Title

Can patient-led surveillance detect subsequent new primary or recurrent melanomas and reduce the need for routinely scheduled follow up? Statistical Analysis Plan for the MEL-SELF randomised controlled trial.

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Abstract

Background: The MEL-SELF trial is a randomised controlled trial of patient-led surveillance compared to clinician-led surveillance in people treated for localised cutaneous melanoma (stage 0, I, II). The primary trial aim is to determine if patient led-surveillance compared to clinician-led surveillance increases the proportion of participants who are diagnosed with a new primary or recurrent melanoma at a fast-tracked unscheduled clinic visit. The secondary outcomes include time to diagnosis of any skin cancer, psychosocial outcomes, acceptability, and resource use.

Objective: The objective of this report is to outline and publish the pre-determined statistical analysis plan before the database lock and the start of analysis.

Methods/design: The statistical analysis plan describes the overall analysis principles, including how participants will be included in each analysis, the presentation of the results, adjustments for covariates, the primary and secondary outcomes, and their respective analyses. In addition, we present the planned sensitivity and subgroup analyses. A separate analysis plan will be published for health economic outcomes.

Results: The MEL-SELF statistical analysis plan has been designed to minimise bias in estimating effects of the intervention on primary and secondary outcomes. By pre-specifying analyses, we ensure the study's integrity and believability while enabling the reproducibility of the final analysis.

Conclusion: This detailed statistical analysis plan will help to ensure transparency of reporting of results from the MEL-SELF trial.

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1 Introduction

Although surgical excision of a localised melanoma before it has spread from the primary site on the skin is potentially curative, patients are recommended to undergo long-term follow-up because of their increased risk of developing a subsequent new primary melanoma, a recurrence of their treated primary melanoma, or new keratinocyte (non-melanoma) skin cancers.[1,2] Clinician-led surveillance in the form of routinely scheduled clinic visits is widely accepted as the usual model of follow up care, although there is a no direct evidence that this leads to improved survival.[1,3] There are substantial financial costs to the patient and healthcare system associated with this model of care,[4] and possible psychosocial harms.[5] Fewer routinely scheduled clinic visits may have little impact on the detection of subsequent new primary or recurrent melanomas[6] and could result in significant cost savings.[7-9]

Patient-led surveillance is a new model of follow-up where there is an increased reliance on patient self-management of their melanoma risk. Patients are trained in skin self-examination (SSE) and provided fast-tracked access to unscheduled clinic visits if they identify a concerning lesion. There is also the potential for fewer routinely scheduled clinic visits,[10] if clinicians are confident in the patient's ability to perform SSE.[11] Self-examination of abnormalities or concerning lesions by a patient may result in earlier detection of a subsequent new primary or recurrent melanoma, which could improve the effectiveness of treatment and survival.[12-15]

Digital technologies (including smartphone apps, mobile dermatoscopes, and teledermoscopy) have been found to be feasible and acceptable to patients for skin surveillance.[16,17] Our pilot randomised controlled trial (n=100) demonstrated the feasibility of a patient-led surveillance intervention comprising increased SSE

support and patient-performed mobile teledermoscopy among patients with early stage melanoma.[18,19]

We initiated the MELanoma SELF surveillance (MEL-SELF) randomised controlled trial to determine if patient-led surveillance results in better health, psychological and economic outcomes than clinician-led surveillance, with results having the potential to influence clinical practice and health policy.[18,20] For transparency of future reporting of results from the trial, we now provide a detailed statistical analysis plan for the primary and secondary outcomes. We have designed the plan in accordance with expert guidance on recommended content and on pre-specifying the analysis approach.[21,22] In accordance with guidelines, we have ordered the content of the statistical analysis plan into the following sections: Study Methods; Statistical Principles; Trial Population; and Analysis.[21]

2 Study Methods

2.1 Trial design

This study is a two-stage randomisation, two-arm, parallel, superiority RCT with an active run-in phase. Following the active run-in phase, eligible participants will be randomised 1:1 to intervention vs the control group. Participants in the intervention arm will undergo a second randomisation step with 1:1 allocation into alternative models of dermatoscope (polarised or non-polarised light source). The primary outcome and secondary outcomes will be compared across randomised groups.

2.2 Randomisation

All eligible participants who consent to participate, have completed the Baseline Questionnaire, and adhered to activities in the run-in phase will be randomised 1:1 into the control and intervention arms. Within the intervention arm, participants will be randomised 1:1 to a mobile dermatoscope that uses a polarised light source and one that uses a non-polarised light source. The first stage of randomisation will be performed offsite using a web-based randomisation system (www.randomize.net). The second stage of randomisation will be done using the randomisation module in REDCap (version 11.0.3). Figure 1 presents a summary of the randomisation of participants into the allocated control and intervention arms.

[insert Figure 1]

The first stage randomisation to intervention and control will use minimisation to ensure the two study groups are balanced on key prognostic factors. Box 1 lists the prognostic factors that we will use for minimization. We will collect data on these through the baseline questionnaire and baseline clinical assessment.

[insert Box 1]

The second stage randomisation to type of device will use permuted blocks of varying size and stratified by key variables that might influence use of the device (attending Specialist vs GP-led treatment centre, age, and gender). The ratio will be adapted depending on adherence with submission of images that are of sufficient quality to allow teledermatology reporting. After 60 participants have been randomised into the intervention group, we will measure the proportion of intervention participants who have had an image reported on at one month after their baseline images (post randomisation) were due. If there is > 30% absolute difference

in the proportion of intervention participants who have had an image reported on, participants who are subsequently enrolled will be randomised 2:1 to the dermatoscope model where more participants had an image reported on. If there is > 50% absolute difference in the proportion of intervention participants who have had an image reported on, then all participants who are subsequently enrolled will be randomised to the dermatoscope model where more participants had an image that was reported on. Calculated confidence intervals for a difference in proportions of 30% and 50% are presented in the table 1 below.

[insert table 1]

2.3 Sample size

Using Fisher's exact test and assuming a two-sided 5% significance level, a sample size of 452 participants (226 to patient-led surveillance and 226 to clinician-led surveillance) was calculated with at least 80% power to detect a 5% absolute increase in the patient-led surveillance group (i.e., 6% have new or recurrent melanoma diagnosed through unscheduled visit at treatment centre vs. 1% in the clinician-led surveillance group). Assuming up to 25% of study participants withdraw consent or dropout, we will recruit 600 participants (300 to patient-led surveillance and 300 to clinician-led surveillance). These calculations assume that 6% of patients in the clinician-led surveillance group have a subsequent new primary or recurrent melanoma diagnosed within the 12 months follow up (based on data from previous studies in this clinical population),[18,23,24] and that 1% have a diagnosis through a fast-tracked unscheduled clinic visit (a conservative assumption as previous data found 0% were diagnosed this way in usual care).[18] Sample size has been calculated assuming no difference between the two models of mobile dermatoscope for the primary outcome. This sample size will also ensure at least 80% power to

detect a hazard ratio of 1.71 for time from randomisation to diagnosis of a skin cancer for the patient-led vs clinician-led surveillance groups (due to earlier and increased detection in the patient-led group). This calculation assumes a 20% event rate in the clinician-led surveillance group (60 events among 300 control participants),[10,23] a 32% event rate in the patient-led surveillance group (96 events among 300 intervention participants), and 26% event rate overall (156 events among 600 trial participants).

2.4 Analytic Framework

As outlined above in Section 2.1, the design of the study is aimed at demonstrating the superiority of patient-led over clinician-led surveillance in terms of the proportion of participants who are diagnosed with a subsequent new primary or recurrent melanoma (any stage) at a fast-tracked unscheduled clinic visit. Secondary outcomes will also be tested for the superiority of patient-led surveillance.

2.5 Statistical interim analysis and stopping guidance

Interim analyses will be conducted by an independent statistician after 33% of trial participants (~200 participants) have been recruited and following this, after every six months. The interim analyses will examine the overall event rate to see if this is lower or higher than we assumed for our sample size estimation. Because we are not comparing the two randomised arms, nor conducting any statistical tests, the type I error rate is not impacted. Interim analyses are described in full in the protocol.[20]

There is no specific stopping guidance according to efficacy, safety, or futility. However, the protocol describes in detail what occurs in the event of a serious adverse event.[20]

2.6 Timing of final analysis

Analysis of primary and secondary outcomes will be undertaken after the 12 months of active follow-up of all participants and after all data collection is completed and the database has been locked. We will repeat analyses after completion of a further 12 months passive data collection through linkage to administrative and health data outlined below.

2.7 Timing of outcome assessments

Full details on the timing of outcome assessments are provided in the protocol.[20]

3 Statistical principals

3.1 Confidence intervals and p-values

We will present 95% confidence intervals (CI) for effect estimates on all primary and secondary outcomes. All hypothesis tests will be two-sided with an α of 5%. P-values from secondary analyses will not be adjusted for multiple testing and so will be interpreted conservatively.

3.2 Adherence and protocol deviations

Full details regarding adherence and protocol deviations are provided in the Appendix.

3.3 Analysis populations

3.3.1 Intention-to-treat (ITT) population

All analyses will adhere to the intention-to-treat principle, unless otherwise stated. That is, all patients will be analysed according to the randomly assigned study arm, regardless of adherence to the study protocol.[20]

3.3.2 Per-protocol population

As a secondary analysis, we will conduct a per-protocol analysis, in which we will estimate the effect that would have been observed had all participants adhered to the protocol. Adherence is defined in the appendix. We will use statistical "G-methods" for causal inference in this analysis (see Section 6.6).

3.3.3 As-treated population

We will also conduct a secondary analysis using an as-treated population, in which we will analyse participants according to the treatment (type of surveillance) they received, irrespective of the treatment (type of surveillance) they were assigned.

4 Trial population

4.1 Screening data

We will report summary characteristics of all potential participants assessed against inclusion/exclusion criteria (including proportion of people not meeting each of these at the screening stage), all potential participants who were invited to participate in the active run-in phase (including proportion of people not meeting each of the criteria to progress past this stage), and those who are finally randomised. We will also report the total number of patients attending clinics where any patients were

screened for the trial. In this way, readers will be able to assess representativeness of the trial sample to the broader clinical population from which it was selected. Readers will also have some indication of potential uptake of the intervention in clinical practice, if it is found to be safe and effective.[25]

4.2 Eligibility

Individuals who meet the eligibility requirements will be recruited from melanoma clinics at three sites in New South Wales, Australia. These include the Royal Prince Alfred Hospital and the Melanoma Institute of Australia (North Sydney), which are specialist-led clinics in metropolitan Sydney, and the Newcastle Skin Check clinic, which is a primary care skin cancer clinic run by general practitioners located in metropolitan Newcastle. Further sites may be opened if needed to meet the recruitment target and may include regional clinics.

4.3 Inclusion criteria

[insert box 2]

4.4 Exclusion criteria

[insert box 3]

4.5 Recruitment

Information that will be included in the CONSORT flow diagram is shown in Appendix Figure 1. The diagram will include the numbers of participants who were randomly assigned, received intended intervention, and were analysed for the primary outcome. For each group, losses, and exclusions after randomisation, together with reasons will be included.

4.6 Withdrawal/follow-up

We will tabulate the number of patients whose consent for trial participation is withdrawn by the participant and those who are withdrawn by the site coordinator due to loss to follow-up. Participants may choose to withdraw from active follow-up, but consent to ongoing passive collection of administrative data (clinic, cancer registry and Medicare Benefits Scheme claims database) during the follow-up period. We will present descriptive summaries for the number of people who withdraw or are lost to follow-up, with separate results for each category (type of withdrawal and loss to follow-up).

4.7 Baseline patient characteristics

The baseline characteristics of the included patients will be reported per randomisation group and shown in a baseline table (Appendix Table 1).

5 Analysis

5.1 Outcomes – definitions and ascertainment

We will collect baseline data before the beginning of the trial and then collect follow-up data at 6 and 12 months during active participation. Passive collection of data through linkage with databases at the clinics, cancer registry and Medical Benefits Scheme will continue for 24 months post randomisation.

[insert table 2]

5.2 Analysis methods

We will present categorical data using counts and percentages, and continuous data using the minimum and maximum, mean, and standard deviation (SD) or median

and quartile 1 (Q1) and quartile 3 (Q3). For each outcome, we will present the number of patients included in the analysis.

Apart from outcomes that are measured in the intervention group only, analysis programs will be developed and finalised blinded to treatment allocations (i.e., using dummy intervention codes).

Primary outcome

We will use a logistic regression model to investigate the difference between patient-led and clinician-led surveillance on the proportion of participants with a subsequent new primary or recurrent melanoma diagnosed through an unscheduled clinic visit. We will present the proportion of participants with the primary outcome in each randomised group, and the between group difference in proportions, along with the p-value and 95% CI. The adjusted and unadjusted analysis will be presented as an odds ratio along with the 95% confidence interval and p-value. For the adjusted analysis, we will include baseline measurements of important prognostic factors for new or recurrent melanoma as covariates in the model, which is recommended in order to improve the power of the study[26,27] and to obtain valid standard errors when using minimisation.[28] These will include variables used in minimisation: age, sex, specialist/GP clinic, melanoma substage, subsequent new primary melanoma risk score[29] and diagnosis of dysplastic naevus syndrome. Given the possibility of low event rates for the primary outcome, we will explore approaches such as inverse probability of treatment weighting (IPTW) or standardisation for covariate adjustment.[28,30] We will check the appropriate assumptions for the model, including the linearity assumption for any covariate modelled as a continuous variable. If a

covariate is found to have a nonlinear relationship with the outcome, another appropriate method such as fractional polynomials or cubic splines will be used.[31]

Secondary outcomes

We will assess the effect of patient-led and clinician-led surveillance on the secondary outcome of time to diagnosis of any skin cancer (melanoma or keratinocyte cancer), using Cox proportional hazards models. We will present unadjusted and adjusted analyses. For the latter, we will include the same covariates as for the primary outcome (important prognostic variables for outcome event) and explore approaches such as IPTW or standardisation to perform covariate adjustment.[28] We will check the proportional hazards assumption using visual inspection of plots (including Schoenfeld residuals) and corresponding test statistics. Other assumptions to be checked include if there is non-informative censoring and if there is a secular trend. If participants withdraw or move interstate, they will be censored at last available follow-up (follow-up is defined as beginning at randomisation and ending 12 months later). The unadjusted and adjusted hazard ratios with 95% confidence interval and p-values will be reported. If the assumptions, including the proportional hazards assumptions for a prognostic factor are violated, these will be addressed using another appropriate method such as a stratified Cox proportional hazards model, proportional hazards regression with time-dependent covariates or restricted mean survival time analysis.[32,33] The time to diagnosis will also be analysed allowing for competing risk of death.

The appropriate generalised linear model will be used to assess the effect of patient-led and clinician-led surveillance on the remaining secondary outcomes, except for the outcome of performance of dermatoscopes, which will be analysed within the

patient-led surveillance arm only. Secondary outcomes measured at multiple time-points (baseline, 6 months, and 12 months) will be analysed using mixed models or generalised estimating equations to allow for correlation in measurements within individuals.[34] We will fit the two follow up measurements as the outcome variable, the baseline measurement and other prognostic factors as covariates,[35,36] and include a variable for time. To estimate the effect of the intervention on average over the 12 month follow-up, we will fit a model with no interaction term, and to estimate effects at 6 and 12 month time-points, we will fit a model with an interaction between the intervention and time variables.[34,36]

In general, Poisson regression will be used for count variables, logistic regression for any proportions and multiple linear regression for any continuous variable. For count variables modelled using Poisson regression, we will assess the model for overdispersion. If overdispersion is present, we will use another appropriate model such a negative binomial regression. For continuous outcomes, we will estimate the between group difference in change from baseline for each outcome (by including baseline measurement as a covariate), together with 95% CI and p-values. We will check the appropriate model assumptions and if any are violated, then we will use other generalised linear mixed models or appropriate transformation of the outcome or covariates (e.g., dichotomisation, log transformation).

Subgroup analysis

We will assess whether the effects of the intervention (patient-led vs clinician-led surveillance) on the primary outcome and relevant secondary outcomes, differ across the following patient characteristics:

- AJCC melanoma substage

- Risk of subsequent new primary melanoma (1-year risk, continuous variable)[29]
- Dysplastic Naevus syndrome status (yes or no)
- Sex
- Age (continuous variable)
- Confidence in digital technology

These analyses will test for an interaction between the intervention variable (intervention vs control) and each of the above patient characteristics in regression models which include the same covariates as for the primary analysis. Continuous variables will only be categorised if needed for ease of interpretation. P-values will be interpreted conservatively.

Secondary analysis

We will undertake secondary analyses to separately estimate the effects of the two types of MoleScope device (MoleScope Lite vs control group and MoleScope II vs control group). While we will have greater certainty for outcomes comparing the performance of the devices (e.g., quality of the images submitted), we will also conduct these analyses for the primary outcome and other relevant secondary outcomes. We will interpret these results cautiously.

Sensitivity analysis

We will undertake sensitivity analyses to account for effects of missing data and for non-adherence/contamination (per-protocol analysis) as detailed in the sections below. We will also undertake a sensitivity analysis adjusting for a covariate that was not prespecified for inclusion in primary analysis, if we find a large imbalance

between randomised groups in this covariate.[37,38] Further sensitivity analyses may be carried out as required for statistical reasons (such as assessing the influence of outliers).

5.3 Missing data

We do not anticipate any missing data on confounders (prognostic variables) as these must be measured at baseline before randomisation can precede. Missing data on outcomes is however possible due to patient withdrawal, non-response or loss to follow-up. Sensitivity analyses accounting for missing data will be performed for an outcome if more than 10% of the data are missing. In order to plan these sensitivity analyses, we will conduct a simulation study using data from our pilot study to explore different methods for handling missing data, such as multiple imputation and inverse probability weighting. We will use the results of our simulation study to pre-specify the analytical approach we will take, prior to the database being locked.[39]

5.4 Per-protocol and as-treated analysis

A per-protocol analysis will be conducted on the primary outcome. We will estimate the effect that would have been observed had all participants adhered to the protocol. We will also conduct an as-treated analysis on the primary outcome, in which we will estimate the effect of the treatment (type of surveillance) actually received by participants, irrespective of their treatment (type of surveillance) assignment.[40] As in section 5.5, we plan to conduct a simulation study using data from our pilot study to further explore methods for dealing with non-adherence and contamination and will use this to specify the analytical approach while the larger trial is ongoing (before database is locked). Methods we will explore include inverse

probability weighting, doubly-robust methods, other G-methods, standardisation, propensity scores, and instrumental variable analysis. We will use prognostic factors that predict adherence to the pilot trial protocol for these methods, which may include variables such as age, sex, AJCC melanoma substage, occupation, level of education, time since melanoma diagnosis, dysplastic naevus syndrome and confidence in using digital technologies (measured at baseline) and adherence at earlier time points in the trial.[37,41,42]

5.5 Harms

Any adverse events (AEs), serious adverse events (SAEs), adverse device effect (ADE) or serious adverse device effects (SADE) will be summarised with the overall proportion reported per randomised group. If appropriate, the proportion of subtypes of AEs, SAEs, ADE or SADEs may be reported as well as the confidence interval and statistical test to estimate the difference between randomised groups.

5.6 Statistical software

All statistical programming and analyses to produce summary tables and figures will be performed using R.

6 Discussion

The MEL-SELF trial will compare the effects of patient-led surveillance and clinician-led surveillance on early detection of subsequent new primary and recurrent melanoma, psychological outcomes, and health resource use. We are publishing a detailed statistical analysis plan for the primary and secondary outcomes while the trial is on-going to enhance transparency and minimize bias during the analysis phase. The statistical analysis plan has been written in accordance with the Journal

of the American Medical Association's recommended guidelines for content of statistical analysis plans in clinical trials,[21] and the PRE-SPEC framework guidance on pre-specification to avoid p-hacking.[22]

The experience of our pilot randomised controlled trial in patients with early-stage melanoma (n=100) has provided valuable information for refining the study design and statistical analysis.[18,19] As well as demonstrating the feasibility of patient-led surveillance, the pilot trial results suggest that the intervention improves the knowledge, attitudes, and practice of SSE, increases the early detection of subsequent new primary melanomas, and does not increase adverse psychological outcomes. Difficulties experienced in the pilot trial included a relatively high withdrawal and non-response rate, and suboptimal adherence to the intervention. The study protocol for the larger ongoing trial has been designed to address these issues, and to improve participant retention and adherence to the intervention.[20] Nevertheless, we assume that these issues may still affect data collection in the larger trial, and so we have designed the statistical analysis plan accordingly. Our planned sensitivity analyses will address potential bias arising from withdrawals, non-response, sub-optimal adherence in the intervention group and potential contamination of the control group. We will use robust methods for dealing with missing data that may result from withdrawals and non-response (such as mutliple imputation or inverse probability weighting). We will undertake per-protocol and as-treated analysis using causal inference methods (such as inverse probability weighting and other G-methods). While our primary analyses will adhere to the recommended intention-to-treat principle, the intention-to-treat effect does not always adequately account for poor adherance, withdrawals or losses to follow-up, and may result in biased effect estimates.[43] The use of causal inference methods in

our secondary analyses will be important when translating results to clinical practice as the findings generated may be more easily understood by patients and clinicians,[44] and better faciliate clinical decision making. While we are unable to yet specify the analysis methods that will be used in these analyses, we will document and justify our choices after the described simulation studies have been undertaken, and prior to database lock and the final analysis of the MEL-SELF trial in order to ensure continued transparency.

The procedures used during the trial's two-stages of randomisation will also be an essential component to obtaining valid results. The use of minimisation during the first stage and stratification by prognostic factors for melanoma during the second stage will help to protect against chance imbalances across study arms. Adaptive randomisation during the second stage of randomisation will also allow for more efficient use of trial resources and better treatment for intervention participants by allowing adjustment of the randomisation processes following interim analyses.

Patient-led surveillance appears to be a promising alternative model of follow-up care for patients diagnosed with early-stage melanoma. By pre-specifying and publishing the statistical approaches that will be used prior to locking the database, this statistical analysis plan ensures that the MEL-SELF trial will generate robust and transparent evidence on the effects of this model of care on health outcomes, psychological outcomes and health resource use that may be translated into clinical practice and health policy.

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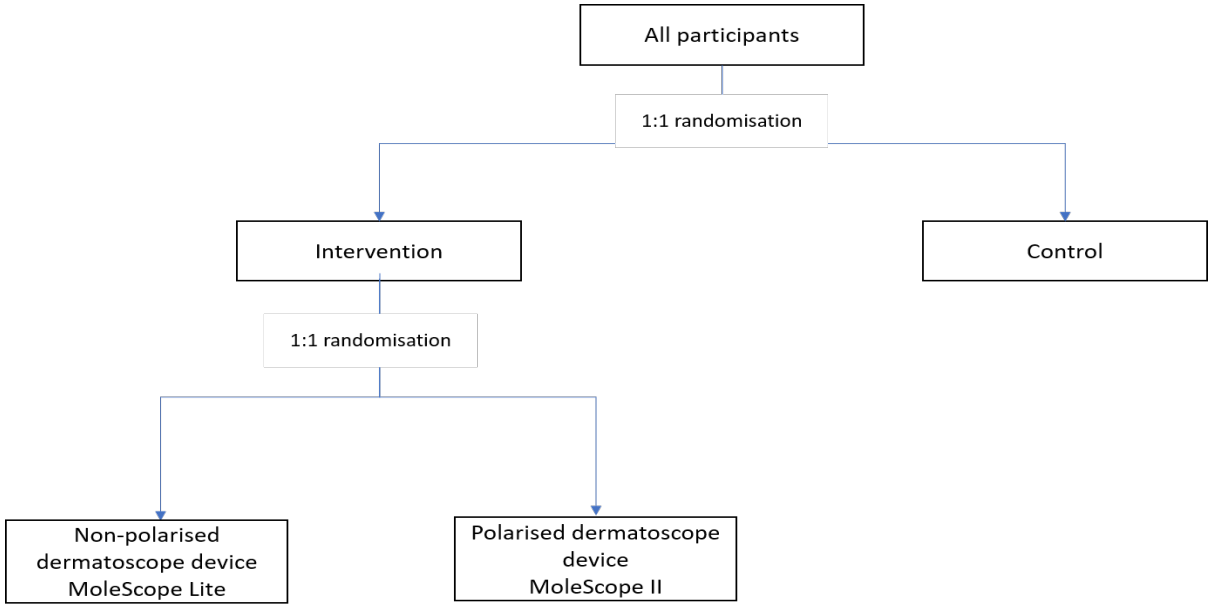
Figure 1 Summary of the two-stage randomisation of participants in MEL-SELF trial



Box 1: Prognostic factors used for minimisation

- Specialist versus GP-led treatment centre (two specialist clinic sites = Melanoma Institute Australia / Royal Prince Alfred Hospital and one GP-led site Newcastle Skin Check)
- Patient date of birth (age groups = 18–39, 40–70, 71+)
- Sex (Male, female, other)
- American Joint Committee of Cancer (AJCC) melanoma substage (Stage 0, IA, IB, IIA, IIB, IIC)[45]
- Risk of new primary melanoma (1-year absolute risk score < 5%, 5-10%, >10%)[29]
- Documented diagnosis of Dysplastic Naevus Syndrome (yes or no) (Dysplastic Naevus Syndrome is defined as the occurrence of at least 100 naevi, of which a minimum of 6 show atypical dermoscopic features that are consistent with dysplastic naevus. At minimum, 1 of these naevi should be at least 8mm in dimension)[46,47]

Table 1: Maximum CI* for differences in proportions assuming n=30 in each group

p1	p2	diff	LowerCI	UpperCI
0.65	0.35	0.30	0.06	0.54
0.75	0.25	0.50	0.28	0.72

**CI based on diff +/- 1.96 * sqrt[p1*(1-p1)/30 + p2*(1-p2)/30]*

Box 2: Inclusion Criteria

- Have completed treatment for AJCC stage 0/I/II cutaneous melanoma[45] and are attending regular melanoma follow-up as indicated by at least one routinely scheduled clinic visit booked within the next 12 months at a recruiting treatment centre
- Are able to conduct SSE
- Have a suitable study partner (spouse, partner, family member, friend) to help with SSE
- Own a smartphone (and have access to Internet, email, and SMS text messaging)
- Routinely scheduled clinic visit frequency at the treatment centre is 6 monthly or less frequent
- Are able to give informed consent
- Have sufficient English language skills to read the materials and complete the questionnaires
- Are at least 18 years of age

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Box 3: Exclusion criteria

- Have ever had stage III/IV melanoma
- Have a known past or current diagnosis of cognitive impairment
- Participated in the MEL-SELF pilot trial (conducted Nov 2018 – Feb 2020)[18]
- Do not own a smartphone that is compatible with the mobile dermatoscopes that are part of the intervention

Table 2 Primary and secondary outcomes

Primary outcome	**Summary Description**
(M1) Proportion of participants who are diagnosed with a subsequent new primary or recurrent melanoma (any stage) at a fast-tracked unscheduled clinic visit during the 12 months follow-up of the trial	Melanomas are histologically confirmed and centrally reviewed by the trial dermatopathologist, Professor Richard Scolyer. Both the original histopathology report and the central review will be done blinded to the study group allocation of the trial participant. Classification of a visit as fast-tracked unscheduled vs routinely scheduled will be done by the endpoint adjudication committee based on the participants clinic letters, blinded to study arm
Secondary outcomes	
(M2) Time to diagnosis of new skin cancer	Time from randomisation to the histopathology diagnosis of a melanoma or keratinocyte skin cancer (as defined by the date on the histopathology report)
(**M3)** Pathological characteristics of new skin cancers	including thickness, stage, and other prognostic factors (melanomas and keratinocyte skin cancers)
(M4) Skin Self-Examination (SSE) including:	
M4.1. Thoroughness, confidence, beliefs, attitude, and knowledge of SSE	Assessed by items adapted from Janda et al. on a 5-point Likert scale[48]
M4.2. Adherence with recommended clinician SSE practice guidelines (total body self-examination conducted three-monthly)	Participants will be asked how often they perform a complete examination of their skin
(M5) Level of fear of new or recurrent melanoma severity	Assessed using a modified (i.e., melanoma-specific) version of the 9-item Fear of Cancer Recurrence Inventory (FCRI) severity subscale on a 5-point Likert scale, the most comprehensive multidimensional scale of FCR available.[7] The final score is calculated by summing the scores for the

	relevant items. The total score for each participant ranges from 0 to 36. A higher score indicates greater FCR
(M6) General anxiety, stress, and depression	Measured using the short version of the Depression Anxiety and Stress Scales (DASS-21).[49] The DASS-21 is a set of three 7-item self-report scales on a 4-point Likert scale designed to measure the emotional states of depression, anxiety and stress. For anxiety, stress and depression scales, the final score is calculated by summing the scores for the relevant items and multiplied by two. The total score for each of the three 7-item scales (anxiety, stress, and depression) ranges from 0 to 42
(M7) Acceptability of hypothetical reduction in scheduled clinic visit frequency	Measured through a 3-item subscale on a 5-point Likert scale designed specifically for this study
(M8) Number of lesions surgically evaluated	Measured through interrogation of clinic data
(M9) Number of clinic visits attended	Routinely scheduled and fast-tracked unscheduled clinic visits measured through interrogation of clinic data
(M10) Technical performance of dermatoscopes	Includes participant ability to submit images (adherence with 3 monthly image submission), participant satisfaction with dermatoscope, quality of the images and number of device deficiencies reported. Quality of images will be measured using items developed and tested in another teledermatology study [50,51] and International Skin Imaging Collaboration guidelines.[52] The final items to be included will be determined in co-design with the trial's teledermatologists, and will focus on the quality of the dermoscopic images (rather than overview images), as this is most relevant for the comparison between mobile dermatoscopes in the trial. The final items will be decided on ahead of database locking and analysis.

Appendix

Adherence and protocol deviations

Participant's' adherence in the intervention group will be measured through:

a. the submission of a minimum of one image at the end of each three-month cycle, AND
b. these images being of sufficient quality to allow dermatological assessment (measured using a validated checklist)[50]

We will also assess use of other non-trial melanoma surveillance including telehealth and other imaging tests for the skin in both intervention and control groups (measured through self-report in the follow-up online questionnaires).

We will report the number and proportion of participants adhering to three-monthly image submission (intervention group only) and using non-trial interventions (intervention and control groups). This will be reported by model of mobile dermatoscope (polarised vs non-polarised light source) in the intervention group.

A protocol deviation is defined as non-compliance with the research protocol that does not impact the trial delivery or integrity and interpretation of the data. Any protocol deviation will be reported by site coordinators and the Trial Management Committee (TMC) will assess and decide on what action is required. Protocol deviations may include incorrect submission of images by intervention arm participants, failing to submit images, or complete surveys in line with protocol timepoints. The TMC will determine whether, or not, the event constitutes a protocol deviation and what action (if any) is required.

A protocol violation is defined as a major deviation from the trial protocol which could affect the trial delivery or integrity and interpretation of the data. A protocol violation may include failure to submit an image at all during the trial, either because no images were uploaded, or images were uploaded but not submitted to the teledermatologist. Other protocol violations include patients who withdraw consent, are withdrawn because they do not meet inclusion or exclusion criteria (for example, when they change phone models), or who are lost to follow-up.

We will report the number and proportion of participants with at least one protocol deviation and/or violation in the intervention and control group.

Appendix Table 1 Baseline characteristics of the participants

Baseline characteristics	Intervention group (N =)	Control group (N =)	Total (N =)
Age (years)*			
Mean (SD)			
Gender*, n (%)			
Male			
Female			
Other			
Melanoma Stage*, n (%)			
0			
IA			
IB			
IIA			
IIB			
IIC			
Dysplastic Nevus Syndrome*, n (%)			
Yes			
No			
Risk of new primary melanoma*, n (%)			
Low (< 5%)			
Medium (5-10%)			
High (> 10%)			
Site ID*, n (%)			
Melanoma Institute Australia / Royal Prince Alfred Hospital			
Newcastle Skin Check			
Indigenous status, n (%)			
Aboriginal and/or Torres Strait Islander Origin			
Neither Aboriginal and/or Torres Strait Islander Origin			
Main language spoken at home, n (%)			
English			
Other			
Marital status, n (%)			
Single and never married			
Married			

De facto or in a committed relationship	
Separated or divorced	
Widowed	
Level of education, n (%)	
No formal education	
Primary school	
High school or leaving certificate	
TAFE Advanced Diploma, Diploma or Certificate	
Postgraduate degree or higher	
Confidence in digital technology, n (%)	
Very confident/confident	
A little/somewhat confident	
Not at all confident	
Digital health literacy	
Median (Q1, Q3)	
Area of residence, n (%)	
Metropolitan area	
Regional area	
Rural area	
Personal history of depression or anxiety, n (%)	
Yes	
No	
Depression	
Median (Q1, Q3)	
Anxiety	
Median (Q1, Q3)	
Stress	
Median (Q1, Q3)	
DASS-21	
Median (Q1, Q3)	
Fear of Melanoma recurrence	
Mean (SD)	

Abbreviations: SD=standard deviation; ID=identification; Q1=quartile 1; Q3=quartile 3; TAFE=Technical and Further Education

*minimisation criteria

Appendix Figure 1 Flow of patients in the MEL-SELF Trial