

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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1 **Abstract**

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

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

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

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

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

23 **Trial registration:** Australian New Zealand Clinical Trials Registry (ANZCTR):

24 ACTRN12621000176864. Registered 18 February 2021,

25 <https://www.anzctr.org.au/ACTRN12621000176864.aspx>

26 **Keywords:** Statistical analysis plan, randomised controlled trial, melanoma, patient-
27 led surveillance.

28

29 **1 Introduction**

30 Although surgical excision of a localised melanoma before it has spread from the
31 primary site on the skin is potentially curative, patients are recommended to undergo
32 long-term follow-up because of their increased risk of developing a subsequent new
33 primary melanoma, a recurrence of their treated primary melanoma, or new
34 keratinocyte (non-melanoma) skin cancers.^{1,2} Clinician-led surveillance in the form of
35 routinely scheduled clinic visits is widely accepted as the usual model of follow up
36 care, although there is a no direct evidence that this leads to improved survival.^{1,3}
37 There are substantial financial costs to the patient and healthcare system associated
38 with this model of care,⁴ and possible psychosocial harms.⁵ Fewer routinely
39 scheduled clinic visits may have little impact on the detection of subsequent new
40 primary or recurrent melanomas⁶ and could result in significant cost savings.⁷⁻⁹

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

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

53 support and patient-performed mobile teledermoscopy among patients with early
54 stage melanoma.^{18,19}

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

65

66 **2 Study Methods**

67 **2.1 Trial design**

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

74 **2.2 Randomisation**

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

84 [insert Figure 1]

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

89 [insert Box 1]

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

98 in the proportion of intervention participants who have had an image reported on,
99 participants who are subsequently enrolled will be randomised 2:1 to the
100 dermatoscope model where more participants had an image reported on. If there is >
101 50% absolute difference in the proportion of intervention participants who have had
102 an image reported on, then all participants who are subsequently enrolled will be
103 randomised to the dermatoscope model where more participants had an image that
104 was reported on. Calculated confidence intervals for a difference in proportions of
105 30% and 50% are presented in the table 1 below.

106 [insert table 1]

107 **2.3 Sample size**

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

123 detect a hazard ratio of 1.71 for time from randomisation to diagnosis of a skin
124 cancer for the patient-led vs clinician-led surveillance groups (due to earlier and
125 increased detection in the patient-led group). This calculation assumes a 20% event
126 rate in the clinician-led surveillance group (60 events among 300 control
127 participants),^{10,23} a 32% event rate in the patient-led surveillance group (96 events
128 among 300 intervention participants), and 26% event rate overall (156 events among
129 600 trial participants).

130 **2.4 Analytic Framework**

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

136 **2.5 Statistical interim analysis and stopping guidance**

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

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

147 **2.6 Timing of final analysis**

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

153 **2.7 Timing of outcome assessments**

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

155 **3 Statistical principals**

156 **3.1 Confidence intervals and p-values**

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

161 **3.2 Adherence and protocol deviations**

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

164 **3.3 Analysis populations**

165 **3.3.1 Intention-to-treat (ITT) population**

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

169 **3.3.2 Per-protocol population**

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

174 **3.3.3 As-treated population**

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

178 **4 Trial population**

179 **4.1 Screening data**

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

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

190 **4.2 Eligibility**

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

198 **4.3 Inclusion criteria**

199 [insert box 2]

200 **4.4 Exclusion criteria**

201 [insert box 3]

202 **4.5 Recruitment**

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

208 **4.6 Withdrawal/follow-up**

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

217 **4.7 Baseline patient characteristics**

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

220 **5 Analysis**

221 **5.1 Outcomes – definitions and ascertainment**

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

226 [insert table 2]

227 **5.2 Analysis methods**

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

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

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

235 **Primary outcome**

236 We will use a logistic regression model to investigate the difference between patient-
237 led and clinician-led surveillance on the proportion of participants with a subsequent
238 new primary or recurrent melanoma diagnosed through an unscheduled clinic visit.

239 We will present the proportion of participants with the primary outcome in each
240 randomised group, and the between group difference in proportions, along with the
241 p-value and 95% CI. The adjusted and unadjusted analysis will be presented as an
242 odds ratio along with the 95% confidence interval and p-value. For the adjusted
243 analysis, we will include baseline measurements of important prognostic factors for
244 new or recurrent melanoma as covariates in the model, which is recommended in
245 order to improve the power of the study^{26,27} and to obtain valid standard errors when
246 using minimisation.²⁸ These will include variables used in minimisation: age, sex,
247 specialist/GP clinic, melanoma substage, subsequent new primary melanoma risk
248 score²⁹ and diagnosis of dysplastic naevus syndrome. Given the possibility of low
249 event rates for the primary outcome, we will explore approaches such as inverse
250 probability of treatment weighting (IPTW) or standardisation for covariate
251 adjustment.^{28,30} We will check the appropriate assumptions for the model, including
252 the linearity assumption for any covariate modelled as a continuous variable. If a

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

255 **Secondary outcomes**

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

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

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

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

296 **Subgroup analysis**

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

- 300 • AJCC melanoma substage

- 301 • Risk of subsequent new primary melanoma (1-year risk, continuous
302 variable)²⁹
- 303 • Dysplastic Naevus syndrome status (yes or no)
- 304 • Sex
- 305 • Age (continuous variable)
- 306 • Confidence in digital technology

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

312 **Secondary analysis**

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

319 **Sensitivity analysis**

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

324 between randomised groups in this covariate.^{37,38} Further sensitivity analyses may
325 be carried out as required for statistical reasons (such as assessing the influence of
326 outliers).

327 **5.3 Missing data**

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

338 **5.4 Per-protocol and as-treated analysis**

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

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

355 **5.5 Harms**

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

361 **5.6 Statistical software**

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

364 **6 Discussion**

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

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

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

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

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

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

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421 collection, analysis, and interpretation of the data; the writing of the report; or the
422 decision to submit the report for publication.

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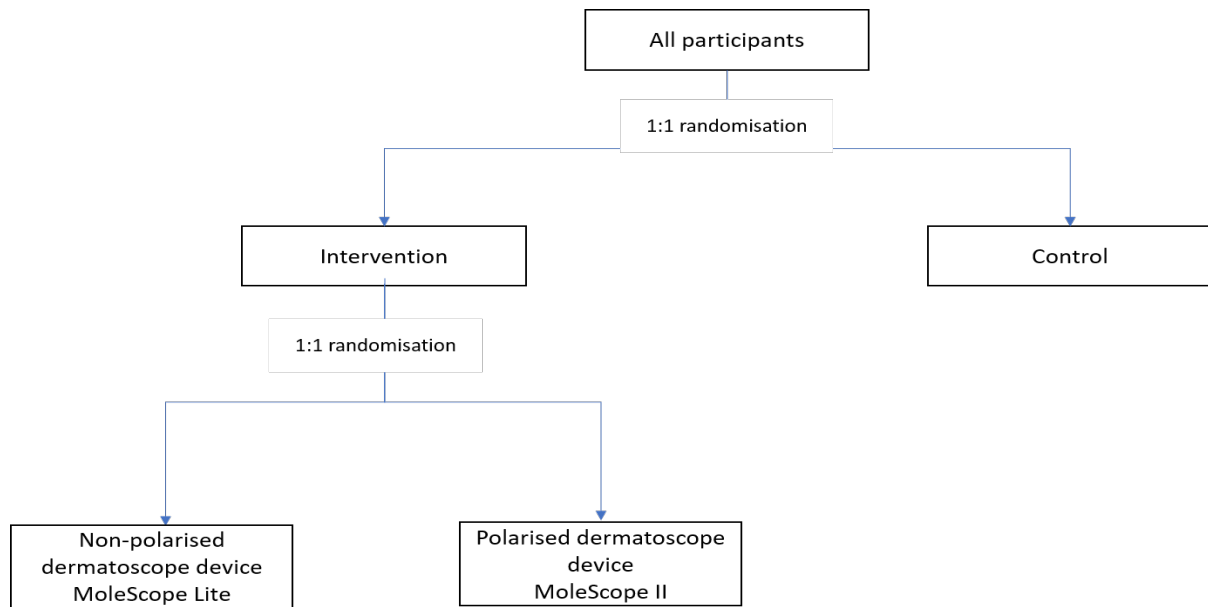
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564 **Figure 1 Summary of the two-stage randomisation of participants in MEL-SELF**
565 **trial**

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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}

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586 **Table 1: Maximum CI* for differences in proportions assuming n=30 in each**
587 **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

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

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Box 2: Inclusion Criteria

- Have completed treatment for AJCC stage 0/I/II cutaneous melanoma⁴⁵ 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

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Table 2 Primary and secondary outcomes

Primary outcome	Summary Description
<p>(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</p>	<p>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</p>
Secondary outcomes	
<p>(M2) Time to diagnosis of new skin cancer</p>	<p>Time from randomisation to the histopathology diagnosis of a melanoma or keratinocyte skin cancer (as defined by the date on the histopathology report)</p>
<p>(M3) Pathological characteristics of new skin cancers</p>	<p>including thickness, stage, and other prognostic factors (melanomas and keratinocyte skin cancers)</p>
<p>(M4) Skin Self-Examination (SSE) including: M4.1. Thoroughness, confidence, beliefs, attitude, and knowledge of SSE M4.2. Adherence with recommended clinician SSE practice guidelines (total body self-examination conducted three-monthly)</p>	<p>Assessed by items adapted from Janda et al. on a 5-point Likert scale⁴⁸</p> <p>Participants will be asked how often they perform a complete examination of their skin</p>
<p>(M5) Level of fear of new or recurrent melanoma severity</p>	<p>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</p>

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

