Statistical Analysis Plan

The SCRIPT Trial: a study of DNA testing to tailor bowel cancer screening in primary care

1. Administrative details

1.1 Date and version number

June 2024 Version 1

1.2 Trial registration and ethics approval

Registered prospectively with the Australian and New Zealand Clinical Trial Registry (ACTRN12621000092897) on the 1st February 2021.
http://www.anzctr.org.au/Trial/Registration/TrialReview.aspx?id=380786&isReview=true

Ethical approval has been granted by the Human Ethics Sub-Committee at the University of Melbourne in Melbourne, Australia (Ethics ID: 14467). All participants will be recruited following an informed consent process involving an approved plain language statement and consent form. The Australian Government Department of Human Services Information Services Branch has approved the release of MBS data (ID: RMS1454) and NBCSP data (ID: EO2021/2/1248). The Victorian Government Department of Health and Human Services System Intelligence & Analytics Branch approved the release of VAED data.

1.3 Funding acknowledgement

This work is funded by a Cancer Australia Grant (PdCCRS grant 1183338). The design, management, analysis and reporting of the trial are independent of the funders.

1.4 Acknowledgements

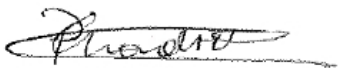
This research is supported by the Primary Care Collaborative Cancer Clinical Trials Group (PC4), Australia.

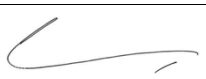
1.5 Protocol reference

SCRIPT protocol V1.0 20062024

Published protocol: Saya S, Boyd L, Chondros P, McNamara M, King M, Milton S, et al. The SCRIPT trial: study protocol for a randomised controlled trial of a polygenic risk score to tailor colorectal cancer screening in primary care. *Trials*. 2022;23(1)[1]

1.6 Roles and responsibilities –signatory names and contribution

Name	Role	Affiliation	Signature
A/Prof Patty Chondros	Lead biostatistician (Contact person)	Department of General Practice and Primary Care, University of Melbourne, Melbourne, VIC, Australia **E-mail:** p.chondros@unimelb.edu.au	

Dr Richard De Abreu Lourenco	Lead health economist	Centre for Health Economics Research and Evaluation, University of Technology Sydney, Sydney NSW, Australia **E-mail:** Richard.deabreulourenco@uts.edu.au	
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1.7 Roles and responsibilities – non-signatory names and contribution

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1.8 SAP revision history

Version 1.0 of the statistical analysis plan was finalised and approved on the **24 June 2024**.

Protocol version	Updated SAP version no.	Section number changed	Description and reason for change	Date changed

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2. List of Abbreviations

The following abbreviations and special terms are used in this Statistical Analysis Plan (SAP).

Abbreviation or special term	Explanation
ACHI	Australian Classification of Health Interventions
CACE	Complier Average Causal Effect
CONSORT	CONsolidated Standards Of Reporting Trials
CRC	Colorectal cancer
CWS	Cancer Worry Scale
DRG	Diagnosis Related Group
GLM	Generalised Linear Model
GP	General Practitioner/Primary Health Care Provider
ICD-10	International Classification of Diseases 10th Revision
ICER	Incremental Cost-Effectiveness Ratio
iFOBT	Immunochemical Faecal Occult Blood Test
IRSD	Index of Relative Socio-Economic Disadvantage
ITT	Intention-to-treat
MBS	Medicare Benefits Scheme
NBCSP	National Bowel Cancer Screening Program
NCSR	National Cancer Screening Register
NHMRC	National Health and Medical Research Council
PREMS	Patient reported endpoint measures
PRS	Polygenic Risk Score
RCT	Randomised Controlled Trial
REDCap	Research Electronic Data Capture database
REML	Restricted Maximum Likelihood
SAP	Statistical Analysis Plan
SCRIPT	Single nucleotide polymorphism Cancer RIsk Prediction Trial
VAED	Victorian Admissions and Emergency Dataset

3. Synopsis

3.1 Background and rationale

Population colorectal cancer (CRC) screening is delivered on a one-size-fits-most basis in Australia. Two-yearly immunochemical faecal occult blood testing (iFOBT) from age 50-74 is recommended for the >95% of the population without a family history of CRC[2]. Those with a family history are recommended colonoscopy. A polygenic risk score (PRS) is a genomic risk test that can predict an individual's personal risk of cancer and this information can be used to tailor cancer screening recommendations accordingly[3,4].

This study is a multi-site individually randomised controlled trial (RCT) that aims to determine whether the SCRIPT intervention delivered within general practice to patients aged 45 to 70 years old who are overdue CRC screening encourages more risk-appropriate CRC screening at 12 months compared to standard cancer prevention information. The SCRIPT intervention incorporates colorectal cancer (CRC) risk prediction using a PRS, tailored risk-based screening recommendations, and risk reports for use by patients and their general practitioner. Risk-appropriate screening is defined as the right test for an individual's risk (iFOBT for average risk and colonoscopy for increased risk) at the right time, also considering their previous screening.

Additionally, the SCRIPT trial will determine the impact of the SCRIPT intervention compared with standard cancer prevention information on participants' CRC risk perception, cancer-specific anxiety, elements known to influence CRC screening behaviour, cancer screening intentions, and health care utilisation.

The trial protocol paper details the study rationale, trial design including the setting, recruitment, eligibility, SCRIPT intervention, sample size calculations and random allocation[1]. The aim of this document is to provide a more detailed and technical description of the statistical and health economics analyses provided in the trial protocol and expands the sensitivity and supplementary analyses.

3.2 Study objectives

Primary Objective

To evaluate the impact of the SCRIPT intervention on risk appropriate CRC screening after 12 months in general practice patients aged 45-70 due or overdue CRC screening, compared with standard cancer prevention information.

Primary hypothesis

The **null hypothesis** is that there is no effect of standardised consultation using the SCRIPT intervention in general practice patients aged 45-49 years or 50-70 years who are due or overdue for CRC screening on risk-appropriate CRC screening at 12-month follow-up compared with general practice attendees that receive generic information about cancer prevention (control). The alternative hypothesis is that a standardised consultation using the SCRIPT risk results in general practice will increase risk-appropriate screening among patients aged 45-49 years or 50-70 years who are due or overdue for CRC screening compared with generic information about cancer prevention at 12-month follow-up.

Secondary Objectives

To examine the effect of the SCRIPT intervention compared with standard cancer prevention information at 1, 6, and 12 months among general practice patients aged 45-49 years or 50-70 years who are due or overdue for CRC screening at baseline in:

1) CRC screening behavioural mechanisms (four elements known to influence CRC screening behaviour)
2) Cancer-specific anxiety
3) CRC Risk perception - Perceived lifetime risk
4) CRC Risk perception - comparative perception of risk
5) Cancer screening intentions (four items)
6) Self-reported behaviours to manage or reduce the risk of CRC (four items)

Health Economics Objectives

To determine the cost and health care utilisation at 12 months of the SCRIPT intervention compared with standard cancer prevention information among general practice patients aged 45-49 years or 50-70 years who are due or overdue for CRC screening at baseline.

4. Trial methods

4.1 Trial design

The SCRIPT trial is a multi-site, phase II, parallel two-arm, individually randomised controlled superiority trial[5]. The trial will test the implementation of the SCRIPT intervention in general practice in Victoria, Australia and aims to increase risk-appropriate CRC screening after 12 months in general practice patients aged 45-70 due or overdue CRC screening, and who have no diagnosis of CRC or inflammatory bowel disease, no recent changes to bowel habits or rectal bleeding, and no monogenic predisposition to CRC. Participants will be randomly allocated 1:1, stratified by general practice, to the intervention arm who will receive the SCRIPT intervention or the control arm who will receive standard cancer prevention information. DNA will be collected from all participants at baseline.

Participants allocated to the **SCRIPT intervention** will receive personalised CRC risk report containing tailored CRC screening recommendations based on the PRS results, which will be available 2-3 weeks after DNA sample provision. Researchers will make a time to meet with the individual to the discuss the risk report, in person in the general practice clinic, via Zoom or telephone (in order of preference). After four attempts to contact the participant/schedule a results appointment, the risk report is sent via secure email/post. Participants will be then encouraged to see their GP immediately after this discussion to discuss further and action the ordering or referral for any CRC screening tests. The final clinical decision on referral for colonoscopy or ordering of iFOBT kits is at the discretion of the GP.

Standard cancer prevention information will be discussed with control arm participants immediately after randomisation. Participants in the control arm will be given the opportunity to complete the SCRIPT intervention (i.e., to receive their CRC personalised risk result) at the end of their 12-month questionnaire (wait-list control). If they indicate that they would like to receive their results, they will be contacted by a researcher to organise a Zoom appointment to discuss their personal risk and screening recommendations.

Participant recruitment started on 19 April 2021 and was completed on the 23 August 2022. The intervention was completed for the last recruited participant on the 01 November 2022. All participants will be followed up via questionnaires at 1, 6 and 12 months and collection of objective data regarding their CRC screening behaviour will be captured from their medical records at 12 months after randomisation.

4.2 Randomisation

Participants were randomly allocated 1:1 to the intervention or control arms. The allocation sequence was computer-generated and stratified by general practice using permuted blocks of random sizes. To ensure allocation concealment, block sizes were not disclosed. Given the nature of the intervention, it is not possible to blind participants to their allocation, however researchers collecting follow-up data will be blinded. Details on the sequence generation, concealment, implementation and blinding are detailed in the published trial protocol.

4.3 Sample size

Full details of the sample size are provided in the trial protocol. In brief, based on the results of the CRISP trial[6], we conservatively assumed that 95% of those aged 45 to 49 years in the average risk group will be appropriately screened in both trial arms (i.e., no CRC screening); those identified as moderate risk, we assumed that 70% in the intervention arm and 10% in the control arm would be appropriately screened (i.e., iFOBT screening). Thus, for those aged 45–49 years, the expected between-arm difference in appropriate screening would be 6% (92.5% intervention vs 86.5% in the control arm). We also assumed that for participants aged 50 years and older who were due a CRC screening test in the next 12 months, 60% would be appropriately screened in the intervention arm and 40% in the control arm. Thus, the weighted average of the proportions of patients aged above or below 50 years would be 68% in the intervention arm and 51% in the control arm, a 17% difference between the two study arms. Based on these, for 80% power and 5% significance level (two-sided) we would require a total sample size of 274 participants at baseline (137 participants per arm) to detect a between-arm difference of 17% difference in the proportion of eligible patients appropriately screened at 12 months, after allowing for 5% of the primary endpoint data to be missing. This sample size also provides 90% power (5% significance level) to detect a 20% between-arm difference for appropriate screening for participants aged 50 years and older (60% in the intervention and 40% in the control arms).

4.4 Framework

The SCRIPT trial's endpoints are testing for superiority of the intervention compared to control arms.

4.5 Statistical interim analyses and stopping guidance

No formal interim analyses are planned. The trial will not be stopped early as it is a low risk for significant adverse effects.

4.6 Timing of final analysis

Final analysis will occur after all sources of data have been collected and the primary endpoint has been derived after a blinded review of the data collected from different data sources (see Appendix A for the definition of the endpoint and data sources).

4.7 Timing of endpoint assessments

CRC screening behaviour at 12 months (primary endpoint) will be derived using information collected via self-report by participants (collected in surveys at baseline, 1, 6 and 12 months post-randomisation) and administrative sources of data (via an audit of the general practice records, and

Victorian Admitted Episodes Data Sets (VAED), Medicare Benefit and the National Bowel Cancer Screening Program (NBSCP). Primary endpoint will be defined after the final participant has completed the follow up (12 months after randomisation) and the administrative data sources (Appendix A) have been received.

Primary endpoint will be defined as 12 months after the provision of the CRC risk information. For participants in the control arm, this will be from the provision of the generic cancer risk reduction information, and for participants allocated to the intervention arm, this will be 12 months after the provision of their personalised CRC risk information and screening recommendations.

Secondary self-reported endpoints will be assessed at 1-, 6-, and 12-months post provision of the intervention in each arm: after provision of personalised CRC risk information and screening recommendations in the intervention arm and after provision of standard cancer risk reduction information in the control arm. Health service use for the Health Economics analysis will be collected at 12 months post-intervention using the administrative datasets (see Appendix A). See Table 1 in the trial protocol[1] for the timing of each endpoint measurement.

4.8 Trial protocol modification

The planned investigation of the five-year impact on the risk-appropriate behaviour and health service utilisation as outlined in the trial protocol will not be conducted. This is because participants allocated to the control arm will be provided the opportunity to receive their personalised CRC risk prediction, tailored risk-based screening recommendations, and risk report at 12 months, and hence we determined that the effect of the intervention would likely be diluted by the 5-year timepoint.

5. General Statistical Methodology

5.1 Confidence intervals and p-values

Estimates of the intervention effect will be reported with two-sided 95% confidence intervals and p-values. There will be no adjustment for multiplicity of testing to control for final type I error rate.

5.2 Adherence to the intervention

The intervention includes the personalised CRC risk assessment, screening recommendations and discussion with the researcher about the results and associated information about CRC screening.

Incomplete-adherence will be defined at two levels:

1) participant does not complete the personalised CRC risk assessment (either they did not complete the genomic test or receive a personalised risk figure – e.g. insufficient sample)
2) participant did not attend the CRC risk result appointments in person, via ZOOM or by telephone).

5.3 Protocol Deviations

Protocol deviations will be reported and assessed in a blinded review whether there is any serious breach if it affects the scientific quality of the trial, effectiveness of the intervention, participants well-being and safety.

5.4 Analysis populations

Box 1 defines the participant analysis data sets that will be used for analyses for the primary and secondary endpoints (Analysis dataset 1) and sensitivity analysis if using complete case analysis (Analysis dataset 2) as described in Section 7 below.

Box 1	
Analysis dataset 1 *For the primary estimand and for the secondary estimands for the primary and secondary objectives.* *For the supplementary estimand for the primary objective*	**Description** All participants who meet trial eligibility criteria who are randomised to the study arms, and do not withdraw their unprocessed data from the trial[1]. They will be analysed according to their randomly assigned arm "as-randomised". All data points obtained at or after randomisation.
Analysis dataset 2 *For Sensitivity analysis for Primary estimand only*	**Description** Participants (as above) but exclude participants with no endpoint data observed up to 12-months of follow-up.

Note: data provided by participants who later withdrew consent to use all their data will be deleted and not included in the primary data analyses, except if the data had already been processed and analysed prior to the consent being withdrawn.

6. Trial Population

6.1 Screening Data

An electronic recruitment log in REDCap[7] containing age in years and sex (male, female, other) of individuals approached for the trial will be kept throughout recruitment period. Reasons for trial ineligibility or participant refusal (if provided) will be also recorded.

6.2 Eligibility

Participants were required to meet the following criteria to be eligible for the trial:

- Aged 45-70 years (inclusive);
- Able to read and write English;
- Competent to give informed consent;
- Contactable over the next 12 months for follow-up;
- For those aged over 50, reported being due for some CRC screening within the next 12 months (e.g., for those with no or minimal family history, according to the NHMRC guidelines[2], have not had an iFOBT within the past year and have not have a colonoscopy within the past 3 years; for those with a moderate family history[2], have not had a colonoscopy within the past 4 years);
- Had an appointment for any reason with a GP consented to the trial within 7 days before or after being approached for recruitment.

Participants were ineligible if they meet one or more of the following criteria:

- Diagnosed with CRC;

- Recent changes to bowel habits (within 4 weeks), rectal bleeding or a diagnosis of inflammatory bowel disease;
- Had a known genetic predisposition to CRC or a family history of cancer that requires referral for assessment of a genetic predisposition to CRC (according to the NHMRC guidelines[2]). This includes:
    - Those confirmed as carrying a pathogenic mutation in a gene associated with a high-risk familial syndrome,
    - Those with a relative confirmed as carrying a pathogenic mutation in a gene associated with a high-risk familial syndrome, who have not themselves been tested,
    - Those with a relative with multiple CRCs,
    - Those with at least three first-degree or second-degree relatives with a Lynch syndrome-related cancer (colorectal, endometrial, ovarian, stomach, small bowel, renal pelvis or ureter, biliary tract, brain) with at least one diagnosed before age 55 years,
- Had a grandparent born in Africa or of African ancestry, given the specificity of the polygenic risk score test.

6.3 Recruitment

A CONSORT flow diagram (Appendix B) will report the number of patients who were:

- assessed for eligibility at screening
    - Not meeting inclusion criteria
    - Declined to participate
    - Did no return for follow-up recruitment appointment
    - Did not return consent
    - Eligible, but not randomised[1]
- eligible and randomised

By study arm, after randomly allocated:

- Allocated to each study arm at baseline
    - received allocated intervention
    - did not receive the allocated intervention[1]
- Lost to follow-up at 1, 6 and 12 months[1]
    - Withdrew all data
    - Withdrew from completing surveys
    - Died
- Participants not lost to follow-up at 1, 6 and 12 months[1]
    - Responded to survey at 1, 6 and 12 months
- Analysed
    - excluded from analysis[1]

[1]reasons will be provided.

6.4 Withdrawal/Follow-up – level of withdrawal

The participant can “withdraw consent from the trial at any time”. They can either completely withdraw from the trial, including withdrawal of all their unprocessed data from the trial, or 2)

withdraw from the further participation in the trial, but not withdraw consent to the data provided up to the time they withdrew and use of health services data.

For those who choose to withdraw consent from the trial and used of all data, their age, sex and study arm will be retained, and no further contact will be made with the participant. Any unprocessed data collected will be deleted and not included in the analyses. Those who withdraw from further participation in the trial will not be sent follow-up questionnaires or be further contacted by the trial staff. However, unless consent is withdrawn, the primary endpoint (CRC screening) will be derived using the health service data (see Appendix A for details of the definition of the primary endpoint). The number of participants who withdraw, and level of consent withdrawal will be presented in the CONSORT diagram at each follow-up time by study arm.

Reasons for withdrawal and loss to follow up (where available) will also be presented, overall and by study arm.

6.5 Baseline general practice characteristics

GP clinics data collected:

- Index of Relative Socio-Economic Disadvantage (IRSD) based on clinic postcode[8]
- Billing type (bulk-billing, private billing or mixed billing)
- Clinic location (Metropolitan/Regional/Rural/Remote) using the Modified Monash Model classification[9]
- Number of equivalent full time GPs in each clinic.

6.6 Baseline participant characteristics

Participants characteristics collected at baseline, prior to randomisation:

Participant characteristics	**Responses**
What is your gender?	Female, Male, Other
Age at enrolment (calculated using date of birth)	years
Which language do you mainly speak at home?	English, Arabic, Cantonese, German, Greek, Italian, Mandarin, Spanish, Vietnamese, Other (please specify)
Which ethnicity do you identify most with?	Aboriginal and/or Torres Strait Islander; Central/South Asian; East Asian; European; Near Eastern; Oceanian; Sub-Saharan African; Latin American; Other (please specify); Prefer not to answer
What is the highest level of education you have completed to date?	Below Year 10; Year 10; Year 11; Year 12 or equivalent; Certificate III/IV; Advanced Diploma / Diploma; Bachelor's Degree; Graduate Diploma / Graduate Certificate; Postgraduate degree
Do you live alone?	Yes, No
Who do you usually live with? (Please tick all that apply)	Husband or wife; Defacto partner; My child/ren; My partner's child/ren; My parent/s; Unrelated flatmate or co-tenant; Other relationship; Other
Family history of bowel cancer (Note: Responses to items below were used to classify the individuals risk category based on NHMRC family history criteria (2017)[2]	

Have any of your close relatives had bowel cancer before 55 years of age? (This means parents, children, brothers, sister)	Yes; No; Not sure
Have any of your first-degree or second-degree relatives had bowel cancer at any age? (This means parents, children, brothers, sister, grandparents, aunts, uncles, nieces, nephews and grandchildren)	Yes; No; Not sure
How many first-degree relatives do you have with bowel cancer? (parents, children, brothers, sisters)	
How many were diagnosed before the age of 55?	
How many second-degree relatives do you have with bowel cancer? (grandparents, aunts, uncles, nieces, nephews, grandchildren)	
How many were diagnosed before the age of 55?	
Have you, or a family member, ever attended a familial cancer clinic or geneticist about your family history of bowel cancer?	Yes; No; Not sure

The codebook for these questions can be found in the trial's REDCap data dictionary, which can be made available on request.

Further, individuals Index of Relative Socio-Economic Disadvantage (IRSD) will also be determined on their postcode of residence.

7. Analysis for primary and secondary endpoints

This section defines the primary and secondary endpoints and describes the estimands for the trial primary and secondary objectives (Section 3.2). The estimands provide the precise description of what will be estimated and consists of five elements: the intervention/treatment condition, the target population, the endpoint, the population level summary measure, and the handling of events that occur after randomisation (intercurrent events)[10]. Included in this section is the descriptive analyses for the participant demographic and baseline measures, and the statistical analysis for the primary and secondary endpoints to estimate the population-level summary measures, including primary, sensitivity and supplementary analyses. Health Economics endpoints and analyses are described in Section 8.

7.1 Endpoint definitions

7.1.1 Primary endpoint

The primary endpoint is the proportion of participants with **risk appropriate screening behaviour at 12 months** based on baseline CRC risk-category. Determining whether screening is risk-appropriate involves four steps:

1. Defining the screening the participant had prior to baseline,
2. Defining their CRC risk category, according to study arm,
3. Defining the screening the participant had within the 12-month follow-up period,
4. Defining whether that screening was risk appropriate.

The endpoints will also include appropriate surveillance of bowel polyps, and appropriate investigation of bowel symptoms during the 12-month follow-up period. Risk category at baseline and appropriate risk screening behaviours will be defined using all data sources (self-report, GP

record, VAED, MBS and NBCSP data). Full details of how the primary endpoint is determined is outlined in Appendix A.

7.1.2 Secondary Endpoints

Table 1 describes the measures for the secondary endpoints to examine the effect of the intervention on CRC screening behavioural mechanisms. These were all patient reported endpoint measures (PREMS) collected via surveys.

Table 1: Secondary endpoints of the SCRIPT Trial

<table>
<tr><th>Secondary endpoints</th><th>Measure</th><th>Responses and scores</th><th>Scoring</th></tr>
<tr><td colspan="4">Risk perception* - Perceived risk, both absolute and comparative, is measured using validated scales from published systematic reviews and primary research on colorectal cancer risk[11,12]</td></tr>
<tr><td>Mean perceived lifetime CRC risk at 1, 6 and 12 months</td><td>Perception of lifetime CRC risk[13]
Participants are asked to state their CRC risk perception numerically, on a scale from 0-100, and comparatively to an ‘average’ person, from 1 – much lower to 7 – much higher[13].
- If you had to put a figure on it, what would you say were your chances of getting bowel cancer at some time in your life?</td><td>0-100%</td><td></td></tr>
<tr><td>Proportion of people who have accurate perception at 1, 6 and 12 months</td><td>Comparative perception of CRC risk[13]
- How likely are you to develop bowel cancer compared to other people of your age?</td><td>1 (much lower) to 7 (much higher)</td><td>Perceived relative risk is compared to ‘true’ relative risk to determine if the perceived risk is accurate, overestimated or underestimated.
‘True’ relative risk is determined based on family history category for those in the control arm and CRC risk category for those in the intervention arm.
<table>
<tr><th>Risk cat</th><th>Response</th><th>Accuracy</th></tr>
<tr><td></td><td>1</td><td>Underestimate</td></tr>
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</td></tr>
</table>

<table>
<tr><td></td><td></td><td></td><td><table>
<tr><td rowspan="2">Near average</td><td>2-5</td><td>Accurate</td></tr>
<tr><td>6-7</td><td>Overestimate</td></tr>
<tr><td rowspan="2">Moderately increased</td><td>1-4</td><td>Underestimate</td></tr>
<tr><td>5-7</td><td>Accurate</td></tr>
</table></td></tr>
<tr><td colspan="4">CRC screening behavioural mechanisms Preventative Health Model[14*] an 16-item, validated scale that measures five elements known to influence CRC screening behaviour:</td></tr>
<tr><td>Mean:
• Salience and coherence at 1, 6 and 12 months,
• Cancer worry at 1, 6 and 12 months,
• Response efficacy at 1, 6 and 12 months,
• Social influence at 1, 6 and 12 months.
• Self-efficacy at 1, 6, and 12 months.</td><td>Elements known to influence CRC screening behavioural
- Salience and coherence (4 items)
- Cancer worry (2 items)
- Response efficacy (2 items)
- Social influence (4 items)
- Self-efficacy (4 items)</td><td>1=Strongly disagree, 2=Disagree, 3=Neither 4=agree nor disagree, 5=Agree, 6=Strongly Agree</td><td>Scores are summed for ranges of:
- Salience and coherence (4 -20)
- Cancer worry (2 - 10)
- Response efficacy (2 - 10)
- Social influence (4 - 20)
- Self-efficacy (4 - 20)
For all sub-scales, a higher score indicates a higher level of the domain being measured.
These sub-domains will be analysed separately.</td></tr>
<tr><td colspan="4">Cancer-specific anxiety* measured using the Cancer Worry Scale (CWS)[15] a six-item scale designed to measure worry about developing cancer and the frequency and impact of worry on mood and daily functioning.</td></tr>
<tr><td>Mean in cancer-specific anxiety at 1, 6 and 12 months.</td><td>Cancer-specific anxiety (6 items)
1) During the past month, how often have you thought about your own chances of developing bowel cancer?
2) During the past month, how often have thoughts about your chances of getting bowel cancer affected your mood?
3) During the past month, how often have thoughts about your chances of getting bowel cancer affected your ability to perform your daily activities?
4) How concerned are you about the possibility that you might get bowel cancer someday?</td><td>1=Not at all or rarely, 2=Sometimes, 3=Often, 4=Almost all the time.</td><td>Scores are summed for a range of 6 – 24.

A high score indicates greater worry, but no clinical cut-off points are currently available.</td></tr>
</table>

	5) How often do you worry about developing bowel cancer? 6) How much of a problem is worrying about bowel cancer to you?		
Intention to screen and other behaviours based on items from the Theory of Planned Behaviour[12,16]			
Proportion of participants who strongly agreed/agreed that they intended in the following 3 months to: • consult with my GP about my cancer risk at 1, 6 and 12 months • complete a bowel cancer screening test using the FOBT (test for blood in your poo) at 1, 6 and 12 months • have a colonoscopy to screen for bowel cancer at 1, 6 and 12 months • ask my GP for a referral to a gastroenterologist at 1, 6 and 12 months.	**Cancer Screening intentions** In the **next 3 months** I intend to: • Consult with my GP about my cancer risk • Complete a bowel cancer screening test using the FOBT (test for blood in your poo) • Have a colonoscopy to screen for bowel cancer • Ask my GP for a referral to a gastroenterologist	Strongly disagree, Disagree, Neither agree nor disagree, Agree, Strongly Agree	For each response create a **binary** variable: 1 = Strongly agree or Agree vs 0= Neither agree nor disagree; disagree or Strongly disagree
Proportion of participants in the last [1,5,6] month(s), since the last questionnaire, who have: • Consulted with my GP about my cancer risk at 1, 6 and 12 months • Made changes to my diet or eating habits at 1, 6 and 12 months • Been referred to a gastroenterologist at 1, 6 and 12 months • Been referred to a familial cancer clinic to discuss my family history of cancer at 1, 6 and 12 months	**Previous CRC risk reduction/management behaviours** Since my last questionnaire, in the last [1,5, 6] month(s), I have: • Consulted with my GP about my cancer risk • Made changes to my diet or eating habits • Been referred to a gastroenterologist • Been referred to a familial cancer clinic to discuss my family history of cancer	1=Yes, 0=No	Binary

* Risk perception, elements known to influence CRC screening behavioural and Cancer-specific anxiety were also collected at baseline. Decisions on how to handle missing responses for the scales will be based on recommended practice for deriving these outcomes. Note: Responses were required for all items listed in Table 2.

7.2 Descriptive analysis for participant demographics and baseline PREMS

Descriptive statistics will be used to summarise demographic, clinical characteristics and PREMs of the study participants measured at baseline, overall and by study arm to assess for imbalance between the arms. Mean and standard deviation will be presented for continuous variables, or medians and inter-quartile range (IQR; 25th and 75th percentile) for variables with a skewed distribution. Frequencies and percentages will be presented for categorical variables.

Descriptive statistics will also be used to compare, as appropriate:

1) age (years) and gender of the trial participants with patients screened but did not consent to the trial
2) baseline characteristics of participants that remained in the study and those who withdrew/lost to follow up.
3) baseline characteristics of participants with and without missing primary endpoint data at 12 months follow-up.
4) baseline characteristics of participants who did and did not respond to the 1, 6 and 12 month surveys.

7.3 Estimands and Statistical analysis for Primary and secondary endpoints

7.3.1 Primary Estimand Attributes

Treatment: Standardised consultation using the SCRIPT intervention compared to receiving generic information about cancer prevention (control arm)

Population: General practice patients aged 45-49 years or 50-70 years who are due for CRC screening, and at baseline have no diagnosis of CRC or inflammatory bowel disease, no recent changes to bowel habits or rectal bleeding, and no monogenic predisposition to CRC. Inclusion and exclusion criteria are provided in Section 6.2 and the trial protocol[1].

Variable & Population-level summary: Difference in the proportion patients (absolute measure) and odds ratio (relative measure) between the intervention and control arms who are screened for CRC in accordance with their risk level at 12-months or appropriately investigated/managed if bowel polyps are detected and/or abnormal bowel symptoms develop during the trial period.

Possible intercurrent events:

1) In usual practice, there may be other indications for investigations, such as investigative colonoscopies when individuals develop abnormal symptoms or have bowel polyps detected that require surveillance with colonoscopies, and thus these investigations will take precedence over the appropriateness of the CRC screening based on their level of cancer risk. These intercurrent events will be incorporated into the endpoint definition using the **composite strategy** (details provided in Appendix A).

2) Patients who become pregnant during the trial will also be included in the analysis as the clinical management of this sub-group of patients would not change (**treatment policy strategy**).

For the primary outcome, we will adopt a **while-alive strategy** if death of a participant occurs during the trial period. The participant may have been screened appropriately up to the time of death, particularly if death occurred towards the end of the 12-month follow-up period. Further, there may be delays in reporting of death for individuals in the records, thus we may not have the information

at the time of analysis about whether the person may have died during the trial period. However, after examining the patterns of missing data (See Section 7.5 below), and whether missing responses may be attributable to reported deaths, we will consider using the **hypothetical strategy** for those we know had died during the trial period.

7.3.2 Statistical methods for the primary endpoint

A generalised linear model (GLM) with the identity link function and binomial family will be used to estimate the absolute between-arm difference in the proportion who are screened for CRC in accordance with their risk level at 12-months or appropriately investigated/managed if bowel polyps are detected and/or abnormal bowel symptoms develop during the trial period. The odds ratio of the intervention arm compared to the control arm for the primary endpoint will be estimated using logistic regression. If the model used to estimate the absolute difference between study arm fails to converge, the risk difference will be derived from the GLM with the logit link function[17,18]. All regression models will include general practice (randomisation stratification variable) as a fixed effect.

The absolute (between-arm difference in the proportions) and relative (odds ratio) estimated intervention effects will be presented with their respective 95% confidence interval (CI), and the p-value will be estimated using logistic regression.

7.3.3 Secondary Estimand Attributes (Objectives 1 to 6)

Treatment condition and **target population** for the secondary endpoints are the same as for the primary endpoint.

Variable and **population-level summary** for Secondary objectives 1 to 6 are presented in the estimands 1 to 6 below.

Secondary estimands 1 to 3: Difference in mean between intervention and control arms at 1, 6 and 12 months in:

1. **CRC screening behavioural mechanisms**
    a. Salience and coherence
    b. Cancer worry
    c. Response efficacy
    d. social influence

2. **Cancer-specific anxiety**

3. **Perceived lifetime CRC risk (0-100%)**

Secondary estimand 4: Difference in proportion of participants (absolute measure) and odds ratio (relative measure) **with accurate perception of CRC risk** (comparative perception) between intervention and control arms at 1, 6 and 12 months.

Secondary estimand 5: Difference in the proportion of participants (absolute measure) and odds ratio (relative measure) who strongly agreed/agreed that they intended at 1, 6 and 12 months to:

a. consult with my GP about my cancer risk in the following 3 months
b. complete a bowel cancer screening test using the FOBT (test for blood in your poo) in the following 3 months
c. have a colonoscopy to screen for bowel cancer in the following 3 months

d. ask my GP for a referral to a gastroenterologist in the following 3 months

Secondary estimand 6: Difference in the proportion of participants (absolute measure) and odds ratio (relative measure) of participants, who have self-reported at 1, 6 and 12 months to:

a. Consulted with my GP about my cancer risk since the last questionnaire
b. Made changes to my diet or eating habits since the last questionnaire
c. Been referred to a gastroenterologist since the last questionnaire
d. Been referred to a familial cancer clinic to discuss my family history of cancer in the since the last questionnaire.

Possible intercurrent events

All observed data will be included in the analysis of secondary endpoints, regardless of the intercurrent events, such as pregnancy, detection of polyps or bowel cancer during the trial period (**treatment policy strategy**).

Hypothetical strategy will be used when death occurs during the trial period, precluding the collection of patients reported secondary endpoint data.

7.3.4 Statistical methods for the secondary endpoints (PREMS)

A constrained longitudinal data analysis will be used for continuous secondary endpoints (Secondary estimands 1 to 3) measured at baseline, 1, 6 and 12 months. Linear mixed-effects model will be used with study arm (intervention and control), general practice (randomisation stratification variable) and time (baseline, 1, 6 and 12 months) will be treated as fixed effects and individual as a random effect, with two-way interaction between study arm and time, except baseline where study arm means will be constrained to be equal. We will use restricted maximum likelihood (REML) estimates, robust standard errors, and an unstructured residual correlation structure to account for autocorrelation.

Intervention effects for each follow up time (1, 3 and 12 months) will be estimated as the difference in means for each endpoint between the intervention and control arm at 1, 6 and 12 months, respectively.

Using longitudinal data analysis, the between-arm difference in proportions (absolute measure) and odd ratio (relative measure) on binary secondary endpoints (Secondary estimands 4 to 6) at each follow-up time point (1, 6 and 12 months), using a generalised linear model with the identity link function and binomial family (where appropriate) and logistic regression, respectively. Study arm, general practice, and time (1, 6 and 12 months) will be fitted as fixed effects in both regression models, with a two-way interaction between study arm and time. Generalised estimating equations with robust standard errors will be used to account for the repeated outcome measures on individuals (1, 6 and 12 months).

The absolute (between-group difference in the proportions) and relative (odds ratio) estimated effect sizes were presented with their respective 95% confidence interval (CI), and the p-value estimated using logistic regression.

7.4 Supplementary analyses for the primary endpoint

7.4.1 Sensitivity analyses 1: Adjustment of additional covariates

Sensitivity analysis of primary endpoint will adjust for additional covariates measured: risk group at baseline, whether recruitment occurred in person or online, age, and gender. These variables will be included as fixed effects to the regression models described for the primary analysis.

7.4.2 Sensitivity analysis 2: Definition of the primary endpoint

Sensitivity analysis using the same approach described for the primary analysis will assess the impact on the estimated intervention effect for the primary endpoint, based on the information that will be available to the GP when consulting with the patients, namely, self-report and GP records only based on the information that will be available to the GP when consulting with the patients. This is to emulate the real-world setting where the GP would not have access to additional administrative data during the consultation to determine what type of CRC screening was due (MBS, VAED).

7.5 Handling missing data

We expect the proportion of individuals who withdraw their data from the study to be small. Further, we expect that the missing data will be minimal for the primary endpoint as it will be derived using multiple administrative data sources. The appropriate approach for handling missing data for the primary and secondary endpoints will be determined after a blinded review of missing data patterns, the reason for missing data, and their corresponding mechanism. Potential techniques are inclusion of additional covariates predictive of data missingness in the model, multiple imputation, best-worst case analysis and/or using a pattern mixture model if more than 10% of participants have missing data for the primary endpoint due to withdrawal or loss to follow up.

Further, we expect the number of participants who may die over the 12 months of the trial period to be less than 5% of the sample size and similar in the two arms. However, if the overall proportion of deaths in the sample exceeds 5% of the sample size, we may conduct an additional sensitivity analysis for the primary endpoint (e.g. excluding patients known to have died during the trial period from the primary analysis).

7.6 Additional Analyses

7.6.1 Adherence-adjusted analysis

We do not expect that all participants will receive the intervention as specified in the trial protocol, thus the analysis conducted for primary estimand will estimate an intervention effect of being assigned to the intervention or control, not the intervention effect of adherence to the intervention amongst participants assigned to the intervention (Section 5.2).

If appropriate, an adherence-adjusted analysis including all randomised participants will be performed for the primary endpoint to investigate the effect on the estimated intervention effect of adherence to the intervention. The estimate for this **supplementary estimand** will apply to participants who adhere to the intervention and will be estimated using a complier average casual effect (CACE) analysis[19-21] .

Two CACE analyses will be conducted where intervention adherence will be defined as follows:

1) Participants received the personalised CRC risk report with screening recommendations.

2) Participants received the personalised CRC risk report with screening recommendations,
AND
An appointment with the researcher to discuss the results via phone/Zoom/in person.

It is hypothesised that behavioural effect of the intervention will be less effective in increasing appropriate screening if the personalised risk figure and screening recommendations are not returned at all or if the information about CRC screening were not discussed verbally with the participant.

We will undertake the analysis using two-stage least squares instrumental variable regression where the adherence variables are binary indicator variables capturing the definitions described above and study arm used as the instrumental variable for adherence to the intervention. Analysis will adjust for the stratification factor (general practice). Sensitivity analyses may also be conducted to assess the robustness of underlying assumptions[21].

7.6.2 Exploratory sub-group analyses

Three exploratory sub-group analysis will be conducted for the primary endpoint. The statistical test for interaction will be used to examine if the intervention effect for the primary endpoint is modified by the sub-groups below:

1. Participants who are determined to be due screening based on their GP record versus those not due screening. As the eligibility criteria for the trial (being due some form of colorectal cancer screening within the coming year) was determined based on self-report, it is possible that some participants randomised would not require screening within the 12 months follow-up period.
2. Age groups: 45-49, 50-59, 60-69. Age-groups may be collapsed further if numbers in sub-groups are small.
3. Participants with and without a family history of CRC.

Using the same methods described for the primary analysis, the statistical analysis will include an interaction term between the nominated subgroup variable and study arm in the regression model. If there is statistical evidence for an interaction (P-value < 0.1), we will present summary statistics for each sub-group within each study arm. Estimates of the intervention effect will be reported as absolute between-arm differences in proportions and odds ratios with a 95% confidence interval for each sub-group, with the corresponding p-value for the interaction term between the study arm and the subgroup variable[22]. The estimates may also be displayed graphically using forest plots.

8. Health Economic Analysis

The cost of the SCRIPT intervention, health service utilisation and health care costs at 12 months will be calculated based on the assessment of GP consultations, colonoscopy services, iFOBT, and associated pathology services obtained from audit of GP records, and data from the MBS, VAED and NBCSP records. Any other associated changes in health care utilisation will be captured through access to participants' MBS and GP record data (including costs of follow-up appointment with GP to discuss the SCRIPT intervention results with the patient, defined as a GP appointment within 4

weeks of the risk results being returned to the participant by the research team). Indirect costs will not be included.

8.1 Within-trial analysis

The health economic analysis entails an analysis of the SCRIPT intervention cost-effectiveness relative to usual care. It relies on an assessment of health care utilisation to inform costs, and of the primary endpoint measure from the trial (the proportion of appropriately screened individuals).

The analysis will be conducted from the healthcare system perspective, with a time horizon of 12 months as per the trial. Given the one-year time horizon, discounting will not be applied. Costs will be expressed in 2023 Australian dollars.

Within-trial resource use will be estimated based on data obtained from general practices, MBS, NBCSP and VAED records. Estimates from different sources will be collated as described in Appendix A. The specific health care resource use categories, their sources and unit prices are presented in Table 2.

Table 2 Resource use and unit costs in the SCRIPT trial

Resource	Resource utilisation source	Unit cost source
Pre-test consultation	Trial records	GP consultation Level B MBS item 5020: $53.65
Control consultation (cancer risk reduction advice)	Trial records [a]	Nurse pay rate
GeneType PRS test (including saliva collection kit, ORAcollect®)	Trial records	Commercial rate
Post-test consultation (research assistant)	Trial records [a]	Nurse pay rate
Post-test consultation (GP)	If recorded in MBS record within 4 weeks of research post-test consultation [b]	GP consultation Level B MBS item 5020: $53.65
SMS reminder	Trial records [a]	SMS provider
Colonoscopies	Audit of GP records, VAED, MBS	MBS items 32222 32223 32224 32225 32226 32228: $366.15 32227: $513.85 32229: $295.35 32084: $122.00 32087: $224.20
iFOBT	Audit of GP records, NBCSP, MBS	MBS items 66764: $8.90 66767: $17.85 66770: $26.70
CT colonography	Audit of GP records, VAED, MBS	MBS item 56553: $563.35

GP: general practitioner; iFOBT: immunochemical faecal occult blood tests; MBS: Medicare Benefits Schedule; NBCSP: National Bowel Cancer Screening Program; VAED: Victorian Admitted Episodes Dataset.

[a] In practice this would not be expected.

[b] Only if CRC screening test is required as follow-up. % requiring screening test determined from trial data

Mean estimates of resource utilisation and costs will be calculated with confidence intervals generated by bootstrapping 10,000 iterations. Cost differences between arms will be estimated using a GLM with a log link and a gamma family to account for the skewed distribution of costs.

Missing data will be addressed as per the study protocol. A possible approach could be using multiple imputation with chained equations and predictive mean matching per study arm[23]. The number of datasets will depend on the percentage of missing data, and results will be combined using Rubin's rule[24].

The SCRIPT intervention cost-effectiveness will be assessed compared to usual care using an incremental cost-effectiveness ratio (ICER), expressed as the cost per appropriately screened individual, calculated as follows:

$$ICER = \frac{Costs\ (SCRIPT - usual\ care)}{Appropriately\ screened\ individuals\ (SCRIPT -\ usual\ care)}$$

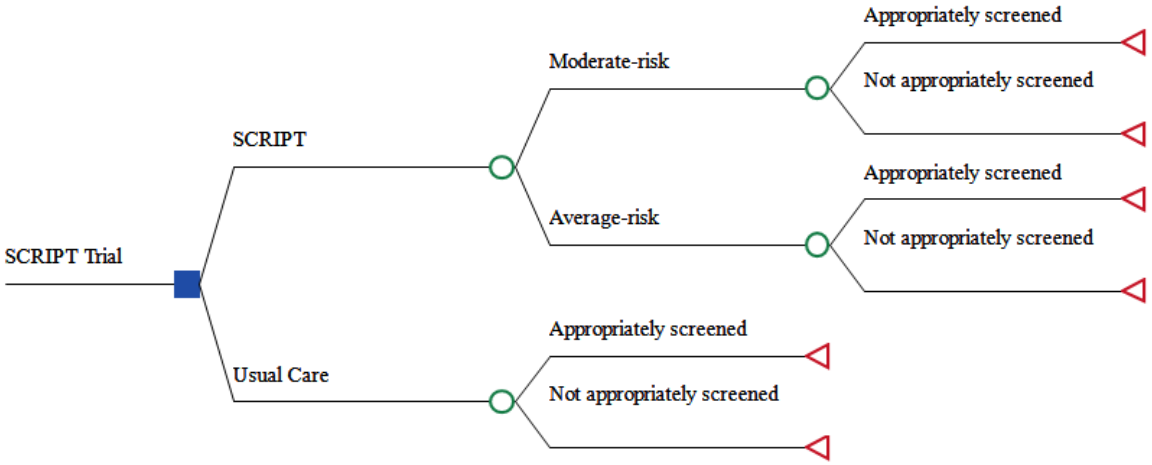
Sampling uncertainty will be represented by bootstrapping 10,000 iterations of the ICER and will be plotted in the cost-effectiveness plane to represent uncertainty graphically. A scenario considering real practice costs as described in Table 2 will also be conducted.

8.2 Decision-analytic model

In addition to the within trial analysis, a modelled analysis will be conducted to consider how the incremental cost per appropriately screened individual might vary given differences in the cost of the PRS, the ability of the PRS to identify those at increased risk, and compliance with screening recommendations.

A decision tree will be developed using the model structure described in Figure 1.

Figure 1 Model structure



The SCRIPT arm will allocate patients to either average (≤ 4%) or moderate risk (> 4%) of CRC as per PRS trial results. Adherence will be assessed by those not appropriately screened.

The SCRIPT trial will inform the proportion of participants who are screened appropriately. The ability of the PRS to identify those at increased risk will be derived from the literature.

The ICER will be estimated as described previously. One-way sensitivity analyses will test the results robustness to inputs variations based on the 95% confidence intervals around the model parameters. Results from the sensitivity analysis will be presented in a tornado diagram. A scenario

analysis using the ability of the PRS to identify those at increased risk will be represented by varying the proportions of patients with moderate and average risk.

A probabilistic sensitivity analysis will also be conducted to evaluate parameter uncertainty simultaneously using a Monte Carlo simulation with 10,000 iterations. Costs will be evaluated using the gamma distribution and probabilities using the beta distribution. Each iteration will be plotted in the cost-effectiveness plane.

The model will not assess the potential link between appropriate screening and subsequent CRC outcomes as this is affected by a number of other intervening measures (beyond the assessment of risk and participation in CRC screening). The cost-effectiveness of participation in CRC screening has been demonstrated elsewhere[25].

9. Data management and workflow

Trial data from participants is collected in REDCap and blinded researchers directly enter screening events from the GP record into REDCap[7].

Administrative data regarding CRC screening events from Services Australia (MBS), the Centre for Victorian Data Linkage (VAED), and Australian Institute for Health and Welfare (NBCSP) will be received securely by the University of Melbourne in Excel/csv files. These data sets will be merged using the de-identified participant codes using R[26] then the merged administrative datasets will be imported into REDCap. The administrative data, general practice audit data, and the participant self-reported CRC events will be reviewed to derive the primary endpoint (Appendix A). This part of the data merging and endpoint derivation will be completed by the Trial Manager (SS).

When this review process is complete and the primary endpoint has been defined for each participant (See Appendix A for details), the REDCap database will be moved to Analysis/Cleanup status prior to commencement of analysis. Data exported into to Stata Statistical software 17[27] and the data collection forms will be locked.

Final data, including participant characteristics and endpoint data, will be imported to Stata Statistical software 17[27]. An independent biostatistician blinded to the study arm status will check the data, prepare data for analysis, and conduct the statistical analyses. Data checking and cleaning will include checking that values are within range, dichotomise or categorise when appropriate, renaming of variables, creating composite variables, deleting variables that are not required. If errors are found these will be corrected as part of the data cleaning process. The trial biostatistician will recode and remove the labels from the randomisation variable (intervention and control) to ensure that the independent biostatistician remains blinded to the participants trial arm status. The trial biostatistician will also work closely with the independent biostatistician to review the data coding and statistical analysis. The health economics analysis will be conducted by the health economists.

9.1 Timing of final analysis and endpoint assessment

Completion of final participant questionnaires will be complete by November 2023 (12 months after completion of the intervention by the final participant).

Collection of GP screening data will be complete by December 2023. Collection of administrative data from organisations will commence in December 2023 and is anticipated to be complete by April 2024. Determination of the primary endpoint for each participant is anticipated to be complete by June 2024. Statistical analysis will be conducted after the primary endpoint has been derived as

outlined in Appendix A, and the SAP has been uploaded on the Australian and New Zealand Clinical Trials Registry.

9.2 Statistical software and technical details

Data management and statistical analyses will be conducted using R[26] and Stata Statistical software (v17)[28] or later. Appendix B provides the proposed table shells for the presentation of the statistical analysis of the primary and secondary endpoints. These results may also be presented graphically, where appropriate. Any post-hoc explanatory analyses not identified in the SAP will be clearly identified in the final statistical report. Any deviations from the planned analyses detailed in the SAP will be documented and reported in a revised version of this SAP.

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Appendix A Determination of the primary endpoint

The following definitions are required to determine the primary endpoint variable at the participant level:

1. Defining the screening the participant had prior to baseline,
2. Defining their CRC risk category,
3. Defining the screening the participant had within the 12-month follow-up period,
4. Defining whether that screening was risk-appropriate.

A.1 Data sources for CRC screening events

CRC screening behaviour will be collected via self-report by participants (via questionnaires at baseline, 1 month, 6 months and 12 months), as well as administrative data sources (GP record, Victorian Admitted Episodes Dataset (VAED), Medicare Benefits Schedule (MBS) and the National Bowel Cancer Screening Program (NBCSP)).

Table 3 shows the fields relating to CRC screening events available from each source (participant self-report, GP record, MBS, NSBCP and VAED).

Table 3: CRC screening data fields collected from each data source

Source	Time period	Fields
Participant self-report (from questionnaires)	Baseline, 1 month, 6 months and 12 months	○ Type of test: iFOBT, colonoscopy; ○ Date of test; ○ Reason for test: ▪ iFOBT: Bowel cancer screening or kit in mail, Bowel symptoms, My family history of bowel cancer, Unsure; ▪ Colonoscopy: Bowel symptoms (e.g. I saw blood in my poo), My family history of bowel cancer / my increased risk of bowel cancer, Positive FOBT (test for blood in your poo), Previous bowel polyp, Screening / for a check-up, Unsure, Other; ○ Result of test: ▪ iFOBT: negative, positive or blood found in poo/sample, Unsure/waiting for results; ▪ Colonoscopy: negative, polyp, other (please specify), bowel cancer (only post baseline), don't know.

Source	Time period	Fields
Audit of GP record	All data available in the participant record up to five years prior to consent	○ Type of test: iFOBT, colonoscopy; ○ Date of result; ○ Indication for the test: ▪ iFOBT: NBCSP, Doctor requested screen, Patient requested screen, Altered bowel habits, Blood in stool, Other symptoms (specify), Other (specify), Unknown ▪ Colonoscopy: Positive FOBT, Altered bowel habits, Blood in stool, Other symptoms (specify), Family history, Previous polyps, Other (specify), Unknown ○ Result: ▪ iFOBT: 1=Normal, 2=Positive, 3=Pending, 4= Inconclusive, 5= Unknown ▪ Colonoscopy: 1= Normal, 2=Polyp, 3=Bowel Cancer,4= Other bowel condition (specify), 5=Pending, 6=Inconclusive, 7=Unknown, 8=Other (specify) ○ Recommended follow-up of colonoscopy findings (from gastroenterologist, free text) ○ Polyp details from histopathology report and/or colonoscopy report (free text)
MBS (via Services Australia)	4.5 years* prior to consent up to five years** post-consent	○ Date of service ○ Medicare item number ▪ Colonoscopies: ▪ Prior to 01/11/2019: items 32084, 32087, 32088, 32087, 32090, 32093 ▪ From 01/11/2019: items 32222-32229, 32084, 32087 ▪ iFOBT: items 66764, 66767, 66770 ○ Item description ○ Provider charge ○ Schedule fee ○ Benefit paid ○ Patient out of pocket ○ Date of referral ○ Referring provider postcode ○ Item category
VAED (only colonoscopies, as this is a hospital admission dataset) (via the Centre for Data Linkage)	5 years prior to consent up to 5 years** post-consent	○ DRG[3] code (procedure code, also indicates complication presence) ○ ICD-10[4] code (diagnosis code for cancer or polyp) ○ ACHI code (procedure code, also indicates polyp presence) ○ Month and year of event
NBCSP (via the AIHW)	5 years prior to consent up to 5 years** post-consent	○ Date result sent to participant ○ Result of FOBT: positive; negative; inconclusive; no result

[1]MBS data are only available for up to 4.5 years before archiving; [2]Data will be requested at the 12-month endpoint for the primary outcome [3]DRG - Diagnostic-Related Group; [4]ICD-10 - International Classification of Diseases 10th Revision

A.1.1 The National Cancer Screening Register

The National Cancer Screening Register (NCSR)[29] was expanded in November 2019 to include the NBCSP, in addition to the National Cervical Screening Program (NCSP).

The Healthcare Provider Portal of the NCSR allows general practices and practitioners to access their patients' NBCSP records. There is additionally the ability of the NCSR to integrate with general practice electronic medical record software. Prior to this advent, only if an individual had included their GP's details on their NBCSP form did the completion of iFOBT tests from the NBCSP make it into their GP medical record. The Portal also allows GPs to order iFOBTs for their patients directly from the NBCSP.

As of May 2023, 16,000 healthcare providers nationally had registered to access the portal, and 2,400 practices had integrated their clinical software with the NCSR[29]. Given this represents less than a quarter of general practices in Australia, we assumed that, for the purposes of the SCRIPT Trial, that GPs were unlikely to have access to NBCSP iFOBT tests that were not scanned into their patient's GP medical record (i.e., were only reported within the NBCSP dataset above, and not the GP record dataset).

A.1.2 Collation and deduplication of CRC screening event data

With multiple sources of data collected on the same screening events, we have defined below when events are defined as a 'true' event, and whether multiple instances from different sources are defined as the same event or a repeat event.

When defining pre-baseline screening, self-reported screening will be included (along with the objective CRC screening data) given that in practice, self-reported previous screening is often used by clinicians to determine when a screen is due, particularly in the absence of any objective data.

Given the comprehensive collection of objective data sources (GP record, MBS, VAED, NBCSP), relative inaccuracy of self-reported data, and that participants are likely to attend the same GP from which they were recruited in the follow-up period, self-reported screening will *not* be included when determining what screening was done during the 12-month follow-up period.

A.1.2.1 Events from administrative data sources

Our previous experience has shown that screening events from administrative data sources[6] (GP record, MBS, VAED, NBCSP) are largely concordant with each other (i.e., for the vast majority of events, dates from each source matched within a few days of each other. Therefore, to deduplicate screening events, if all other details match (type of test and result, if available) then dates within three weeks will be considered the same screening event. This allows for discrepancies in different types of dates reported (date of result, date of test ordered, date result sent to the patient) and lags in event reporting to MBS or VAED.

A.1.2.2 Events from administrative data sources and self-reported screening events (only relevant to pre-baseline events)

We will use the following rules when including self-reported screening data with data available from the administrative data sources. Table 4 below shows the discrepancies in dates that will be allowed according to when the screening event occurred. Any self-reported events that do not occur within the given timeframes of the events recorded in the objective datasets it will be considered as a separate true event.

Table 4: Leeway for self-reported date recall when matching with objective event

Time between date that participant reported screening (i.e., date of questionnaire) and date of screen (as per participant report)	Leeway for self-reported date recall when matching with objective events
<1 year	+/- 6 months
1-2 years	+/- 1 year
2-4 years	+/- 1.5 years
4-6 years	+/- 2 years
>6 years	+/- 3 years

A.2 Defining the primary outcome

A.2.1 Defining the screening the participant had prior to baseline

As outlined above, all data sources (self-report, GP record, VAED, MBS and NBCSP) will be used to determine screening prior to enrolment of participants in the trial. Self-reported events will be included, as this reflects what information a GP would use if considering screening to order in a standard consultation.

A sensitivity analysis (see Section 7.4.2) will be conducted *only* including screening data prior to baseline reported in sources that the GP (who was ultimately responsible for ordering screening tests) would likely have access to, namely self-report and the GP record. As discussed above, despite the expansion of the NCSR soon before the commencement of the trial, we did not assume that GPs would have access to the NCSR and NBCSP.

A.2.2 Defining CRC risk category and recommended screening

The appropriate type and repeat interval of CRC screening test is also dependent on the participant's category of CRC risk. The currently endorsed NHMRC guidelines for CRC screening define the family history criteria that place an individual into a category of risk. For example, a first-degree relative diagnosed with CRC under age 55 places someone into the moderately increased risk category. Box 3 of Jenkins et al.[2] provide the criteria for each combination of CRC family history.

Table 5 shows the criteria for the SCRIPT trial to place participants into a screening risk category and the relevant screening test and frequency, based on their personalised risk and/or NHMRC guidelines.

Table 5: SCRIPT criteria for placing participants into a CRC screening risk category

Age	Arm	Criteria	Screening – Near average risk	Screening – Moderately increased risk
45-49	Control	NHMRC family history guidelines	None	iFOBT 2-yearly
50-70	Control		iFOBT 2-yearly	Colonoscopy 5-yearly
45-49	Intervention	Highest cat. of NHMRC family history guidelines and 10-yr PRS-derived CRC risk (<1% No screening, 1-4% iFOBT, >4% Colonoscopy)	None	iFOBT 2-yearly
50-70	Intervention		iFOBT 2-yearly	Colonoscopy 5-yearly

A.2.3 Defining what screening was completed within the 12-month follow-up period

Only objective administrative data sources (GP record, VAED, MBS and NBCSP) will be used to determine whether a screening event has occurred within the 12-month follow-up period. Self-reported events will not be included, given their unreliability, as discussed above.

A.2.4 Defining whether screening was risk-appropriate at 12 months

Table 5 above provides general screening categories and recommendations that will be applicable to most participants. However, there are scenarios where these screening recommendations will be negated due to other events, meaning the participant is no longer appropriate for 'screening', for example, previously identified bowel polyps that require surveillance colonoscopy, or development of bowel symptoms necessitating investigation by colonoscopy. These scenarios may represent appropriate or inappropriate management, surveillance or screening. The **primary endpoint** is defined in relation to these intercurrent events (events that occur post-randomisation). These scenarios may represent appropriate or inappropriate management, surveillance or screening. The rules below have been developed to ensure consistency of determining the primary endpoint for all participants in relation to these scenarios.

For participants with complex past histories, a Clinical Consensus Group (consisting of gastroenterologists and GPs, blinded to study arm allocation) will review and use all available data sources as described above to determine what risk-appropriate screening would be consistent with NHMRC surveillance and screening guidelines.

- Follow-up after a colonoscopy:
    - Those whose last test was a colonoscopy (for any reason), whose risk does not warrant colonoscopic screening and where the colonoscopy results did not require colonoscopic follow-up (e.g., due to a finding of bowel polyps) would be due an iFOBT after four years,
    - If bowel polyps were found on a previous colonoscopy, the timing and mode of follow-up test resulting from previous polyps would take precedence over the screening recommended from the trial. This timing and mode of follow-up screening/surveillance should be in line with the 2019 Australian guidelines for surveillance after polyps[30] to be deemed 'appropriate'.
- Indication for colonoscopies:
    - Colonoscopies to investigate abnormal symptoms (e.g., altered bowel habits, blood in stool, anaemia etc.) will be deemed 'appropriate',
    - Colonoscopies not reported in the GP record and therefore whose indication is unknown will be assumed to be conducted for screening purposes, not for symptom investigation,
    - Diagnosis of diverticulosis will be considered an appropriate indication for a colonoscopy, but surveillance of diverticulosis is not appropriate.
- Timing of screen:
    - If a screen is due anytime between baseline and the 12-month endpoint, it will be considered 'appropriate' if completed within the 12-month period,
    - If a screen completed more than six months earlier than recommended in the guidelines, it is considered over-screening, and coded as not appropriate.
- Over-screening by iFOBT:
    - Given the that the trial took place when the NCSR was still being rolled out and use by GPs is patchy, we do not expect that the NBCSP will know if a GP had ordered an iFOBT outside of the program. Therefore, if a participant completed an NBCSP iFOBT

earlier than two years since the last completed iFOBT, this is not considered as over-screening and coded as not appropriate,
    - If a GP orders an iFOBT >6 months before it was due, this will be marked as 'overscreening' and coded as not appropriate.
- Following up of positive iFOBTs:
    - Diagnostic colonoscopy after a positive iFOBT is not considered part of the 'risk-appropriate screen', i.e., if a participant is due an iFOBT, this iFOBT is done and is positive but the diagnostic colonoscopy was not completed, this is 'appropriate' screening, not 'under screening'. This is because the colonoscopy was no longer deemed screening but diagnostic.
- Bowel polyps:
    - When the indication of a colonoscopy is stated in the record as 'previous polyps', but there is no evidence of the previous colonoscopy in the GP record, it will be assumed that these follow-up colonoscopies are 'appropriate'.
    - For colonoscopies, particularly those only reported in the MBS or the VAED record and not in the GP record, it can be noted that there were polyps found but no further details available. In this case, we will assume that a repeat colonoscopy could be indicated after 3 or 5 years, as per the two most common categories in the guidelines. If the colonoscopy was repeated after between 3 to 5 years, it will be deemed 'appropriate',
    - If the only information available about the polyp is that it was a rectal polyp, we will assume it was a hyperplastic polyp and therefore requires no colonoscopic follow-up.

Appendix B Table shells and figures

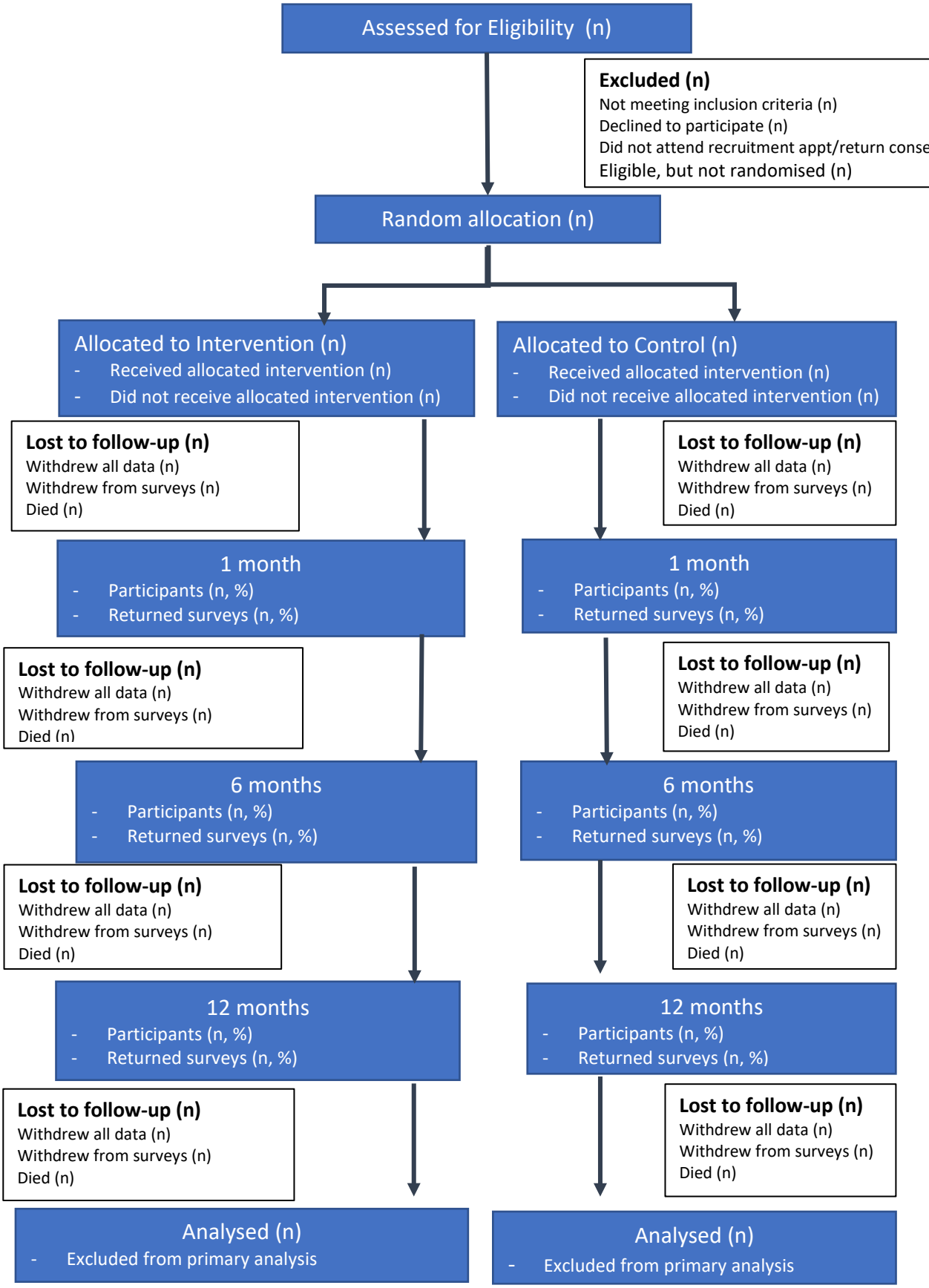

Figure B1: Template Consort diagram; Denominator for the percentages (%) is the total number allocated to each study arm

Table B1: Participant demographics by study arm

	Intervention (n=) n (%)	Control (n=) n (%)	All participants (n=) n (%)
Total			
Age (years) – Mean (SD)			
Gender			
Female			
Male			
Other			
English spoken at home			
Ethnicity[1]			
European (European Australian, U.K., Greece, France, Germany, Spain, Italy)			
Aboriginal and/or Torres Strait Islander			
Central/South Asian (Pakistan, Sri Lanka, Bangladesh, India)			
Near Eastern (Northern Africa, Middle East, Turkey)			
East Asian (Japan, Korea, China)			
Oceanian (Hawaiian, Papua New Guinea)			
Latin American			
Sub-Saharan African			
Other			
Index of Relative Socio-economic Disadvantage (IRSD quintiles) for participants residence			
Disadvantaged 1			
2			
3			
4			
Advantaged 5			
Highest level of education completed			
Less than year 10			
Year 10			
Year 11			
Year 12 or equivalent			
Certificate III/IV			
Advanced Diploma/Diploma			
Bachelor's Degree			

Graduate Diploma/Graduate Certificate	
Postgraduate Degree	
Lives alone	
Living arrangements if do not live alone[1]	
Husband or wife	
Defacto partner	
My child/ren	
My partner's child/ren	
My parent/s	
Unrelated flatmate or co-tenant	
Other	
Risk category based on NHMRC family history criteria (2017)[2]	
Average risk	
Moderate risk	
High risk	
Risk category based on genomic risk test	
Average risk	*As per the NHMRC family history criteria*
Moderately increased risk	
High risk	

Counts (n) and percentages (%) presented unless otherwise stated

[1]Participants were able to tick all boxes that applied, so percentages may not sum to 100%

Note: Categories may be collapsed in the final table presented in the publications

Table B2: Appropriate colorectal cancer screening at 12-month follow-up between study arms (N=)

Appropriately screened at 12 months	Intervention (n=)	Control (n=)			
	n (%)	n (%)	Difference (95% CI)[1]	Odds ratio (95% CI) [2]	p-value
Primary analysis					
Sensitivity analysis[3]					
Sensitivity analysis[4]					
Sensitivity analysis[5]					
Adherence adjusted analysis 1					
Adherence adjusted analysis 2					
Effect-modification[6]					
Due CRC screening at baseline					
Yes					
No					
Age group					
40-49 years					
50-59 years					
60-69 years					
Family history					
Yes					
No					

n – count; CI – Confidence Interval

[1]Difference in the percentage and respective 95% CI between the intervention and control arms estimated using generalised linear model with the identity link function and binomial family adjusted for general practice

[2]Odds ratio of the intervention arm compared to the control arm and respective 95% CI estimated using logistic regression adjusted for general practice.

[3]Sensitivity analysis 1: Adjustment of additional covariates

[4]Sensitivity analysis 2: Definition of the primary endpoints

[5]Sensitivity analysis for missing data may also be included based on blinded review of the missing data patterns and reasons.

[6]Effect modification by (1) whether participants were due colorectal cancer screening (CRC) during 12-month follow-up or not (p-value for interaction effect X.XXX), (2) age-group (p-value for interaction effect X.XXX) and (3) family history of CRC (p-value for interaction effect X.XXX)

Table B3: General and cancer-specific anxiety, and risk perception between study arms (N=)

	Intervention (n=)	Control (n=)		
	Mean (SD)	**Mean (SD)**	**Difference (95% CI)[2]**	**p-value**
Preventative health model				
Salience and coherence (range 4-20)				
Baseline			--	
1 month				
6 months				
12 months				
Cancer worry (range 2-10)				
Baseline			--	
1 month				
6 months				
12 months				
Response efficacy (range 2-10)				
Baseline			--	
1 month				
6 months				
12 months				
Social influence (range 4-20)				
Baseline			--	
1 month				
6 months				
12 months				
Self-efficacy (range 6-30)				
Baseline			--	
1 month				
6 months				
12 months				
Cancer-specific anxiety (range 6-24)				
Baseline			--	
1 month				
6 months				
12 months				
Mean perceived risk of colorectal cancer (0 to 100%)				
Baseline			--	
1 month				
6 months				
12 months				
	n (%)	n(%)	**Diff (95% CI)** **OR (95% CI)[2]**	**p-value**
Proportion who reported accurate comparative risk perception for colorectal cancer				
Baseline				
1 month				
6 months				
12 months				

n - count; SD – Standard Deviation; CI - confidence interval

[1] Difference in mean in the intervention minus the mean in the control arm with respective 95% CI estimated using constrained linear mixed effects model with study arm, general practice and time (baseline, one, six and 12 months) included as fixed effects and individuals treated as random effects, with two-way interaction between study arm and time, except for baseline where study arm means were constrained to be equal.

Table B4: Intentions and self-reported behaviours to manage risk of colorectal cancer between study arms (N=)

	Intervention (n=)	Control (n=)	Diff (95% CI)[1]	OR (95% CI)[2]	
	n (%)	n (%)			p-value
In the three months, I intend to:					
Consult with my GP about my cancer risk					
1 month					
6 months					
12 months					
Complete a bowel cancer screening test using FOBT					
1 month					
6 months					
12 months					
Have a colonoscopy to screen for bowel cancer					
1 month					
6 months					
12 months					
Ask my GP for a referral to a gastroenterologist					
1 month					
6 months					
12 months					
Since the last questionnaire, I have:					
Consulted with a GP about my cancer risk					
1 month					
6 months					
12 months					
Made changes to my diet or eating habits					
1 month					
6 months					
12 months					
Been referred to a gastroenterologist					
1 month					
6 months					
12 months					
Been referred to a familial cancer clinic to discuss my family history of cancer					
1 month					
6 months					
12 months					

n – count; % - Percentage; CI- Confidence interval

[1]Diff - Difference in the percentage and respective 95% CI between the intervention and control arms estimated at each time point using generalised linear model with the identity link function and binomial family adjusted for general practice, using generalised estimating equations with robust standard errors, with study arm, time (one, six and 12 months) and general practice as fixed effects, with two-way interactions between study arm and time.

[2]OR - Odds ratio of the intervention arm compared to the control arm and respective 95% CI estimated using logistic regression using generalised estimating equations with robust standard errors, with study arm, time (one, six and 12 months) and general practice as fixed effects, with two-way interactions between study arm and time.