The Daffodil Centre

MAIL, GP & SCALE trial: A general practice led intervention to increase National Bowel Cancer Screening Program participation.

RESEARCH PROTOCOL

Version and date:	V2 08 August 2023
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1. Abbreviations

AI	Associate Investigator
CCNSW	Cancer Council NSW
CFIR	Consolidated Framework for Implementation Research
CIS	Clinical Information System
CPI	Coordinating Principal Investigator
CRC	Colorectal cancer
CTC	Clinical Trial Coordinator
DC	The Daffodil Centre
ERIC	Expert Recommendations for Implementing Change
GP	General Practitioner
HREC	Human Research Ethics Committee
NBCSP	National Bowel Cancer Screening Program
NCSR	National Cancer Screening Register
PHN	Primary Health Network
PICF	Participant Information Sheet and Consent form
RCT	Randomised controlled trial
RDS	The Research Data Store
TDFI	Theoretical Domains Framework Implementation

2. Contacts

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3. Principal Investigator Declaration

I will conduct the clinical trial in accordance with Good Clinical Practice, Declaration of Helsinki, National Statement on Ethical Conduct in Human Research 2007 (as updated), Australian Code for the Responsible Conduct of Research 2018 and the moral, ethical and scientific principles that justify clinical research. The clinical trial will be conducted in accordance with all relevant laws and regulations relating to clinical studies and the protection of participants.

I agree to adhere to the protocol as approved by the Human Research Ethics Committee/s in all circumstances other than where necessary to protect the participant's wellbeing.

Coordinating Principal Investigator name:	A/Prof Eleonora Feletto
Coordinating Principal Investigator signature:	
Date of signature:	08 August 2023

4. Study Synopsis

<table>
<tr><td>Long title</td><td>MAIL, GP & SCALE trial: A general practice-led intervention to increase National Bowel Cancer Screening Program participation.</td></tr>
<tr><td>Short title</td><td>MAIL, GP & SCALE trial</td></tr>
<tr><td>Lead Investigator</td><td>A/Prof Eleonora Feletto</td></tr>
<tr><td>Aims, Objectives and Outcome</td><td>This study aims to pilot a co-designed general practice-led intervention and implementation strategies in up to 100 general practices in New South Wales (NSW) and Western Australia (WA).

The objectives of the pilot trial are to:

1. Increase the number of guideline-appropriate CRC screening recommendations provided.

2. Increase the number of guideline-appropriate CRC screening tests completed.</td></tr>
<tr><td>Study Design</td><td>The study is a hybrid type 2 effectiveness-implementation intervention trial that will be conducted in up to 100 general practices to test the effectiveness of a general practice-led intervention and a suite of implementation strategies.</td></tr>
<tr><td>Blinding/Masking</td><td>This will be a single-blinded cluster randomised controlled clinical trial. Only the trial investigators involved in the intervention delivery will know the allocation. Participants will be allocated to either the control or intervention and monitored through the trial by the Clinical Trial Coordinators (CTC). Due to the nature of the intervention and implementation support, practices may discern their allocation.</td></tr>
<tr><td>Study Setting and Data Collection</td><td>This study will recruit up to 100 General Practices within Primary Health Network (PHN) regions of New South Wales (NSW) and Western Australia (WA). Data collection will be facilitated by CTCs.</td></tr>
<tr><td>Study Duration</td><td>
<table>
<tr><th>Timeframe</th><th>Activity</th></tr>
<tr><td>November 2022 - February 2023</td><td>Complete co-design and refinement of multicomponent intervention (University of Sydney HREC 2022/755)</td></tr>
<tr><td>August 2023</td><td>Ethics approval (University of Sydney Clinical Trials)</td></tr>
<tr><td>January – August 2023</td><td>Engagement with PHNs and establishment of research agreements</td></tr>
<tr><td>August 2023</td><td>Recruitment of CTCs</td></tr>
<tr><td>September 2023</td><td>General Practice Recruitment</td></tr>
<tr><td>October 2023</td><td>Baseline data collection</td></tr>
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	<table><tr><td>March - August 2024</td><td>Delivery of intervention</td></tr><tr><td>March - August 2024</td><td>Implementation support of intervention arm</td></tr><tr><td>March - August 2024</td><td>Monitor of control arm (usual care)</td></tr><tr><td>September - October 2024</td><td>Post-intervention data collection</td></tr><tr><td>October 2024</td><td>Effectiveness evaluation</td></tr></table>
Intervention	The intervention is a multi-component, co-designed general practice-led intervention designed based on the evidence review and co-design process in a larger project, MAIL, GP & SCALE. The co-design process was completed in April 2023 (University of Sydney HREC 2022/755). The intervention comprises the following components: 1. Decision support aids 2. Electronic point-of-care prompt 3. Clinical system enhancement 4. Education The intervention will be provided after an initial six months of usual care and data collection. The 6-month period between recruitment and intervention delivery is being used as a wash out period to ensure best measurement of study effects. The intervention will be supported by the CTC. The CTC will guide and facilitate the implementation strategies identified in the evidence review and through the co-design process.
Number of participants	The trial includes up to 100 general practices within the jurisdictions of NSW and WA. There will be 50 practices per jurisdiction, with 25 practices randomly allocated to a control arm and 25 randomly allocated to an intervention arm in each jurisdiction.
Population	The target population residing within NSW and WA is General Practices, including GPs, practice nurses and practice staff.
Selection and enrolment	Inclusion criteria: • Has at least two full-time equivalent GPs willing to participate in the trial • Nominated Practice Champion who is willing and able to liaise with the Daffodil Centre research team • Uses Medical Director software • Uses Pen CS, Polar or Primary Sense • Available over the trial period October 2023 – October 2024 • Windows 10 or high, i5/i7 16GB processing or willing to upgrade • Has over 1000 active patients and sees minimum of 35 adult patients per day Exclusion criteria: • Shares server with another practice • Uses paper-based medical records • Does not share data with PHN

5. List of Study Documents

The following table lists each of the study documents:

Appendix	Document Title	Purpose
Recruitment Templates		
1A	General practice recruitment templates	Will be provided to CTC and used to approach and recruit general practices into the study.
1B	General Practitioner and Practice Staff recruitment templates	Will be provided to CTC and used to approach and recruit GPs and practice staff into the study.
1C	General practice recruitment study questionnaires	Will be provided to CTC and used to approach and recruit GPs and practice staff to participate in study questionnaires.
Participant Information Statements		
2A	General practice PIS	Provide a brief overview of the study and general practice requirement.
2B	Individual GP and general practice staff PIS	Provide a brief overview of the study and requirements specific to GPs and practice staff. Obtain GP and practice staff consent to participate in the study.
Participant information and Consent Forms		
3A	General practice PCF	To obtain general practice consent to participate in the study.
3B	Individual GP and general practice staff PCF	To obtain GP and practice staff consent to participate in the study.
Data Collection Tools		
4A	Clinician and general practice staff IPSBQ questionnaire pre-trial	To be completed by all participating GPs and practice staff. Will be used to collect pre-trial information from general practice staff. This survey will assess current awareness of bowel cancer screening and use of the NCSR HCP portal and behaviour change using a modified version of the **IPSBQ** questionnaire.
4B	Clinician and general practice staff IPSBQ questionnaire post-trial	To be completed by all participating GPs and practice staff. Will be used to collect post-trial information from general practice staff. This survey will assess current awareness of bowel cancer screening and use of the NCSR HCP portal as well as behaviour change using a modified version of the **IPSBQ** questionnaire.
4C	Implementation Outcomes survey mid-trial	To be completed by all participating GPs and practice staff of the intervention arm. Will be used to collect mid-trial information from general practice staff. This survey will assess implementation outcomes, including adoption and fidelity of the intervention.
4D	Implementation Outcomes survey post-trial	To be completed by all participating GPs and practice staff of the intervention arm. Will be used to collect post-trial information from general practice staff. This survey will assess implementation outcomes, including adoption and fidelity of the intervention.
4E	General Practice Readiness for Change Questionnaire pre-trial	To be completed by a practice representative 'Practice Champion' from practices participating in the *Pilot of a general practice-led intervention to increase National Bowel Cancer Screening Program participation.* Will be used to assess practice 'readiness' to implement changes that support bowel cancer screening and to obtain practice staff demographics.
4F	General Practice Readiness for Change Questionnaire post-trial	To be completed by a practice representative 'Practice Champion' from practices participating in the *Pilot of a*

		general practice-led intervention to increase National Bowel Cancer Screening Program participation. Will be used to assess practice 'readiness' to implement changes that support bowel cancer screening and to obtain practice staff demographics.
4G	CTC Project Log	To document the steps taken to complete each implementation task, and the time and resources involved.
Ongoing trial monitoring activities		
5A	Delegation of duties	Pending
5B	Trial monitoring	Pending
6A	Intervention Design	Provides a description of the intervention components.

CTC=Clinical Trial Coordinator, GP=General practitioner, PHN=Primary Health Network, PCF=Participant information and Consent Form; PIS = Participant Information Sheet

6. Introduction

6.1. Background and rationale

Colorectal cancer (CRC) is the fourth most common cancer in Australia and screening for precancerous lesions and early stage cancer is proven to decrease CRC mortality and morbidity (1,2). In Australia, the National Bowel Cancer Screening Program (NBCSP) provides a self-administered stool test, the immunochemical faecal occult blood test (iFOBT), mailed to the home of all Australians aged 50-74 years. If an individual has above average risk of CRC (e.g., a family history of the disease), specialised screening regimens via colonoscopy are recommended in place of NBCSP screening (3). Optimising the NBCSP and ensuring people at above average risk are screening appropriately are critical to reducing CRC mortality and morbidity in Australia. The NBCSP alone has the potential to save 84,000 lives by 2040 if participation can reach and be sustained at 60% (4).

The CRC burden in Australia remains high and there are many people who do not screening according to the evidence-based guideline recommendations (3). That is, they either do not screen at all (under-screened) or screen using colonoscopy when they are not at above average risk (inappropriately screened). Under-screened individuals are at higher risk of developing advanced-stage CRC, whereas inappropriately screened individuals can place unnecessary strain on the healthcare system through low-value colonoscopies (5). Improving guideline-appropriate CRC screening will improve CRC outcomes and optimise the use of CRC-specific health services.

Evidence-based interventions can change screening behaviours and are generally targeted at the individual (e.g. personal reminders, modifications to simplify kit use, etc. (6)) or the whole of population (e.g. mass-media awareness campaigns (7)). Healthcare professionals, especially general practitioners (GPs), play a critical role in advocating for cancer screening (6,8) and have the clinical expertise to support guideline-appropriate care (9) but do not currently play an active role in the NBCSP. Existing Australian evidence suggests that GPs' perceptions of CRC screening can be improved by more formal engagement in the routine screening through the NBCSP (10). From 2020, the National Cancer Screening Register (NCSR) allowed GPs to access up to date patient specific screening history for the NBCSP. Additionally, a pilot program was launched by the Department of Health and Aged Care in late 2022 to enable GPs to provide NBCSP kits directly to an eligible patient during a regular consultation (11). More research is required to explore how to mobilise general practice to support guideline-appropriate CRC screening.

6.1.1. Current project and preliminary work conducted

The MAIL, GP & SCALE project (National Health and Medical Research Council: Targeted Call for Research 2021/GNT2014964) was designed to explore CRC screening behaviours in Australia and the involvement of GPs in the NBCSP. As part of the MAIL, GP and SCALE project, a preliminary evidence review has been conducted, which has identified effective evidence-based intervention components and implementation strategies for emerging and existing CRC screening interventions (12). The extracted data and other information were coded against the Expert Recommendations for Implementing Change (ERIC) and the Consolidated Framework for Implementation Research (CFIR) (13,14) to describe determinants affecting implementation and the effective strategies.

The information from the evidence review was then explored further as part of a co-design process with GPs and general practice staff completed in April 2023 (HREC 2022/755). The co-design included an analysis of participants' perspectives on CRC screening in general practice, the NBCSP, potential intervention components and implementation strategies, using ERIC and CFIR. Together, this has informed the design of a multicomponent intervention and implementation strategies for the MAIL, GP & SCALE trial.

6.2. Addressing the problem: a general practice led-intervention to increase NBCSP participation.

The MAIL, GP & SCALE trial is the pilot of a co-designed intervention to increase National Bowel Cancer Screening Program participation. The trial will use a two-arm cluster-randomised Hybrid Type 2 effectiveness-implementation randomised controlled trial (RCT) (15)**.**

The MAIL, GP & SCALE co-designed intervention (also referred to as the intervention) will target general practice staff including GPs, practice nurses, practice managers and administrative staff and is multi-component. The intervention will include CRC decision support tools, point of care prompts, clinical system enhancement, and general practice staff education. The implementation of the intervention will be supported by Clinical Trial Co-ordinators (CTCs) with a suite of co-designed strategies to facilitate behaviour change and the recommendation of guideline-appropriate CRC screening.

7. Aim, objectives, and hypothesis

The MAIL, GP & SCALE trial aims to pilot the co-designed intervention and implementation strategies in up to 100 general practices in New South Wales (NSW) and Western Australia (WA). In each state there will be 50 intervention general practices and 50 control (usual care) general practices. The objectives are to:

1. Increase the number of guideline-appropriate CRC screening recommendations provided.
2. Increase the number of guideline-appropriate CRC screening tests completed.

The following hypotheses will be tested:

1. The intervention will statistically significantly increase the number of guideline-appropriate CRC screening recommendations provided compared to the control arm.
2. The intervention will statistically significantly increase the number of guideline-appropriate CRC screening tests completed by patients compared to the control arm.

8. Outcomes

8.1. Primary Outcomes

The trial will evaluate the primary outcomes of implementation and clinical effectiveness of the intervention by general practice.

A. The co-primary **implementation effectiveness outcome** is guideline-appropriate CRC screening recommendations provided.

B. The co-primary **clinical effectiveness outcome** is guideline-appropriate CRC screening tests completed by patients.

8.2. Secondary Outcomes

The secondary trial outcomes include service and implementation outcomes by general practice.

A. The **service outcome** is general practice awareness and understanding of guideline-appropriate screening.

B. The **implementation outcome** is the adoption of in-practice activities and implementation strategies to support CRC screening.

The outcomes will be reported in accordance with the Consolidated Standards of Reporting Trials (16). Previous work on the theory-grounded implementation method for translating clinical guidelines and policy into practice – the Theoretical Domains Framework Implementation approach (TDFI) (17–19) – will be adapted. This is a proven method to help healthcare professionals deliver evidence-based care. As this trial will support guideline-appropriate CRC screening in general practices, the TDFI will be critical to implementing the trial intervention. The type and quality of the implementation strategies will be described and reported according to the StaRI Statement and Checklist (20).

9. Participating Sites

The trial will be conducted in up to100 general practices in NSW and WA in one of the following Primary Health Networks (PHNs):

- Central and Eastern Sydney
- Perth North
- Perth South

PHNs provide ongoing support to general practices in Australia to deliver high-quality care (21). PHN regions have been selected based on Australian Institute of Health and Welfare (AIHW) NBCSP screening participation and cancer diagnoses data (22).

The Department of Health PHN Grant Programme Guidelines outlines the PHN's role to support continuous improvement, including research (21). PHNs hold formal Data Sharing Agreements with general practices in their regions, including a framework for PHN collection, aggregation, and analysis of general practice data via data extraction tools. PHN Data Sharing Agreements permit third parties to use de-identified and aggregate data collected for research purposes.

The Daffodil Centre, a joint venture between Cancer Council NSW and the University of Sydney, is the coordinating centre of the study. Each participating PHN will enter into a Standard Clinical Trial Agreement with the University of Sydney that outlines the trial schedule and the PHN role at a participating site. The Agreement will outline the objectives of the study and support of the PHN in recruitment of practices and facilitation of general practice data collection and sharing (see section 10.4). The executed Agreement will permit the use of de-identified aggregate general practice data to be shared with The Daffodil Centre for the research purposes of the trial. The Agreement will outline the management and use of the data in accordance with published guidance material and the Australian Code for the Responsible Conduct of Research, 2018 (23). Individual data-sharing agreements will not be needed between the Daffodil Centre and participating general practices.

9.1. Clinical trial coordinators (CTCs)

Four CTCs, two per state, will be appointed to coordinate trial activities and to undertake data collection. MAIL, GP & SCALE funding will support four x 0.8 FTE positions for one year. Ideally, the CTCs will have a professional understanding of primary care, cancer screening, the ability to learn implementation techniques, and the ability to engage with and motivate participating general practices.

Each CTC will be employed either by the PHN or through the University of Sydney as contract employees and trained by The Daffodil Centre research team. The CTCs will be trained to understand

their responsibilities to conduct ethical research and be provided with a Project Log for record keeping (Appendix 4G). In addition, CTCs will receive support and training in strategies to improve the implementation of the intervention in the primary healthcare setting. A previously developed training toolkit and 1-day course will be refined for the MAIL, GP & SCALE trial (18). Each CTC will be responsible for 25 general practices that will be a combination of intervention and control sites.

10. Research Plan

10.1. Study design

10.1.1. Cluster-randomised hybrid type 2 effectiveness-implementation trial

The MAIL, GP & SCALE trial is a hybrid type 2 effectiveness-implementation trial that will be conducted in up to 100 general practices. It will test the clinical and implementation effectiveness of the intervention and a suite of implementation strategies. The trial has been designed as a pilot as the outcomes are essential to inform a later objective of the broader MAIL, GP & SCALE project for intervention sustainably and scaled-up in general practices across Australia.

10.1.2. Population & sample size

An indicative sample size has been calculated based on documented approximate rules for pilot trials (24). For a main trial designed with 90% power and two-sided 5% significance, pilot trial sample sizes with 50-75 practices per arm for standardised effect sizes ranging from extra small (≤0.1) to large (0.8) are recommended (24). We aim to recruit up to 50 general practices per arm with at least two GPs per practice, in line with previous studies despite the sample size calculated based on patient screening behaviour change (25,26). A pilot with up to 100 general practices will yield sufficient information to assess the effectiveness of the intervention.

10.1.3. Recruitment of participating general practices

The PHNs will provide a list of potentially eligible general practices to the CTC. The CTCs will be responsible for facilitating recruitment with support from the PHN. PHNs communicate directly to general practice via practice-approved email updates, website updates and newsletters. Eligible general practices will be sent an email inviting them to participate by the CTC (Appendix 1A). The email will contain information about the trial and a link directing them to a research landing page on Redcap where they may submit an expression of interest form. CTCs may call practices that have not yet expressed interest and provide information about the trial over the phone. If the practice is not interested, no further contact will be made. In addition, PHNs may circulate information about the study through their communication channels such as emails and newsletters. Information circulated will contain a link to the online REDCap landing page where practices may read the Participant Information Statement and provide digital consent.

The CTCs will follow up practices that have expressed interest. CTCs will email additional trial information and will continue to follow-up with interested practices up to three times by phone and/or email. After three failed follow-up attempts, it will be assumed that the practice is no longer interested in taking part in the trial. As part of the recruitment process, CTCs will establish practice eligibility based on the following criteria.

- Inclusion criteria:
    - Has at least two GPs (2 FTE) willing to participate in the trial
    - Nominated Practice Champion who is willing and able to liaise with the CTC
    - Uses Medical Director software
    - Uses Pen CS, Polar or Primary Sense

- Available over the trial period October 2023 – October 2024
- Windows 10 or higher, i5/i7 16GB processing or willing to upgrade
- Has over 1000 active patients and sees minimum of 35 adult patients per day

- Exclusion criteria:
  - Shares server with another practice
  - Uses paper-based medical records
  - Does not share data with PHN

Exclusion criteria is based on the need to deliver the intervention using the Clinical Information Systems (CIS) (or practice software) in the general practice.

10.1.4. Informed Consent

➢ *General practice*

As outlined in section 9, the PHNs as the participating site will enter into a Standard Clinical Trial Agreement facilitated by the University of Sydney. General Practices have existing agreements to work with and share data with PHNs. General Practices participating in the trial will be listed on the Standard Clinical Trial Agreement applicable to their corresponding PHN region. General Practices, via the CTC, will be provided with an Information Statement about the study (Appendix 2A) outlining their roles and responsibilities and The Daffodil Centre research team (including the CTCs)'s role. The CTC will set out the pilot trial timeline and expectations of participating practices.

If allocated to the intervention arm, the practice will nominate a "Practice Champion" who will maintain ongoing contact with the CTC. This will involve monthly meetings via phone or zoom of 30 minutes to monitor progress outlined in Appendix 2A. If deemed appropriate by the PHN and general practice, in addition to consent obtained via the Standard Clinical Trial Agreement, the participating general practice will be provided with a Consent Form by the CTC (Appendix 3A) via an online developed REDCap portal.

Once consent is obtained from a General Practice, the practice will be provided with a unique identification number generated by the REDCap platform. General Practices will be identifiable to the core research team using this unique identification number which will be stored and accessible only to the core research team.

➢ *Individual GP and practice staff consent*

At least two GPs (2 FTE) from each practice need to participate in the pilot trial to achieve statistical power of the primary outcomes. Practice nurses, practice managers and other practice staff (e.g., receptionists) may also participate but not all staff are required to be part of the trial. Participating GPs and practice staff will be required to sign a consent form (Appendix 3B) to participate in trial activities, including baseline and post-trial evaluation surveys. The CTC will facilitate consent upon receiving participation confirmation. The CTC will email the General Practice (Appendix 1B) to seek individual participation and provide a Participant Information Statement (Appendix 2B) and a link to an online RedCap portal where consent may be provided (Appendix 3B). The CTC will be trained in undertaking responsible research and how to facilitate informed consent.

➢ *Individual patient consent*

Individual patient consent will not be sought for participation in the trial as no identifying information about patients will be collected and aggregate de-identified data reports will be used.

- *Withdrawal and termination*

Participation is voluntary. General practices can withdraw at any time without providing a reason. Individual GPs or practice staff within a participating practice may also withdraw at any time without providing a reason. Participants will be provided with a withdrawal of consent form by the CTC and the information will be recorded in the CTC project log, with the reason if provided. If an individual GP withdraws from the study the CTC will work with the participating general practice to identify an alternative replacement. If this is not possible, the general practice will be withdrawn from the study.

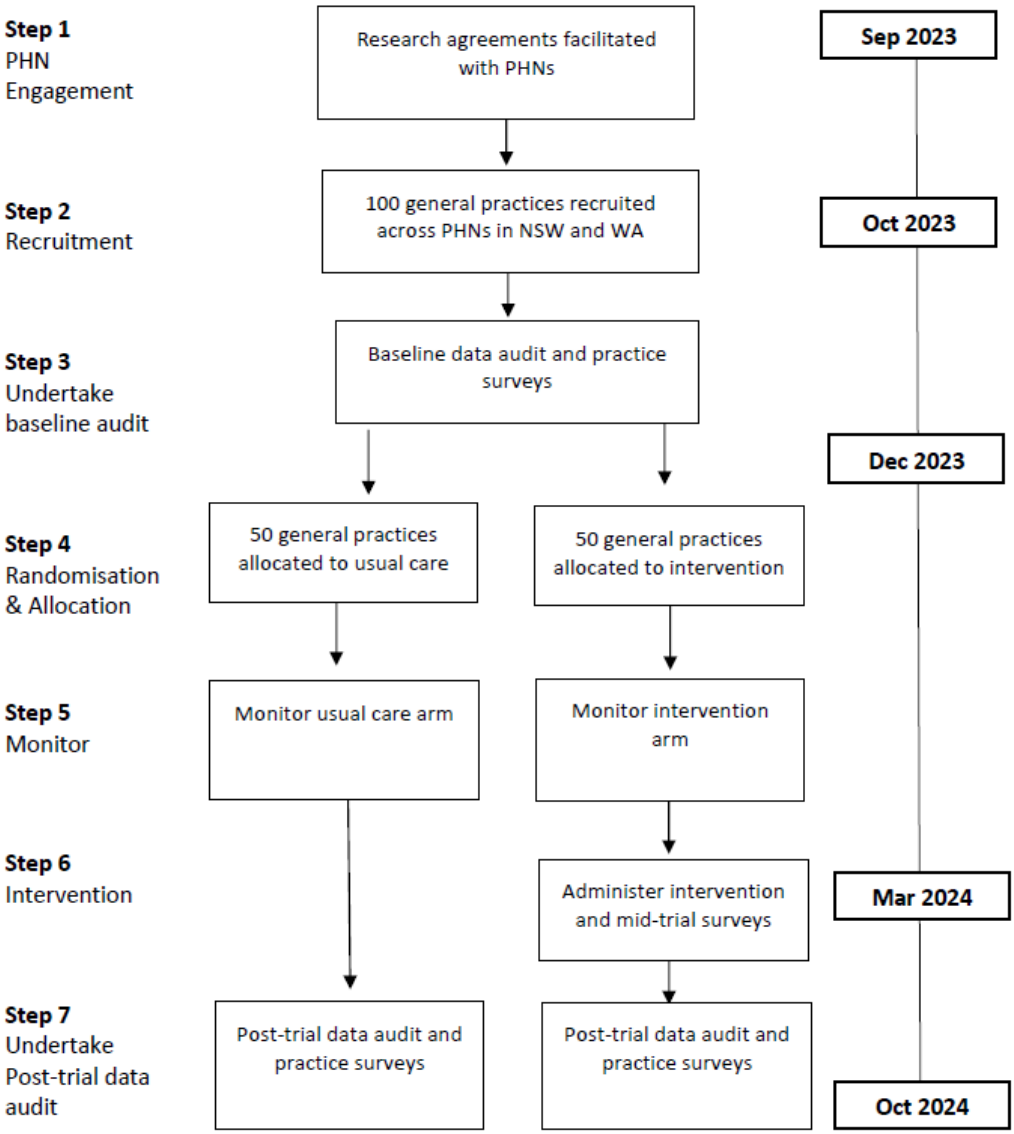
10.2. Trial design

Following recruitment and informed consent, baseline data audits and practice surveys will be undertaken. After baseline data collection, practices will be allocated to the intervention and control arms. After an initial 6 months of usual care in all sites, the intervention will be delivered, and a mid-trial implementation survey undertaken with the intervention sites. At 12 months, the post-trial audit will be undertaken and post-trial surveys to measure the implementation effectiveness and secondary outcomes.

The 6-month period between recruitment and intervention delivery is being used as a **wash out period**. At recruitment, all practices may be exposed or most susceptible to incidental messaging relating to the NBCSP. The wash out period will ensure that we are best able to study the effects of the intervention. During this 6-month period, we will provide briefing and support to the intervention practices via the CTCs.

The flowchart of study procedures is provided in Figure 1 with the trial timeline outlined in the schedule of events (see 10.8). The dates displayed in the Figure 1 timeline are indicative and dependent on HREC approval. No activities will commence without HREC approval.

Figure 1. Trial Flowchart



10.2.1. Intervention

The intervention is a multi-component, co-designed general practice-led intervention designed based on the evidence review and co-design process in the MAIL, GP & SCALE project.

A co-design process with GPs and practice staff (University of Sydney HREC 2022/755) assessed the intervention components to determine their practicability, acceptability, and perceived risk within general practice.

The intervention components are evidence-based and available from existing tools and systems. A brief outline of the intervention components is provided in Table 1 and further description in Appendix 6A._Where required, permission to use resources has bene or will be sought, and the original sources will be appropriately acknowledged. Practices in both the intervention and control arms will have had some level of exposure to NBCSP related material prior to the intervention. Practices of the intervention arm will be actively supported and encourage to use materials and the evaluation will help determine whether it is the added support that improves the use of the available intervention components.

The intervention components will not change but the specific details may be refined over the trial. For example, GP education is a critical component of the intervention and existing educational webinars, resources and factsheets developed by Cancer Council Australia will be used (27). This component may be modified in future as information relating to the National Bowel Cancer Screening Program (NBCSP) are updated. The research team is aware that the NBCSP is currently undergoing review by the Department of Health and Aged Care that may impact the information provided to GPs and any education may require updating. The fundamental component will not change, and updates will be requested as future modifications for committee reviews.

Table 1 Intervention Components

Intervention component	**Target**	**Description**
Decision support tools	GPs and practice nurses	Decision-aids to support GPs/patients determine guideline-appropriate screening pathways.
Electronic point-of-care prompt	GPs	Electronic reminders integrated into CIS
Clinical system enhancement	Whole-of-practice	Use of cancer screening toolkit and clinical audits of patient data to identify under-screened patients and integrate practice CIS with the NCSR
Education	Whole-of-practice	Structured learning to educate on guideline-appropriate screening pathways and access to digital educational resources. This will include communication checklist to address screening barriers in non-participants.
CIS = Clinical Information System used by general practice to store and manage medical record data; GPs = general practitioners; NCSR = National Cancer Screening Registry		

10.2.2. Implementation strategies

A core component of the CTC's role is to support implementation using these strategies. Evidence-based implementation strategies (listed in Table 2) will be used to support the intervention arm by preparing and supporting the general practices in engaging with the intervention. The strategies have been developed against ERIC refined compilation of strategies (13).

Implementation outcomes, the adoption of in-practice activities and implementation strategies to support CRC screening, are also secondary outcomes of the trial.

Table 2 Implementation strategies

ERIC Strategy (13)	**Stage of trial**	**Target of implementation strategy**	**Example**
Alter incentive/allowance structures	During trial	GPs	Work to incentivise the adoption of intervention components by facilitating Continuing Professional Development points for completion. NB: the CTC will highlight the available opportunity for practices to pursue
Audit and provide feedback	During trial	Whole of practice	Provide general practice with bowel cancer screening data performance reports over the trial to increase engagement with intervention components.
Change physical structure and equipment	Pre-implementation	Whole of practice	Support access and distribution of physical NBCSP test kit to be provided in the general practice.
Change record systems	Pre-implementation	GPs	Enable recording of screening behaviours and subsequent recommendations.
Conduct cyclical small tests of change	During trial	Whole of practice	Implement intervention components using small tests of change (by GP) and refine before implementing practice wide.
Conduct educational outreach visits/ meetings	During trial	GPs and practice staff	CTC available via phone or in person to teach participants about intervention components.
Distribute educational materials	During trial	Whole of practice	CTCs to distribute guides to the practice to learn about the intervention components and how to implement them.

Problem solving support	During trial	GPs and practice staff	CTC available via phone or in-person to support practices with challenges implementing the intervention.
Identify and prepare champions	Pre-implementation	GPs and practice staff	Practice trial champion liaising with CTC, supporting intervention activities and overcoming resistance within practice.
Remind clinicians	During trial	GPs and practice staff	CTC reminding participants to use intervention components.
CTC=clinical trial coordinator, GP=general practitioner.			

10.3. Data collection

Data collection, transfer and management will be facilitated by the CTC in conjunction with the PHN (as outlined in the Data Management section below). Table 3 outlines the different methods of data collection for the primary and secondary outcomes.

Table 3 Data collection methods outcomes

Study Outcomes	Time point	Data collection method
Primary Outcomes		
Implementation effectiveness: guideline-appropriate CRC screening recommendation	12-month tracking	Study specific data collection tool integrated into Clinical Information System used in General Practice.
Clinical effectiveness: CRC screening tests completed by patients	12-month tracking	Health analytics/data extraction software used in General Practice.
Secondary Outcomes		
Service outcome: General practice awareness and understanding of guideline-appropriate screening	Pre-, and Post-	Adapted questionnaires (Appendix 4A and 4B)
Implementation outcomes: adoption of in-practice activities and implementation strategies to support CRC screening.	Pre, Mid- and Post-	Adapted questionnaires (Appendix 4C, 4D, 4E and 4F)

10.3.1. Primary Outcomes

- *Implementation effectiveness outcome*

For the implementation effectiveness primary outcome (*number of guideline-appropriate CRC screening recommendations provided*), a study specific data collection instrument will be used and integrated into Clinical Information Systems (CIS) used in general practice. CISs are used by general practices to facilitate care at an individual patient level. Medical records are stored within the CIS and used by GPs to store information during consultations, such as patient bowel cancer screening history. The National Cancer Screening Register (NCSR) integrates with CIS to allow health providers access to patients' NBCSP participation history from within their CIS.

Medical Director is a CIS used widely across Australia and is already integrated into practices across NSW and WA. Medical Director will enter into an agreement with the University of Sydney under a "Education Support – Master Services Agreement". The agreement will include the development of an electronic prompt which will act as a study specific data collection instrument. Medical Director obtains consent from general practices where their software has been installed to participate in research project. Data will be extracted from the general practice CIS via Medical Director and is de-identified, and no identifiable data leaves the CIS. Medical Director data are managed in accordance with relevant privacy and health records legislation.

- *Clinical effectiveness outcome*

For the clinical effectiveness primary outcome of the *number of guideline-appropriate CRC screening tests completed by patients,* de-identified, aggregate patient data will be extracted from CIS. These data will be obtained from the PHN (Health Analytics Software).

PHNs collect data from general practice electronic medical records stored within their CIS through Health Analytics Software tools. The tools used render the data drawn from practice databases unidentifiable, enabling it to be disclosed for research purposes under the Privacy Act 1988 (Privacy Act). PHNs facilitate the licensing of Health Analytics Software to support the extraction, analysis and management of general practice data in the form of population health reports, including bowel cancer screening participation.

Data collection is facilitated by established Data Sharing Agreements between the PHN and general practices within their regions. The Agreement permits the extraction, sharing and use of de-identified practice data to the PHN to support the provision of health services and to improve health policies. The de-identified data may be disclosed to third parties to develop health prevention strategies or support research. PHNs are governed by the PHNs Cooperative's National Data Governance Committee and the PHNs National Data Governance Framework (28). The PHN has ownership and legal accountability of the management and use of the extracted and shared de-identified data through legislative and policy obligations. The software providers are governed by an organisational Privacy Policy related to the collection and storage of de-identified health data (28–30). The software providers encrypt de-identified data for transmission over secure channels.

General practices are required to display privacy notices within the practice of which Health Analytics Software they are using with disclosure that the information is secure and cannot identify patients. Patients may request that the general practice not collect or share their data. It is the responsibility of the general practices to obtain and manage patients' consent for their de-identified data to be shared beyond the practice CIS.

10.3.2. Secondary Outcomes

For the secondary outcomes, questionnaires have been adapted from previous Australian studies to determine these outcomes (18,31). The questionnaires will be conducted at three time points:

1. Pre: on recruitment to determine baseline awareness and existing activities
2. Mid: before the intervention is delivered to determine the potential impact of non-study activities to build awareness and/or encourage CRC screening (if they have been in field)
3. Post: on completion to determine intervention outcomes

A practice 'readiness for change' questionnaire was developed based on the Cancer Institute NSW 'Primary Care Toolkit: readiness checklist' (20). In addition to assessing 'readiness for change' the survey will determine General Practice characteristics and staff demographics. As these items are directly relevant to the trial, all practices in both the intervention and control group are required to complete the questionnaire, pre- and post- intervention delivery by a general practice representative. This questionnaire will take up to 10 minutes to complete and is available in the Appendix 4E and 4F.

Participating clinicians (GPs, nurses) and general practice staff will be invited to complete the 'Awareness and current knowledge of the NBCSP' questionnaire at baseline and trial close, adapted from the South Eastern Melbourne Primary Health Network Evaluation Report 2019 (31). The questionnaire has been adapted to include the validated Influences on Patient Safety Behaviours Questionnaire (IPSBQ) (32). The questionnaire will take up to 20 minutes to complete and is provided in full in Appendix 4A and 4B but will be available via a REDcap link.

Participating clinicians (GPs, nurses) and general practice staff in intervention practices will be invited to complete the implementation outcomes survey. This questionnaire is adapted from the validated Acceptability of Intervention Measure (AIM) scale and will assess the perceive acceptability,

appropriateness and feasibility of intervention by participants (33). The questionnaire will be available via a REDCap link at mid-trial and post-trial and will take up to 10 minutes to complete (see Appendix 4C and 4D).

The surveys and questionnaires used in this trial have been previously used and validated and will be used as published. The CTC will invite general practice participants to participate in the questionnaires at the relevant time points via email that contains a REDCap link (see Appendix 1C). The REDCap link will direct participants to a landing page containing the Participant Information Statement and questionnaire.

10.4. Statistical analysis and data analysis

Descriptive statistics will be used to summarise the general practice characteristics for each trial arm and the outcome results.

Intention-to-treat analysis will be used, where all general practices allocated to the trial group will be included and analysed in the group that they were assigned. Both the primary and secondary outcomes will be compared between the intervention and control groups using poisson or negative binomial regression and generalised linear modelling with an identity link function and binomial family to estimate the odds ratio and difference in proportions respectively. The regression models will use generalised estimating equations with robust standard errors to allow for clustering by general practice and will adjust for the randomisation stratification factors (e.g., practice size, state, rurality, socioeconomic indexes for areas (SEIFA) (34)). Both the relative and absolute measures of the estimated intervention effect will be reported with their respective 95% confidence intervals, and a *p* values calculated from the logistic regression.

The intra-practice correlation, which quantifies the proportion of the total variation in the outcome attributable to between-cluster variation in the outcome will also be estimated using mixed effects modelling and reported with 95% confidence intervals.

Results from the IPSBQ will be analysed using descriptive statistics and multivariate analysis of variance (MANOVA) to assess difference in perceived barriers pre- and post-intervention implementation. Mediation analysis will be performed to assess the degree to which changes in specific barriers influence changes in behaviour (i.e. mechanisms of action).

10.4.1. Guideline-appropriate screening

Guideline-appropriate screening in Australia is determined based on a clinicians' judgement of a patient's risk of CRC and recommendations in the 2017 Guidelines (3). In this study, patients aged 50-74 years will be classified as either guideline-appropriate screeners (those who undergo screening appropriate for their risk level as directed by their GP) or non-guideline-appropriate screeners (encompassing both under-screeners and over-screeners). For a detailed description of the criteria for guideline-appropriate, under- and over- screening (see Table 4). Contingency tables will be generated to represent the proportion of guideline-appropriate screeners and non-guideline-appropriate screeners in each trial arm, risk category, age group and sex.

For the primary clinical effectiveness outcome (*number of guideline-appropriate CRC screening tests completed by patients),* an incremental approach will be used to test the effect of the intervention. The first model (unadjusted model) will use the trial group as the sole fixed predictor. The second model (adjusted model) will add guideline risk category, gender, age, and socioeconomic status of the practice (based on SEIFA (34)) to the unadjusted model. The final model (effect modification model) will look at the interaction between treatment group and risk category to test whether the effect of the intervention was modified by risk category.

If the final model demonstrates significant effect modification, simple post hoc analyses will be performed at each risk level. Comparisons involving categorical predictors with more than two levels

will be corrected using the Westfall method, a step-down form of error correction that offers similar protection against type I error as traditional single-step methods such as the Bonferroni procedure but is less conservative and, therefore, less likely to overinflate p values and conceal genuine effects (35).

Table 4 Guideline-appropriate screening categorisation (3)

Risk category	Not guideline-appropriate/under screening	Guideline-appropriate screening	Not guideline-appropriate
At or slightly above average risk *No FDR or SDR with colorectal cancer* *One FDR with colorectal cancer diagnosed at 55 years or older* *One FDR or SDR with colorectal cancer diagnosed at 55 years or older*	No iFOBT in previous 2 years if 50 -74 years of age	One iFOBT every 2 years. if 50 -74 years of age as part of the NBCSP	More than one iFOBT in previous 2, OR Any colonoscopy
Moderately increased risk *One FDR with colorectal cancer diagnosed under 55 years* *Two FDR with colorectal cancer diagnosed at any age* *One FDR and at least two SDR with colorectal cancer diagnosed at any age*	No colonoscopy in previous 5 years	One colonoscopy every 5 years. CT colonography may be offered if colonoscopy is contraindicated	More than one colonoscopy in previous 5 years, OR iFOBT if colonoscopy has already been performed
Potentially high risk *At least three FDR or SDR with colorectal cancer, with at least one diagnosed under 55 years* *At least three FDR with colorectal cancer diagnosed at any age*	No colonoscopy in previous 5 years	One colonoscopy every 5 years. CT colonography may be offered if colonoscopy is contraindicated	More than one colonoscopy in previous 5 years
FDR = first-degree relative; iFOBT= immunochemical faecal occult blood test; SDR = second-degree relative			

10.5. Allocation and blinding process

Randomisation for this study will be carried out at the level of general practice. Each practice will be allocated to the intervention or usual care arm using a random computer-generated sequence by the Daffodil Centre research team. To account for differences in region-specific NBCSP screening rates, the randomisation will be stratified by participating states (NSW and WA). In each state, the same number of practices will be allocated to the intervention and usual care arms. Accordingly, GPs, general practice staff and their patients will be assigned to the intervention or usual care arm based on the assignment of their general practice.

10.6. Concealment mechanism

General practices will know which arm they have been allocated to, however, due to the nature of the intervention and implementation support, practices may decern their allocation. The statistician and investigators not involved in intervention delivery will be blinded using a code for the two trial groups. The codes for the trial groups will be retained by the CTC. Upon allocation, the CTC will record the practice's code and trial group allocation but will not report the allocation to the statistician.

10.7. Breaking the blind

Allocation of the trial groups will only be revealed to the statistician and investigators after all the primary and secondary outcome data have been collected and the results presented to the investigators.

10.8. Schedule of events

Table 5 Pilot trial schedule of events

	STUDY PERIOD								
	Enrolment		Allocation	Post-allocation					Close-out
TIME POINT**	***Aug 2023***	***Sep 2023***	***Nov 2023***	***Jan 2024***	***March 2024***	***May 2024***	***July 2024***	***Sep 2024***	***Oct 2024***
Visit window	**+/- 30 days**	**+60 days**	**+/- 14 days**	**+/- 60 days**	**+/- 14 days**	**+/- 14 days**	**+/- 14 days**	**+/- 30 days**	**+/- 30 days**
PHN Research Agreement	X								
Recruitment of CTCs	X								
ENROLMENT:									
Eligibility screen		X							
Informed consent		X							
Randomisation / Allocation			X						
INTERVENTIONS:									
Preparation of intervention			X	X					
Delivery of intervention					X				
Ongoing support from CTC (Intervention arm)					X	X	X	X	
Monitoring from CTC (Control arm)					X	X	X	X	
ASSESSMENTS:									
Baseline data collection clinical audit (primary outcome)		X	X						
Baseline surveys (secondary outcome)		X	X	X					
Ongoing data collection (secondary outcomes)				X	X	X	X	X	
Post-intervention data collection clinical audit (primary outcome)									X
Post-intervention surveys (secondary outcome)									X

Note: Pilot trial schedule of events: Study specific adapted from The University of Sydney Clinical Trials Study Protocol template.

10.9. Ethics approval

Ethics approval will be obtained from the University of Sydney Human Research Ethics Committee (HREC) before trial activities are commenced. Site-specific governance will be sought from the relevant PHN Research Governance Organisation (RGO) upon receiving notification of the approval.

10.10. General practice reimbursement

The Research Agreement will set out the trial timeline and expectations of participating practices, as well as how and when the practices will be paid (in two instalments, AUD$1,000 6 months after trial commencement at the point of intervention delivery and $AUD 1,000 upon completion of the trial, $2,000 in total).The costing is in line with appropriate costing for research based in primary care outlined by PC4 ‘A guide to understanding budgets for primary care practice-based research’.

10.11. Monitoring of clinical trial

The Daffodil Centre, a joint venture between Cancer Council NSW and the University of Sydney research team, will monitor this trial. All members of the Daffodil Centre research team will complete Good Clinical Practice training.

The Coordinating Principal Investigator will send monitoring communication, including site visit confirmation emails, agendas, follow-up emails, etc, to the study sponsor and the University of Sydney Clinical Trials Risk and Governance team.

10.12. Continuation of therapy

The trial intervention activities, resources and support will be provided only within the 12-month trial period. The results will ascertain the effectiveness of the intervention and will contribute to the broader MAIL, GP & SCALE project, including a Scale-Up Plan.

Jurisdictional representatives of local health organisations that support the delivery of health programs have contributed to the design of the intervention. They will participate in activities to inform sustainability and scalability.

Resources used within the intervention, such as cancer screening toolkits, educational guides, and reminder prompts are existing and available to General Practice to access and utilise. Upon trial completion these resources will be made available through participating PHN websites and The Daffodil Centre website The Daffodil Centre - The Daffodil Centre. Access links to resources will be disseminated to participating practices via a study-specific newsletter and through bowel screening outlets via the Research Team.

11. Data Management

11.1. Data storage and transfer of data to the Daffodil Centre

11.1.1. Data storage

All study data will be stored on the University of Sydney Research Data Store (RDS) and REDCap during the project and at completion. A project page will be established in the RDS and REDCap. The RDS is a secure, enterprise-grade Network Attached Storage device located within NSW. Study materials will be stored on the RDS during the project.

11.1.2. Process at General Practice Sites

The CTC (i.e., the persons named on the Site-Specific Assessment form) will be appointed as the trial REDCap and RDS Coordinators. The CTCs will oversee data collection, transfer and storage processes for each general practice site assigned to their coordination, n = 25 practices per CTC.

Table 6 summarises the General Practice data sets and storage.

Table 6 Description of General Practice data sets

Dataset	Contains identifiers	Data Custodian	Trial Storage location	Access provided to The Daffodil Centre
National Bowel Cancer Program Screening Data	✓	National Cancer Screening Register	General Practice	X
Clinical Information	✓	General Practice	General Practice	X

Systems software – medical records				
Health Analytics Software – POLAR, PenCS, Primary Sense Aggregate bowel cancer screening reports.	X	Primary Health Network	Research Data Store	✓

- *General Practice data*

The CTCs will work with the General Practice sites to coordinate data extraction within Clinical Information Systems by providing a dictionary of required metrics and practice support. The PHN receives the extracted de-identified data from the General Practice, facilitated through an established data-sharing agreement and Health Analytics Software. Once the de-identified practice data is uploaded to PHN, the PHN owns all rights and interests in and to the de-identified data. The PHN may use the de-identified data for any purposes that contribute to population health care.

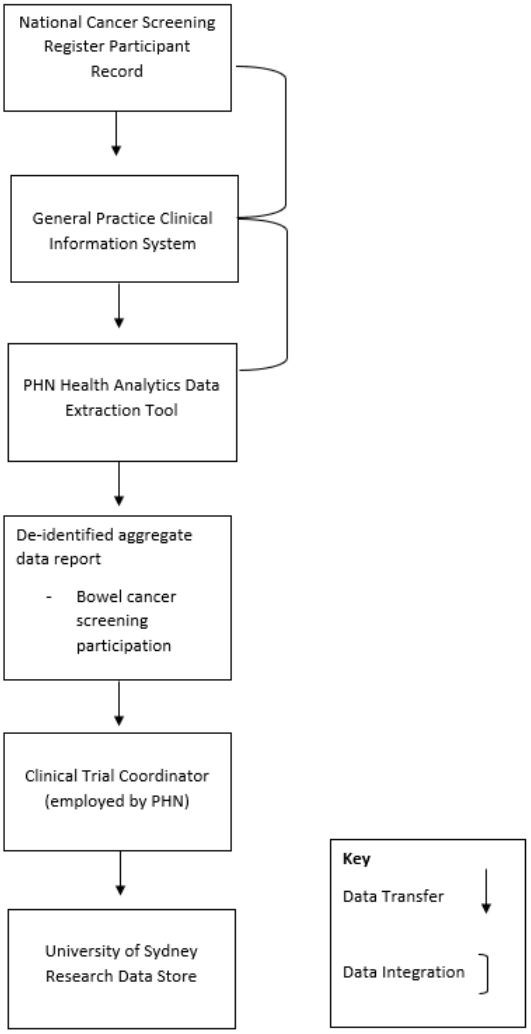
The CTCs will coordinate the upload of extracted data in the form of de-identified aggregated reports from the PHN to the RDS. All data is de-identified - no identifiers (patient name, patient date of birth) will be extracted or included in the data reports. This mechanism means that the patient record data will not leave the General Practice sites. The CTC will not be involved in the de-identification of the patient datasets as the PHN data extraction tools have the required functionality (see section 10.3).

PHN Data Governance Officers will be contacted for advice on organizational procedures for collecting, storing, and transferring de-identified aggregate data reports. The outlined process of data transfer to the RDS will be provided to the PHN Data Governance Officers for advice and modification.

- *Transfer of general practice data to The Daffodil Centre (at CCNSW)*

The de-identified General Practice dataset will be securely transferred in the form of de-identified aggregate reports by the CTCs directly to the RDS. In the event the CTCs are unable to be established as external collaborators on the RDS project, the reports will be shared with the Daffodil Centre (at CCNSW) project team using a protected SharePoint Site administered by the Daffodil Centre, unless another transfer method is advised by the Data Governance Officers of the PHNs such as encrypted files with an encryption key shared separately to the data. CTCs using SharePoint Sites will only be able to access the Site for their designated General Practices. The Daffodil Centre (at CCNSW) project team will upload the de-identified data report to the RDS after the transfer is complete. The data stored on the RDS will be accessible only by the approved Daffodil Centre project team. Figure 2 below summarises the transfer of general practice data to the Daffodil Centre (at CCNSW) project team.

Figure 2 Transfer of General Practice data sets



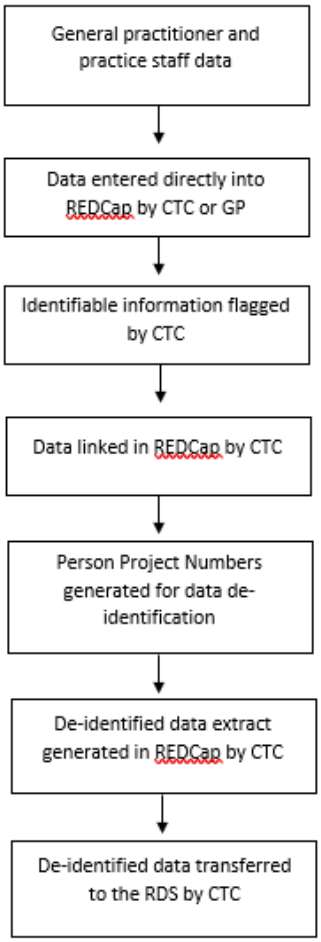
➤ *General practitioner and practice staff data*

Independent REDCap projects will be created for each participating GP or practice staff member. GP and practice staff consent for study involvement will be obtained in REDCap. Once a General Practice has signed a Research Agreement to participate, the CTC will provide the staff members within the General Practice with a link to the REDCap study landing page that includes The Participant Consent form. After individual consent is obtained in REDCap, the CTC will flag identifiable information in REDCap and assign each participant a study-specific project person number (PPN) to create a de-identified dataset within REDCap. The CTC will manage the REDCap projects for their General Practice sites. The CTC will support the collection of data within REDCap at the site during the trial. As data is entered into REDCap for trial monitoring and process evaluation purposes, the CTC will flag the identifiable information, de-identify the data and link the data in REDCap to the PPN.

De-identified data will be retrieved from REDCap by the CTC and stored within the RDS. The REDCap project will be designed to enable data transfer throughout the study to the RDS, for the monitoring of implementation outcomes. The approved Daffodil Centre project team will have access to the RDS data sets. Access to the REDCap project will be restricted only to the CTCs. CTCs will be unable to access data and study files for other general practice sites enrolled in the study.

Figure 3 is provided at the end of this section summarising the transfer of datasets for the sub-study process evaluation described above.

Figure 3 Transfer of GP, practice staff data



11.2. Data governance at The Daffodil Centre (CCNSW office)

11.2.1. Data access, use and disclosure

Only research personnel (as approved by ethics) will have access to stored REDCap and RDS data. All staff in The Daffodil Centre are required to: (1) sign an undertaking which outlines information privacy and confidentiality requirements upon commencement of employment; and (2) sign an undertaking to confirm that they have read, understood and accepted their obligations set out in The Daffodil Centre's guidelines. The guidelines are guided by the National Statement on Ethical Conduct in Human Research and the Australian Code for the Responsible Conduct of Research.

11.2.2. Data retention

In accordance with the NHMRC/ARC Australian Code of the Responsible Conduct of Research (2007), RCT data will be stored for a minimum of 15 years after the completion of the project and the publication of results. After this time all electronic files stored on the local network will be deleted. Data disposal. Only electronic files will be used in this study to eliminate the need for paper-based file storage and destruction.

At the end of the retention period, disposal of research data will be authorised and documented. Authorisation to destroy the research data will be undertaken with the confirmation of the University Disposal Officer.

12. Ethical considerations

The study will be coordinated by the research team based at The Daffodil Centre (at CCNSW). The Daffodil Centre research team will maintain regular weekly contact to monitor adherence to the research protocol and to ensure that the study is running smoothly and that recruitment is on target. Protocol violations or operational issues will be discussed and resolved at project team meetings, with appropriate reporting to the University of Sydney CTSO. The study will be conducted according to the NHMRC National Statement on Ethical Conduct in Human Research (2007 and updates) and the World Medical Association Declaration of Helsinki (2013 and updates). Ethics approval from the Human Research Ethics Committee (HREC) at The University of Sydney will be obtained prior to study commencement.

This study is non-invasive and, has minimal risk to patients and participating general practices and general practice staff. The intervention aims to increase bowel cancer screening within the Australian Colorectal Cancer Guidelines (3) through a combination of provider prompts, clinical audit and feedback activities and provider education. GPs will be encouraged to defer to their clinical judgement and what (if any) screening recommendations they provide to their patients.

12.1. Modifications to the protocol

Modifications to the protocol will be communicated to The Daffodil Centre (at CCNSW) research team (associate and chief investigators) by email and quarterly meetings. The Daffodil Centre research team will meet weekly to discuss any modifications to the trial protocol and updates on data collection and intervention delivery. The CPI will liaise with the funding body (NHMRC) and the ANZCTR to communicate modifications to the protocol or progress as necessary. All protocol amendments will be reported to the University of Sydney HREC, as per HREC requirements.

12.2. Protocol violations, deviations and suspected serious breaches in clinical trial

Protocol violation refers to any deviation, change or departure from the HREC-approved protocol that does not have prior approval by the HREC unless the change is necessary to remove an apparent immediate hazard to one or more study participants. Any protocol violation will be documented in the study files and reported to the University of Sydney Clinical Trials Support Office (CTSO) by the CPI.

The CPI will be responsible for reporting protocol deviations on an annual basis to the CTSO with the Annual Report. Site staff or a study monitor may document protocol violations in the study files and prepare the protocol deviation form, but this form will need to be signed by the CPI. This form will be kept in the trial master file for each relevant site. Once signed by the CPI, a new form will be required for any further breaches.

If changes need to be made to the Protocol, Participant Information Sheet and Consent Form(s) or any other documents approved by the HREC, then the amended document(s) will be submitted along with a HREC Amendment Form for review by the HREC.

All suspected and/or confirmed serious breaches to the study protocol will be reported to CTSO as soon as possible, and no later than 72 hours after the CPI becomes aware of the breach.

Where it is suspected that the deviation or breach of GCP may be serious, i.e. likely to affect to a significant degree:

(a) the safety or rights of a trial participant, or

(b) the reliability and robustness of the data generated in the clinical trial

this will be reported as per the (suspected) serious breaches in approved clinical trials timelines (see Table 7 below).

Should the deviation or breach raise a significant safety issue, this will also be reported to the University as per the safety reporting guidelines. Where the suspected breach has been notified to the approving HREC by a third party, the CPI will be responsible for liaising with the HREC and advising the University of any outcomes. The CPI will be responsible for providing any follow-up information as required by the University and/or approving HREC.

As this trial will not involve any therapeutic goods or medical devices, no Therapeutic Goods Administration CTN/CTA scheme reporting requirements exist.

Table 7 Serious breach reporting timelines for trials conducted at external sites with USYD as a sponsor

Event	CPI reporting to the CTSO	How this will be reported
Suspected serious breach	As soon as possible BUT no later than 72 hours of the CPI becoming aware of the breach	Protocol deviation/violation form (or similar) and related correspondence to CTSO and external sponsor (if applicable).
Confirmation of serious breach	Within 7 days of confirming serious breach	Copy of correspondence provided to HREC together with acknowledgement
Third party notifications to HREC of suspected serious breach.	Within 7 days of confirming serious breach or findings that the notified breach is not a breach	Copy of correspondence provided to HREC together with acknowledgement.
CPI=Coordinating principal investigator, CTSO=Clinical Trials Support Office, HREC=Human Research Ethics Committee, RGO=Research Governance Organisation, SAE=Significant Adverse Event, SSI=Significant Safety Issue, URSAE= Unexpected and related serious adverse event.		

National Health and Medical Research Council (NHMRC) 2018 Reporting of Serious Breaches of Good Clinical Practice (GCP) or the Protocol for Trials Involving Therapeutic Goods.

13. Safety considerations

13.1. Assessment and documentation of adverse events

The CPI will ensure the assessment and documentation of adverse events over the trial duration. Site staff, CTCs or a study monitor may document Serious Adverse Events (SAE), Significant Safety Issues (SSIs), Unexpected and Related Serious Adverse Events (URSAE) and Urgent Safety Measures (USM) and prepare the relevant SAE or notification of SSI forms, but these forms will need to be signed by the CPI. In the event of an SAE or SSI, the CPI will report to the Research Governance Office (RGO, i.e. PHN) for the general practice site where the event occurred. A copy of the Report submitted to the RGO and acknowledgement will be forwarded to the CTSO upon receipt.

13.2. Eliciting adverse event information

The Daffodil Centre staff/students working on this trial at external sites will be required to comply with the reporting requirements of the sponsor, USYD and the external Research Governance Organisations (RGO, i.e., the PHNs and participating general practices). The CTCs will be required to keep a comprehensive project log of trial activities, where they must track any information relating to adverse events. They will be required to report this information to the Daffodil Centre research team.

13.3. Adverse event reporting including any special requirements for serious or significant adverse events

The CPI is responsible for all safety reporting to the University of Sydney HREC, as per HREC requirements. In addition to annual safety reports, the CPI will report any:

(a) Serious Adverse Events

(b) Significant Safety Issues (SSIs) that result in:

(i) implementing of an Urgent Safety Measures (USM) not defined by the protocol to protect participant's health and safety.

(ii) amendment(s) to the approved protocol.

(iii) temporary halts to the trial for safety reasons.

(iv) early termination of the trial for safety reasons.

(e) Unexpected and Related Serious Adverse Events (URSAE)

These must be reported as per the timeline and reporting requirements of the CTSO. To report an SSI or SAE, the CPI will complete the Significant Safety Issue form or Serious Adverse Event Form as applicable, which is available from the CTSO intranet.

If the CPI reports an USM, this will first be reported by email to clinical-trials.research@sydney.edu.au with "URGENT SAFETY MEASURE" in the subject line, followed by submission of a Significant Safety Issue Form.

As this trial will not involve any therapeutic goods or medical devices, there are no Suspected Unexpected Serious Adverse Reactions (SUSAR) or Unanticipated Serious Adverse Device Effects).

Table 8 Safety reporting timelines for trials conducted at external sites with USYD as a sponsor

Event	CPI reporting to the CTSO	How this will be reported
Annual Safety Report (cumulative AE and SAE line listings)	Annually within the annual progress report	Copy of report submitted to reviewing HREC and acknowledgement by HREC
SAEs where reporting to CTSO is mandated (refer section 3).	As soon as possible BUT no later than 24 hours of the CPI becoming aware of the SAE	Submission of Serious Adverse Event Form to CTSO
SSI implemented as an Urgent Safety Measure	As soon as possible BUT no later than 24 hours of the CPI becoming aware of the USM.	CPI to report to the Research Governance Office (RGO) for site where event occurred. A copy of the Report submitted to RGO together with acknowledgement should be forwarded to CTSO upon receipt.
SSI implemented as a: - Notification of an amendment - Temporary halt of a trial for safety reasons - Early termination of trial for safety reasons	Within 72 hours of the CPI aware of the SSI.	CPI to Report to the RGO for Site where event occurred. A copy of the Report submitted to RGO together with acknowledgement should be forwarded to CTSO upon receipt.

URSAE occurring at the site	As soon as possible BUT no later than 72 hours of the PI becoming aware of the URSAE	CPI to Report to the RGO for Site where event occurred. A copy of the Report submitted to RGO together with acknowledgement should be forwarded to CTSO upon receipt.
AE=adverse event, CPI=Coordinating principal investigator, CTSO=Clinical Trials Support Office, HREC=Human Research Ethics Committee, RGO=Research Governance Organisation, SAE=Significant Adverse Event, SSI=Significant Safety Issue, URSAE= Unexpected and related serious adverse event.		

14. Funding

This study is part of the MAIL, GP & SCALE project and is funded by the National Health and Medical Research Council Targeted Call for Research into Participation in Cancer Screening Programs 2021, grant number 2021/GNT2014964.

15. Publication policy & dissemination of results

One or more publication(s) will be produced outlining the study findings of the RCT and process evaluation. These publications will be published in peer-reviewed academic journals. All information will be provided so that participants cannot be identified.

A lay summary of findings will be provided to the PHNs and participating general practices. The lay summary of findings will contain a link to the peer-reviewed academic publication.

As part of the MAIL, GP & SCALE project, the results from this trial will be incorporated into a predictive model of bowel cancer in Australia (*Policy-1-Bowel*) to conduct effectiveness and cost-effectiveness analyses. This will be used to determine the optimal combination of interventions to increase participation in the NBCSP and make a policy recommendation for a national scale-up plan.

The CPI will oversee all publications. Acknowledgements, authorship and copyright obligations will be determined before publication and dissemination of study results.

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17. Document version history

Title	Clinical Trials Protocol – Non-drug / Non-device			
Version	**Author**	**Modifications made**	**Date**	**Status**
1	A/Prof Eleonora Feletto	Initial Submission	10 July 2023	Draft
2	A/Prof Eleonora Feletto	Amendment	08 August 2023	Draft
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