for assessment of lesions at these sites in practice (unless further studies were undertaken) and this would need to be made clear to clinicians.

Macroscopic and polarised dermoscopic images are obtained for each lesion, and are uploaded to an electronic Case Report Form (eCRF) containing the participant's unique numerical study identifier, with the location of each lesion recorded on a digital avatar. The registrar records their initial favoured diagnosis and management plan for each lesion in the eCRF. Once entered, the diagnostic classification and management plan is locked and cannot be altered.

The treating consultant dermatologist then assesses the participant, recording their favoured diagnosis and management plan for each lesion in the eCRF. If the consultant identifies additional lesions of concern, these are imaged and uploaded to the eCRF and are assessed by the consultant only.

The participant receives recommended management advice from the consultant dermatologist for each lesion, and the final patient-agreed management plan is recorded in the eCRF.

All lesion images are reviewed remotely by one of three experienced teledermatologists. The teledermatologist records their favoured diagnosis and management plan in the eCRF for each lesion. This information is not visible to the treating doctors.

At the conclusion of the pre-intervention period, the AI algorithm will be applied to generate assessment of all lesions for an interim Quality Assurance analysis to evaluate safety of the AI algorithm prior to its use in the post-intervention period. The algorithm's sensitivity, specificity and agreement (using Kappa statistics) will be calculated, using histopathology as gold standard for biopsied lesions, and treating dermatologists' classifications as gold standard for lesions which are not biopsied to ensure acceptable accuracy prior to proceeding to the intervention phase. That is, whether the algorithm performs with a similar accuracy to the laboratory setting (sensitivity of 72%, specificity of 88%); and with a similar accuracy to that of other AI algorithms which have been shown to classify skin cancer with a sensitivity (ranging 76 – 96.3%) and specificity (ranging 53.5 – 92%) equal or superior to that of

dermatologists[30]. Images collected during the pre-intervention period will not be used for algorithm retraining.

Post-intervention period

Following the same procedure described above for the pre-intervention period, participants will be examined by the registrar. Lesions of concern and non-suspicious lesions will be selected, photographed, and uploaded to the eCRF. The registrar will record their initial favoured diagnosis and management plan for each lesion and will then submit the images to be analysed by the AI algorithm. The AI assessment will be visible to the registrar in the form of a benign, malignant or uncertain classification for each lesion. Upon review of the AI assessment, if they choose to, the registrar can update their diagnosis and management plan for each lesion, which will be recorded as an additional AI-assisted diagnosis and management plan in the eCRF.

The consultant dermatologist will then assess the participant and record their favoured diagnosis and management plan for each lesion in the eCRF. The consultant dermatologist will also submit the same images to be analysed by the AI algorithm. The AI assessment will then become visible to the consultant. Upon review of the AI assessment, if they choose to, the consultant dermatologist may update their diagnosis and management plan for each lesion, which will be recorded as an additional AI-assisted diagnosis and management plan in the eCRF.

The participant will then receive recommended management advice from the consultant dermatologist, which will be recorded on the eCRF. The final plan agreed upon between the

participant and treating doctors will be recorded. If either the consultant dermatologist initial or AI-assisted management plan included the decision to biopsy, the biopsy will be undertaken. This is to ensure that standard of care is provided.

The teledermatologists will assess all lesion images remotely following the patient visit and record their favoured diagnosis and management plan in the eCRF, maintaining blinding to the AI assessments. The teldermatologists' diagnoses and plans will not be visible to the treating doctors during either period. The teledermatologists' diagnoses and plans will therefore not influence management decisions in the clinic. Rather, they will be collected for the purpose of comparing and evaluating the accuracy of the AI assessments. All management decisions will ultimately be determined by the treating consultant dermatologist in the clinic (after discussion and agreement with the participant), in line with the standard of care.

Participant timeline and follow-up procedures

The participant will exit the study after the single study visit is completed if the participant's lesions have all been managed by either: 1) reassurance that no action is required; or 2) non-surgical treatment, such as cryotherapy or imiquimod cream.

If a participant has lesions which have been biopsied or surgically treated, and has no lesions to be monitored, they will exit the study at the time of receipt of the histopathology result.

If any lesions are to be monitored, participants will exit the study when either: 1) the monitored lesion(s) progress to biopsy at the three- or six-month follow-up, and the

histopathology results are received; 2) the monitored lesion(s) are classified as benign at the three- or six-month follow-up; or 3) the participant is lost to follow-up (Figure 3).

Upon study completion, participants will continue to undergo routine surveillance depending on their level of risk and will receive treatment for all lesions as per Australian Guidelines (Figure 3).

Primary outcomes

The primary outcome measure for this study is lesion classification, using a three-point scale: benign, uncertain, or malignant. Definitions and examples for these classifications are given in Table 1. The intention of the 'uncertain' classification option for clinicians is to highlight lesions for which a diagnostic tool is most likely to be called upon. The aim of the 'uncertain' class for the algorithm is to enable AI categorisation of lesions which are not definitely benign or malignant (for example, severely dysplastic naevi or low grade actinic keratoses), without misleading the clinician.

The primary analysis to evaluate AI performance will compare lesion classification accuracy determined by the AI algorithm to lesion classification accuracy according to teledermatologist assessment, using histopathology as reference standard where available, and the treating dermatologist's assessment as reference standard where histopathology is not available. The rationale behind this comparison of AI and teledermatologist accuracy is that: 1) AI and teledermatologists have the same available information (lesion images are available, although they cannot feel the lesion and cannot assess the rest of the patient's skin and non-imaged lesions); and 2) an AI diagnostic aid could serve a function similar to a

teledermatologist in the future, reducing workload for specialists and improving access to people living in areas poorly serviced by dermatologists.

The primary safety measures include: 1) for all lesions, the proportion of false positive lesion classifications of the AI algorithm that lead to inappropriate registrar management decisions; and 2) for all biopsied lesions, the proportion of false negative lesion classifications of the AI algorithm, using histopathology as the reference standard.

Secondary outcomes

The secondary outcome is the management decision made by treating doctors, per lesion using the five categories: leave; manage – monitor; manage – biopsy; treat – elective; or treat – essential. Table 2 describes management decision outcome categories.

There are seven secondary endpoints: 1) lesion classification of the AI algorithm compared with dermatologist classification; 2) lesion classification of the AI algorithm compared with registrar classification; 3) lesion classification of the AI algorithm compared with histopathology results of any lesions biopsied; 4) initial management decision of the registrar compared with their AI-assisted management decision, using the consultant dermatologist's initial management decision as the reference standard; 5) discordance in the initial and AI-assisted dermatologist management decision during the post-intervention period; 6) management decision of the teledermatologist compared with the AI-assisted registrar, using the initial consult dermatologist management decision as the reference standard; and 7) the benign to malignant ratio for lesions biopsied in the post-intervention period compared with the pre-intervention period.

Data collection and management

Participant demographic and risk factor data, including personal and family history of melanoma and keratinocyte carcinoma, ascertained by participant recall will be collected during interview by study staff, recorded directly to paper CRFs and transcribed to the electronic CRFs at study visit completion.

Pathology reports will be obtained from participants' medical records and relevant histopathology data will be transcribed directly to the eCRF.

Data entered to the custom eCRF platform by study site staff will be automatically synchronised to the electronic database tables built in Microsoft Access. The database will contain only de-identified, re-identifiable data appended to the participant's unique numerical study identifier. The database will be securely stored and backed-up within an approved data-sharing platform with infrastructure enabling at rest encryption using 256-bit Advanced Encryption Standard and Secure Sockets Layer /Transport Layer Security to protect data in transit with 128-bit or higher Advanced Encryption Standard encryption.

Data Monitoring

Routine risk-based monitoring will be undertaken by MASC Research Centre at Monash University for the purpose of source data verification at regular intervals throughout the trial. Data management is also centralised to MASC Research Centre at Monash University, who will be responsible for ongoing surveillance of data quality and integrity.

The Trial Management Committee will conduct regular meetings to review all aspects of study conduct, compliance and progress, in addition to data quality assurance, protocol deviation and monitoring of adverse events and device safety where relevant. Adverse events and protocol violations will be reported to the approving HREC according to HREC-specific guidelines.

Statistical methods

Sample size

The study aims to recruit 220 participants, providing a minimum of three lesions per participant to the final analysis, thus providing sufficient power to estimate, with reasonable precision, the AI algorithm lesion classification accuracy using teledermatologist assessment as the reference standard. Sample calculations are based on the assumption that 20% of lesions will be categorised as malignant and 10% will be categorised as uncertain; therefore, approximately 30% of lesions will be categorised as 'not benign' by teledermatologist assessment. If a kappa statistic of 0.8 signifies 'almost perfect' agreement[31], we will require approximately 220 participants in order to achieve a 95% confidence interval of +/- 0.05 (i.e. 95% CI 0.75 to 0.85).

Statistical analysis

AI algorithm lesion classification accuracy

The AI algorithm lesion classification accuracy will be compared to relevant physician assessors and histopathology results (for lesions biopsied). Kappa statistics will be used to evaluate agreement between benign/uncertain/malignant lesion classification, with quadratic weights used for kappa calculation. Standard validity indices will be used to

evaluate discriminatory ability of the AI algorithm for malignant lesions, including sensitivity, specificity, and positive and negative predictive values.

Performance errors of the CNN will be examined closely. Specifically, all lesions which are classified as benign by the CNN and malignant by the consultant dermatologist or histopathology, and all which are classified as malignant by the CNN and benign by the consultant dermatologist or histopathology, will be reviewed by a dermatologist to determine the nature of these errors.

Appropriateness of AI-assisted management

The impact of the AI diagnostic aid on appropriateness of the registrar's management decision will be evaluated by measuring the proportion of false positive lesion classifications of the AI algorithm that lead to inappropriate registrar management decisions; comparing the initial registrar management decision with the AI-assisted registrar management decision; and comparing the management decision of the teledermatologist with the AI-assisted registrar decision (all using the dermatologist's initial management decision as the reference standard). The appropriateness of the AI-assisted management will be further assessed by measuring discordance between the initial and AI-assisted management decisions of the dermatologist; and by comparing the benign to malignant ratio (for lesions biopsied) between the pre-intervention and post-intervention periods. Appropriate management of a malignant lesion may vary depending on the diagnosis and the patient's situation. Appropriateness of management decisions will be reviewed for all lesions biopsied or monitored where there is discordance with the dermatologists' initial diagnostic assessment.

Where a lesion's follow up is unavailable the lesion will be included in analysis according to the treatment path (for example, a lesion that was planned for biopsy will be considered malignant if histopathology is not available). This approach will be supplemented by sensitivity analyses in which the opposite status is assumed (i.e. a lesion that was planned for biopsy will be considered benign if histopathology is not available).

Interim quality assurance analysis

Following the conclusion of the pre-intervention period, an interim Quality Assurance analysis will be conducted to evaluate safety of the AI algorithm to be implemented in the clinical setting during the post-intervention period. The safety of the AI algorithm will be evaluated by its agreement with the consultant dermatologists' classification (as benign, malignant or uncertain) for all lesions, and with the histopathology classification for biopsied or excised lesions. Kappa statistics and standard validity indices will be used to assess agreement, evaluating safety of the AI diagnostic aid with reference to gold-standard clinical care provided by consultant dermatologists. The focus of this analysis will be to ensure that the accuracy of the AI algorithm is on par with that of previously produced algorithms[30].

Ethics and dissemination

Ethics approval was obtained from the Alfred Hospital Ethics Committee. The protocol has been developed to comply with international standards of Good Clinical Practice (ICH-GCP E6(R2) and TGA Annotation 2016), NHMRC *National Statement* (2018) and *The Code* (2018), and all relevant national, state and local legislative requirements governing data privacy and handling. Study conduct will adhere to principles set out in Declaration of Helsinki 1962 (rev. 2000) and the aforementioned standards.

The findings from this study will be disseminated through peer-reviewed publications, non-peer reviewed media outlets, and conferences.

The Participant Information Sheet and Consent Form (PICF) requests participants indicate whether they consent for their de-identified skin lesion images to be used freely for other research studies. Participants can indicate their consent by completing an additional check box on the PICF.

Protocol Version:

Protocol No. 04.17 SMARTI Version 2.1, 16th June 2020.

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Contributors:

CF, SM, WC, NW, MW, NA, ZG, AS, AB, MH, RW and VM were all involved in developing the study protocol. VM, RW, MH and ZG worked together on the funding proposal. ZG developed the AI algorithm to be used in the study. RW provided support for the development of the statistical analysis plan. AB and AS provided technical support with the MoleMap computer software. All authors reviewed, edited and approved the final version.

Competing Interests:

VM is supported by an NHMRC Early Career Fellowship. VM reports personal fees from Novartis, personal fees from Bristol-Myers-Squibb, personal fees from Merck, outside the submitted work.

MH reports personal fees from MoleMap Ltd, during the conduct of the study; and is a shareholder in MoleMap Ltd.

AB reports personal fees from MoleMap Ltd, during the conduct of the study; personal fees from Molemap Ltd, outside the submitted work; and is a shareholder in Molemap Ltd.

AS reports personal fees from MoleMap Ltd, during the conduct of the study; personal fees from Molemap Ltd, outside the submitted work.

ZG reports personal fees from MoleMap Ltd.

NW and SM are former employees of the Cancer Collaborative Trials Group contracted to implement the SMARTI Study - Melanoma and Skin Cancer Trials (MASC Trials) Ltd.

CF is supported by a Monash University Research Training Program Scholarship.

RW, NA, WC and MW have nothing to disclose.

The study is sponsored by Monash University and endorsed by MASC Trials Ltd.

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Tables

Table 1. Classification definitions

Classification	Definition/situation	Examples
Benign	When the clinician is confident that the lesion is benign	Benign naevus, or seborrheic keratosis
Uncertain	When the clinician is unsure and would like a second opinion	Any skin lesion about which the clinician is not confident with regards to its benign/ malignant status
Malignant	When the clinician is confident that the lesion is malignant	Melanoma, basal cell carcinoma, squamous cell carcinoma, actinic keratosis*

* The malignant classification includes pre-malignant conditions, such as actinic keratosis.

Table 2. Management decision definitions

Management decision	Definition	Example
Leave	Reassure patient and take no further action.	Benign lesion requiring no further monitoring or medical management.

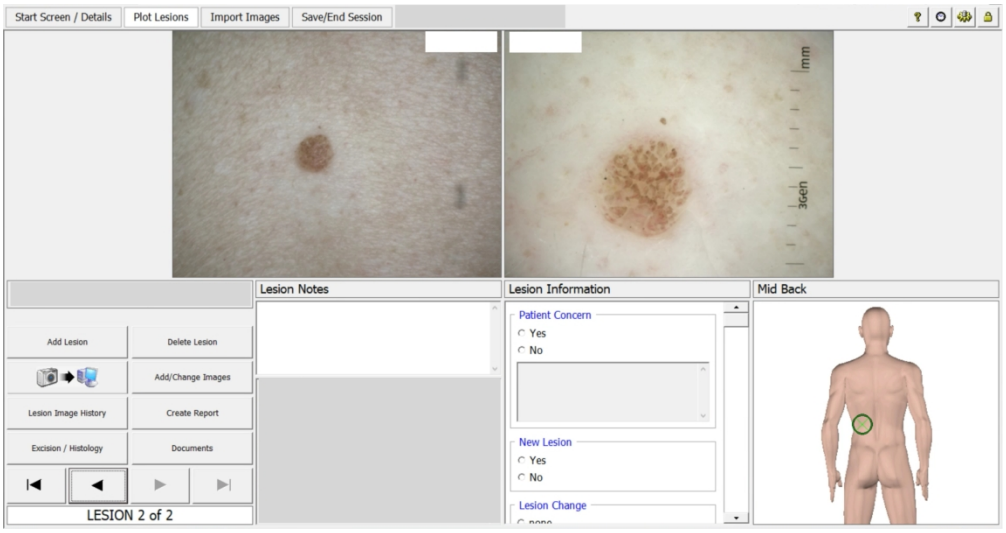
Manage - monitor	Reassessment of lesion at later time point according to Australian Guidelines.	Patient advised to self-monitor for period of 3 months prior to follow-up monitoring visit.
Manage - biopsy	Partial or complete biopsy of the lesion required to confirm diagnosis.	Shave or excisional biopsy of suspected malignancy.
Treat - elective	Benign or pre-cancerous lesion where treatment is not essential.	Patient requesting cryotherapy of a benign seborrheic keratosis
Treat - essential	Malignancy requiring non-surgical intervention.	Cryotherapy, pharmacotherapy or non-surgical intervention to treat malignancy.

Figures

Figure 1. The SMARTI computer display: Participant avatar indicating the lesion location.

Figure 2. The SMARTI computer display: Clinician diagnosis and management plan entry, where: 'Diagnosis 1' is the clinician's initial assessment; 'Assessment' is the AI algorithm's classification; 'Diagnosis 2' is the clinician's AI-assisted assessment; and 'Action Plans' detail the recommended and final agreed-upon plan.

Figure 3. Participant flow chart.



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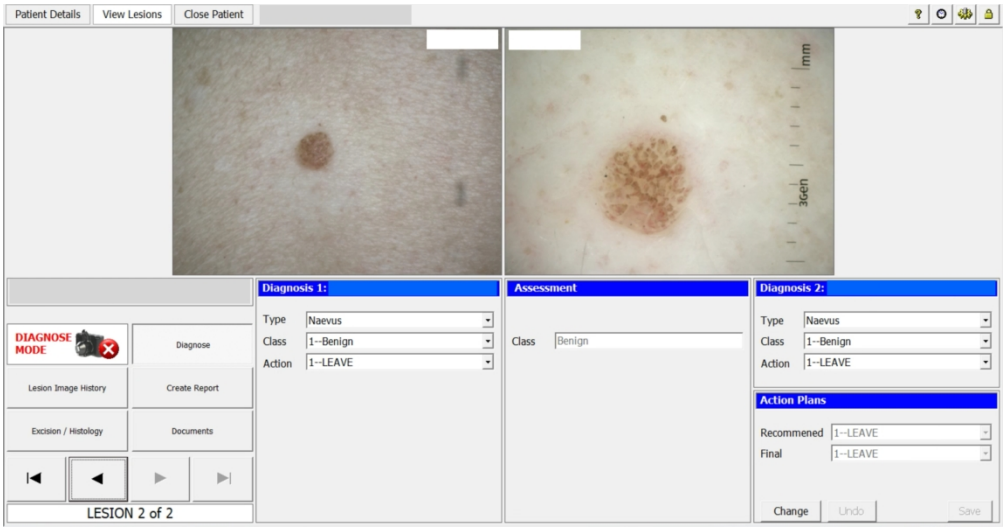

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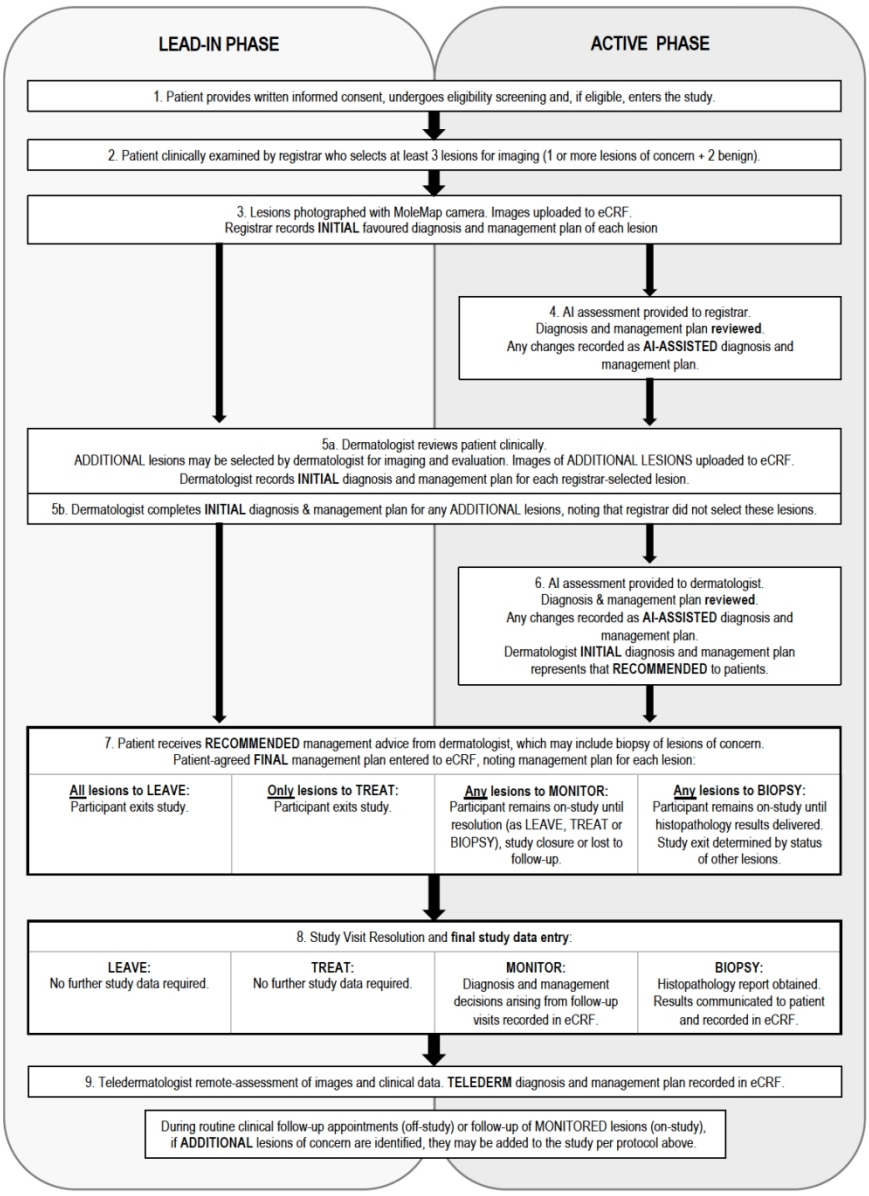

Figure 3. Participant flow chart.

SPIRIT Checklist

SECTION	ITEM	PAGE NUMBERS
#1 TITLE	Descriptive title identifying the study design, population, interventions, and, if applicable, trial acronym	1
#2A+B TRIAL REGISTRATION	Trial identifier and registry name. All items from the World Health Organization Trial Registration Data Set	4
#3 PROTOCOL VERSION	Date and version identifier	23
#4 FUNDING	Sources and types of financial, material, and other support	24-25
#5A ROLES AND RESPONSIBILITIES	Names, affiliations, and roles of protocol contributors	1, 23-24
# 5B ROLES AND RESPONSIBILITIES	Name and contact information for the trial sponsor	See Appendix
#5C ROLES AND RESPONSIBILITIES	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	See Appendix
#5D ROLES AND RESPONSIBILITIES	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)	19-20 and See Appendix
#6A BACKGROUND AND RATIONALE	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	6-8
#6B BACKGROUND AND RATIONALE	Explanation for choice of comparators	6-10, 17-18
#7 OBJECTIVES	Specific objectives or hypotheses	8-9
#8 TRIAL DESIGN	Description of trial design including type of trial (e.g. parallel group, crossover, factorial, single group), allocation ratio, and framework (e.g. superiority, equivalence, noninferiority, exploratory)	9-11

#9 STUDY SETTING	Description of study settings (e.g. community clinic, academic hospital) and list of countries where data will be collected	9
#10 ELIGIBILITY CRITERIA	Inclusion and exclusion criteria for participants. If applicable, eligibility criteria for study centres and individuals who will perform the interventions	10
#11A INTERVENTIONS	Interventions for each group with sufficient detail to allow replication, including how and when they will be administered	11-17
#11B INTEVRENTIONS	Criteria for discontinuing or modifying allocated interventions for a given trial participant (e.g. drug dose change in response to harms, participant request, or improving/worsening disease)	Not Applicable
#11C INTEVRENTIONS	Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence (e.g. drug tablet return; laboratory tests)	13
#11D INTEVRENTIONS	Relevant concomitant care and interventions that are permitted or prohibited during the trial	13-14
#12 OUTCOMES	Primary, secondary, and other outcomes, including the specific measurement variable (e.g. systolic blood pressure), analysis metric (e.g. change from baseline, final value, time to event), method of aggregation (e.g. median, proportion), and time point for each outcome	17-19; Tables 1 and 2
#13 PARTICIPANT TIMELINE	Time schedule of enrolment, interventions (including any run-ins and washouts), assessments, and visits for participants	16-17; Figure 3
#14 SAMPLE SIZE	Estimated number of participants needed to achieve study objectives and how it was determined, including clinical and statistical assumptions supporting any sample size calculations	20
#15 RECRUITMENT	Strategies for achieving adequate participant enrolment to reach target sample size	10-11
#16A-C ALLOCATION	Method of generating the allocation sequence; mechanism of implementing the allocation sequence; who will generate the allocation sequence, who will enrol	Not Applicable

	participants, and who will assign participants to interventions	
#17A BLINDING	Who will be blinded after assignment to interventions (eg, trial participants, care providers, outcome assessors, data analysts), and how	11
#17A BLINDING	If blinded, circumstances under which unblinding is permissible, and procedure for revealing a participant's allocated intervention during the trial	Not Applicable
#18A DATA COLLECTION PLAN	Plans for assessment and collection of outcome, baseline, and other trial data, including any related processes to promote data quality (e.g. duplicate measurements, training of assessors) and a description of study instruments (e.g. questionnaires, laboratory tests) along with their reliability and validity, if known	11-19; Figures 1 and 2
#18B DATA COLLECTION PLAN	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	Not Applicable
#19 DATA MANAGEMENT	Plans for data entry, coding, security, and storage, including any related processes to promote data quality (e.g. double data entry; range checks for data values)	19-20
#20A STATISTICS	Statistical methods for analysing primary and secondary outcomes	20-21
#20B STATISTICS	Methods for any additional analyses	Not Applicable
#20C STATISTICS	Definition of analysis population relating to protocol nonadherence and any statistical methods to handle missing data	21-22
#21A DATA MONITORING	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	19-20
#21B DATA MONITORING	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	14-15, 22
#22 HARMS	Plans for collecting, assessing, reporting, and managing solicited and spontaneously reported adverse events and other unintended effects of trial interventions or trial conduct	See Appendix

#23 AUDITING	Frequency and procedures for auditing trial conduct, if any, and whether the process will be independent from investigators and the sponsor	See Appendix
#24 RESEARCH ETHICS APPROVAL	Plans for seeking research ethics committee / institutional review board (REC / IRB) approval	4, 22-23
#25 PROTOCOL AMENDMENTS	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)	See Appendix
#26A CONSENT OR ASSENT	Who will obtain informed consent or assent from potential trial participants or authorised surrogates, and how	10-11
#26B CONSENT OR ASSENT	Additional consent provisions for collection and use of participant data and biological specimens in ancillary studies, if applicable	23
#27 CONFIDENTIALITY	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	19
#28 DECLARATION OF INTERESTS	Financial and other competing interests for principal investigators for the overall trial and each study site	23-25
#29 DATA ACCESS	Statement of who will have access to the final trial dataset, and disclosure of contractual agreements that limit such access for investigators	See Appendix
#30 ANCILLARY AND POST TRIAL CARE	Provisions, if any, for ancillary and post-trial care, and for compensation to those who suffer harm from trial participation	Not Applicable
#31A DISSEMINATION	Plans for investigators and sponsor to communicate trial results to participants, healthcare professionals, the public, and other relevant groups (e.g. via publication, reporting in results databases, or other data sharing arrangements), including any publication restrictions	4, 22-23
#31B DISSEMINATION	Authorship eligibility guidelines and any intended use of professional writers	23-24 and See Appendix
#31C DISSEMINATION	Plans, if any, for granting public access to the full protocol, participant-level dataset, and statistical code	See Appendix

#32 INFORMED CONSENT MATERIALS	Model consent form and other related documentation given to participants and authorised surrogates	See Attachment
#33 BIOLOGICAL SPECIMENS	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	Not Applicable