SUPPORTING UPTAKE OF BREAST CANCER PREVENTION MEDICATIONS AND MINIMISING TREATMENT DISCONTINUATION: A PROCESS EVALUATION

Version 5, 6 March 2025

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VERSION HISTORY

Version 5, 06 March 2025 The primary reason for this protocol amendment is the addition of Aim 8; i.e. to evaluate persistence with RRMeds for women who choose to commence a preventive medication. This involves data collection at two additional time points (2 years and 4.5 years). In addition, editorial changes have been made following a comprehensive review of the protocol to amend minor in-text errors and promote greater clarity. This includes clarifying the time point for inviting eligible clinicians to complete a questionnaire and (optional) semi-structured interview.	
Applicable section number(s)/title	**Nature of revision**
BACKGROUND **1.3 Use of Breast Cancer Risk-Reducing Medications in Australia**	The definition of "persistence" has been added to this section to promote clarity.
AIMS **2.2 Specific Aims**	"Aim 8" has been added to the protocol to evaluate women's persistence with RRMeds at 2 years and (for those women planned for a 5 year course) 4.5years after commencement of the RRMed. Persistence with RRMeds is vital information given these medications are given for 3-5 years and low persistence has been identified as an in issue in previous research. Prior versions of the protocol have recognised persistence as an important issue; however, the addition of this aim was only felt to be of value if uptake of RRMeds was relatively high. Preliminary data is now suggestive that collection of persistence data would be valuable given the high rates of uptake of RRMeds for women who attend the PCMed Intervention.

METHODS 3.2 Participants iii) Active follow up	Additional information is provided in this section to promote clarity around the participants who will receive phone calls during active follow-up and the timing of these phone calls. This includes the addition of follow-up phone calls to women who commence RRMeds at 2yrs and 4.5 yrs (the later being relevant only to women planned for a 5 year course) which is relevant to data collection for Aim 8.
3.2.2 Eligibility of Clinicians	Minor editorial change to clarify the recruitment process for Eligible Clinicians.
3.3 Identification of Eligible Women and Clinicians 3.3.3.2 Recruitment of Women to Participate in Aim 8.	Given that Aim 8 was added to the protocol in March 2025, this section has been added to provide clarity regarding the reconsent process for women who were recruited to the study prior to the addition of Aim 8.
3.3.4 Recruitment of Clinicians (Aim 5)	Minor editorial change. For "eligible clinicians", participant recruitment and completion of the intervention (questionnaires and semi-structured interviews) has been defined in previous versions of the protocol as being "at the end of the study period". For clarity, "at the end of the study period" in this context, refers to when sufficient clinicians have made referrals to the Service that it is feasible for the sample size to be met. The wording of the protocol in this section (3.3.4) and other relevant sections (3.2, 3.5.3, 3.6.2, 4.0) has been changed to reflect this.
3.5 Study Consent Process 3.5.2 Dual Opt-out and Opt-In Consent for Women who attend the PCMed Service	Minor editorial change to reflect that women will be asked to consent to follow-

	up phone calls at 2 years and 4.5years (for women planned for a 5 year course) if they choose to commence a RRMed.
3.6 Data Collection 3.6.2 Prospective Data Collection	"Data Collection at 2 years" and "Data Collection at 4.5 years" are new sections that have been added to reflect data collection at these time points for Aim 8.
4.0 ENDPOINTS 8) Persistence	The addition of Endpoint 8 has been made to reflect data collection specific to Aim 8.
5.0 STATISTICAL ANALYSIS AND SAMPLE SIZE CONSIDERATIONS 5.2.3 Aim specific analyses	The plans for statistical analysis of data collected for Aim 8 have been described.
REFERENCES	Updated for clarity.
APPENDICES Appendix A – The PCMed Service Intervention Appendix F – Email invitation for semi-structured interview for Clinicians Appendix G – Telephone scripts for data collection at 6 and 12 months, 2years and 4.5years.	References updated for clarity. Minor editorial changes have been made to the wording in Appendix F "Email to Clinicians" to improve clarity. Updated to include a telephone script to reconsent women for ongoing participation in the study (where relevant) if they had already provided consent prior to this Protocol Amendment (March 2025). Appendix G has also been updated with a telephone script for the planned phone calls at 2years and 4.5years.
PATIENT INFORMATION AND CONSENT FORM	Updated to reflect the addition of Aim 8 to the protocol.

Version 4, 8 August 2024 The primary reason for this protocol amendment is to elaborate on the methods for the semi-interviews evaluating the acceptability of the PCMed Service. In addition, editorial changes have been made following a comprehensive review of the protocol to amend minor in-text errors and promote greater clarity.	
Applicable section number(s)/title	**Nature of revision**
STUDY GLOSSARY	Addition of the term "Catchment Clinics". This term refers to the specialty clinics relevant for aims 1 and 2 of the study. The term has replaced the need to name the individual specialty clinics throughout the study protocol. These minor editorial changes are not referred to again in this document.
BACKGROUND **1.1 Breast Cancer Overview** **1.2 Barriers to Clinicians Discussion and Prescribing Risk-Reducing Medications** **1.8 The PCMed Service Responds to the Evidence-Implementation Gap** **1.9 Embedding Health Services Research into the PCMed Service**	Update of in-text citations to reflect changes in References. In-text citations amended due to error in previous protocol. Abbreviations of services inserted. Addition of in-text citation previously omitted.
AIMS <u>2.2 Specific Aims</u>	Rewording of Aims to promote clarity.
METHODS **3.2 Participants** iii) Active follow-up <u>3.2.1 Eligibility of Women</u>	Additional information provided to promote clarity around the participants who will receive phone calls during active follow-up and the timing of these phone calls. Separation of eligibility criteria for women in the prospective and retrospective components to provide further clarity. Change of female to "assigned female at birth".

3.3.3.1 Recruitment of women for the PCMed Service Acceptability Interview	New section expanding on the methods for interviews, in particular the recruitment and sampling strategy.
3.3.4 Recruitment of Clinicians (Aim 5)	Addition of information provided on the recruitment and sampling strategy.
3.5 Study Consent Process 3.5.3 Clinicians	Option for clinicians to indicate on the TFA questionnaire if they wish to be approached for the interview has been removed. All eligible clinicians will be invited to participate in an interview by email.
3.6 Data Collection 3.6.1 Historical Cohort (retrospective component) for Aim 1	Addition of parity due to accidental omission.
3.6.2 Prospective Data Collection *Data Collection at 12 months*	Rewording of section to promote clarity.
Interviews with Women	Additional information provided on the development of the interview guide for women and software to be used in the thematic analysis.
Interviews with Clinicians	Additional information provided on the development of the interview guide for clinicians and software to be used in the thematical analysis.
4.0 ENDPOINTS 5) Acceptability	Addition of Endpoints for semi-structured interviews.
6) Evaluation of service delivery	Minor editorial changes to improve clarity. Change in timeline with all variables to be assessed at the end of the study period.
5.0 STATISTICAL ANALYSIS AND SAMPLE SIZE CONSIDERATIONS 5.2.3 Aim Specific analyses	

Aim 5	Additional information inserted on data analysis for interviews.
REFERENCES	Reference 1 and 2 updated to reflect.
APPENDICES **APPENDIX A: THE PCMED INTERVENTION** **Eligibility for PCMed Service**	The insertion of new documents Removal of criteria that women (in the prospective component) needs to be an existing patient of the PMCC Family Cancer Centre (FCC), Breast Unit (BU) or Late Effects Clinic (LEC) or external GP or RMH FCC or BU or RWH BU to reflect current practice (that is, the PCMed Service accepts referrals if all other eligibility criteria met). Some minor editorial changes.
APPENDIX E: TFA Questionnaire for Clinicians	Question 9 asking clinicians if they consent to being approached for a phone interview has been removed. All clinicians will be contacted via email and invited to participate. Consent is implied if they choose to participate in the interview.
APPENDICES	Development of new documents pertaining to the semi-structured Interviews. 1. Telephone call to request and consent participants participation in semi-structured interviews" (APPENDIX C). 2. Email inviting clinicians to participate in semi-structured interview (APPENDIX F). 3. Interview Guide for semi-structured interview with women (APPENDIX I). 4. Interview Guide for semi-structured interview with clinicians (Appendix K).
LIST OF APPENDICES	Renaming of Appendices due to the insertion of the new documents above.
VERSION CONTROL Initial PCMed Service Protocol Version 3, 20 September 2023.	Renamed PCMed Service Protocol Version 1, 20 September 2023 due to error.

PCMed Service Protocol Version 4, 27 November 2023. PCMed Service Protocol Version 5, 14 March 2024.	Renamed PCMed Service Protocol Version 2, 27 November 2023. Renamed PCMed Service Protocol Version 3, 14 March 2024.

Version 3, 14 March 2024 Changes to the protocol are summarised below.
Primary reason for the protocol amendment was the addition of Royal Melbourne Hospital Familial Cancer Centre (RMH FCC) as a study site to improve recruitment for Aims 1 and 2 (see sections 2.2; 3.3.1 and 3.3.2). Addition of reason for declining referral to the PCMed Service if readily available (section 3.3.2, paragraph 2).

Version 2, 27 November 2023 Changes to the protocol are summarised below
Minor editorial changes have been made to two documents, The “Explanatory Pamphlet” and Appendix C Initial Consultation appointment letter with PICF with the later document renamed to “Research Invitation with PICF”. The minor changes were a result of consumer feedback received when consumer testing of our processes for intake into the Preventing Cancer with Medications (PCMed) Service were undertaken and to accommodate the capability of the REDCap database which was built after initial ethics submission.

Version 1, 20 September 2023
Initial Creation

STUDY GLOSSARY

Term	Definition
Active follow-up	This is the phase where women who attend the PCMed Service and consent to the study are followed up with a questionnaire, phone calls and an optional telephone interview
AH	Atypical hyperplasia
AIs	Aromatase inhibitors
BU	Breast unit
Catchment Clinics	Catchment clinics refers to the Royal Melbourne Hospital Familial Cancer Clinic (RMH FCC), the Peter MacCallum Cancer Centre Familial Cancer Centre (PMCC FCC), the PMCC Breast Unit (PMCC BU) and Peter MacCallum Late Effects Clinic (PMCC LEC).
DCIS	Ductal carcinoma in situ
EMR	Electronic medical record
EPIC	The database management system for electronic medical records
FCC	Familial cancer centre
GPs	General practitioners
Initial Consultation	The first consultation in the PCMed Service in which the woman will receive personalised information on her breast cancer risk and the pros and cons of risk-reducing medications
LCIS	Lobular carcinoma in situ
LEC	Late-effects clinic
NWAU	National Weighted Activity Unit - a measure of health service activity, expressed as a common unit, against which the National Efficient Price (NEP) is paid
Parkville Precinct	Hospital network consisting of the Peter MacCallum Cancer Centre, Royal Melbourne Hospital and Royal Women's Hospital
PCMed Service	Preventing Cancer with Medications Service
PICF	Participant information and consent form
PMCC	Peter MacCallum Cancer Centre
Post-Prescription Consultation	A planned consultation after a prescription for risk-reducing medication is provided to a woman. This will be booked 8-10 weeks after commencing this medication
Post-Prescription Consultations (ad hoc)	Unplanned consultations requested by the of the woman or her referring clinician or GP to address concerns during the treatment period
Pre-Service Questionnaire	A form to be completed by women prior to attending the Initial Consultation. This form will request information to confirm eligibility for the PCMed Service and help to streamline the Initial Consultation
PURN	Patient Unit Record Number
REDCap	A secure web platform to capture data for research purposes
Repeat Consultation	A subsequent consultation for women who did not take a prescription at the Initial Consultation. This will generally occur within 3 months from the Initial Consultation
Risk Assessment Tool	Online tools that enable healthcare professionals to calculate an individual's future risk of breast cancer risk, e.g., CanRisk, iPrevent, IBIS Breast Cancer Risk Evaluation Tool
Risk Management Consultation	Consultation with the referring clinic where information is provided on a woman's personal risk of breast cancer and options to manage this risk
RMH	Royal Melbourne Hospital
RRMeds	Risk-reducing medications
RWH	Royal Women's Hospital
SERMs	Selective estrogen receptor modulators

SEIFA	Socio-Economic Indexes for Areas ranks areas according to socio-economic advantage or disadvantage using Census data
TFA	Theoretical Framework of Acceptability

1.0 BACKGROUND

1.1 Breast Cancer Overview

Breast cancer is a major public health problem in Australia. It is the most common cancer in women and is the leading cancer cause of disease burden[1]. In 2018, the average lifetime risk (before age 80 years) for a breast cancer diagnosis in Australian women was 11.6%[1]. However, approximately 20% of women are at considerably higher risk due to either genetic or non-genetic factors[2]. Importantly, many breast cancers can be prevented[3].

1.2 Breast Cancer Risk-Reducing Medications Overview

One strategy found to be efficacious to prevent breast cancer is the use of cancer preventing medications. These risk-reducing medications (RRMeds), a single tablet daily, can reduce the relative risk of breast cancer by 30%-60% if taken for 3-5 years[4-13]. RRMeds include the selective estrogen receptor modulators (SERMs), tamoxifen and raloxifene, and the aromatase inhibitors (AIs), anastrozole and exemestane. Tamoxifen is the only RRMed that is appropriate for pre- or peri-menopausal women. Post-menopausal women can choose between the SERMS or the AIs. These medications are often well-tolerated. The most common side-effects are vasomotor symptoms, but there are a range of other possible side-effects depending on which drug is chosen[4-13]. They can also have rare serious side-effects; tamoxifen increases the risk for endometrial cancer in post-menopausal women and both SERMs increase thrombosis risk, while the AIs increase risk of osteoporosis[4-13]. Guidelines recommend consideration of RRMeds for Australian women who have a breast cancer risk that is at least 1.5 times the population risk [14-16].

1.3 Use of Breast Cancer Risk-Reducing Medications in Australia

Despite evidence and guidelines supporting the use of RRMeds, currently only 2% of Australian women, who know they are at increased risk for breast cancer, have used prevention medications[17]. International data also reports low uptake of RRMeds in women with uptake around 8.7% in non-trial settings[18]. For women who use preventative medications, long term persistence is an important factor to ensure women experience the full preventative effect of the medication. Persistence is defined as the act of continuing the medication for the defined duration. A meta-analysis examining data on persistence found low long-term persistence, with persistence declining over time [18]. Trials with 5-year follow up data, found long-term persistence with tamoxifen ranged from 61% to 81%, with several studies reporting lower persistence with tamoxifen compared to the placebo and raloxifene arms,[18] suggesting side effects may be a contributing factor. Some studies suggested persistence with RRMeds was higher in woman with lower depressive symptoms with no sociodemographic factors associated with persistence [18]. Data suggests providing the opportunity for a personalised discussion including the risks and benefits of RRMeds and the provision of ongoing specialist support for women using RRMeds may be of benefit.

1.4 Barriers to Use of Risk-Reducing Medications by Women at Increased Risk

Most women at increased risk of breast cancer have never heard of RRMeds [19]. Lack of awareness of their existence is obviously a strong barrier to using these medications. In our research, among women who knew of their existence, lack of information and concern

about side-effects (which is potentially exacerbated by lack of information) are both strong barriers to using these medications[19]. These barriers for women may, at least in part, be consequences of lack of clinician knowledge (see Section 1.5) with resultant inability of clinicians to impart tailored and appropriate information to each woman.

1.5 Barriers to Clinicians Discussing and Prescribing Risk-Reducing Medications

In Australia there is a major gap in terms of a medical workforce that is willing to manage women at moderate risk of breast cancer (i.e., 1.5-3 times population risk). These women are key candidates for cancer preventing medications, as surgical prevention is usually not appropriate for this risk level, and RRMeds are efficacious in this subgroup. Our research has shown that breast surgeons and Family Cancer Clinicians consider that they do not have capacity to manage moderate-risk women (as they are already at full capacity managing women with breast cancer and high-risk women respectively)[20], and that general practitioners (GPs) generally lack the knowledge to manage them[21]. Thus, most of these women do not get a risk-reducing intervention, despite the fact that almost 50% of breast cancers occur in this group. This is a major unmet need in breast cancer control.

At least one third of GPs who manage women at increased risk of breast cancer are unaware that RRMeds exist. GPs who <u>are</u> aware of these medications generally do not feel they have the required knowledge about the medications to initiate them for their patients[19]. In fact, only 3% of GPs feel "very confident" in providing information to women about these medications, and only 31% of GPs felt it was their role to write an initial prescription. Not enough knowledge or training was the strongest barrier to prescribing for 60% of GPs.

For breast surgeons who manage women at increased risk of cancer, only 3% had never heard of RRMeds and 56% felt "very confident" in providing information to women about these medications. Most (81%) were willing to write an initial prescription, although only a minority (43%) thought it was their role to write ongoing scripts. The major barrier to prescribing for breast surgeons was concern about the side-effects of the medications; this was the strongest barrier for 40%. The next most common strongest barrier was lack of knowledge or training (15%). An important minority (14%) identified lack of time in a consultation as the strongest barrier[19].

We have also previously shown that most Family Cancer Clinicians have never prescribed RRMeds and that, again, lack of knowledge is a major barrier to these clinicians even discussing the subject with women[20].

1.6 Specialist Support a Key Facilitator for Clinicians to Discuss and Prescribe Risk-Reducing Medications

The ability to access specialist support and clear guidance was identified by 59% of GPs and 27% of breast surgeons as the strongest potential facilitator for prescribing RRMeds[19].

1.7 The Evidence-Implementation Gap

Thus, currently there is a large evidence-implementation gap, with few women being offered RRMeds despite their clear efficacy and guidelines that suggest they are a standard

of care option. Our research suggests that lack of a medical workforce capable of, and willing to, discuss and initiate prescription of these medications is a major driver of this evidence-implementation gap.

Given the sparse uptake of RRMeds across the Australian community currently, it is unlikely that socioeconomic, cultural, and linguistic factors currently play a major role. A UK study revealed no socio-demographic determinants of cancer preventing medication uptake, but all participants had to have been to a clinic to discuss their breast cancer risk[23]. Interest in having a personal breast cancer risk assessment is greater in women on higher incomes[24], so any strategy to increase uptake of RRMeds should evaluate whether uptake is influenced by these factors.

1.8 The PCMed Service Responds to The Evidence-Implementation Gap

As a response to our research showing that lack of workforce capability is at least in part driving the identified evidence-implementation gap, and following stakeholder consultation, the Peter MacCallum Cancer Centre (PMCC) will launch the novel Preventing Cancer with Medications (PCMed) Service (see Appendix A). This Service will be a consultative telehealth Service with the primary aim of initiating evidence based RRMeds for women at increased risk of breast cancer and supporting women and their referring clinicians and GPs throughout the prolonged treatment period.

In the initial phase covered by this research protocol, the Service will accept women referred by specialists from the Familial Cancer Centre (FCC), Breast Unit (BU), and Late Effects Clinic (LEC), within the Parkville Precinct (PMCC, Royal Melbourne Hospital (RMH) and Royal Women's Hospital (RWH)), as well as from doctors external to these sites. These will be women at increased risk of breast cancer due to a family history of the disease, a personal history of lobular carcinoma in situ (LCIS) or atypical hyperplasia (AH), or history of chest irradiation. It is expected that women attending the aforementioned clinics will have a discussion regarding their breast cancer risk and possible risk management options (subsequently referred to in this protocol as the "Risk Management Consultation"). If eligible for referral to the PCMed Service, they will receive information on the PCMed Service (verbal and a pamphlet), and a referral will be generated as appropriate.

1.9 Embedding Health Services Research into the PCMed Service

This protocol describes research that will be conducted to evaluate the implementation of the new PCMed Service, which is a complex intervention. Figure 1 describes a Knowledge to Action Framework, which is a conceptual framework that can be used to describe the concept of moving knowledge into action[25]. It integrates the roles of knowledge creation (depicted in the centre of the below diagram) and knowledge application (labelled the 'Action Cycle'). Figure 2 illustrates the adaption of the Knowledge to Action Framework to RRMeds for breast cancer and highlights how and where the study described in this protocol fits. As detailed in the overview above, the knowledge creation component for breast cancer RRMeds is complete (although of course knowledge is always being honed). This protocol specifically relates to the components of the action cycle highlighted in the red boxes in Figure 2.

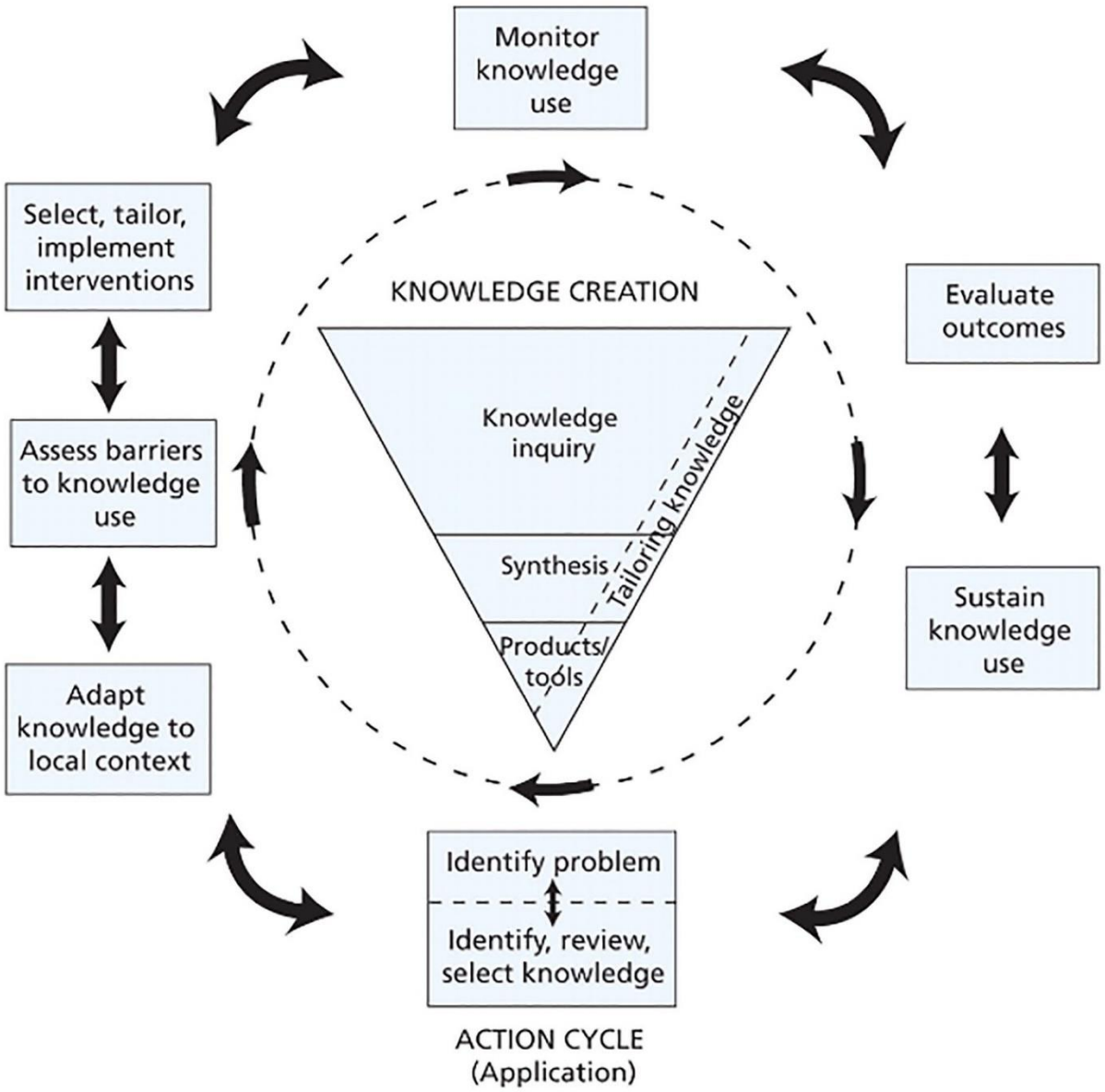

Figure 1: The Knowledge to Action Process[25]

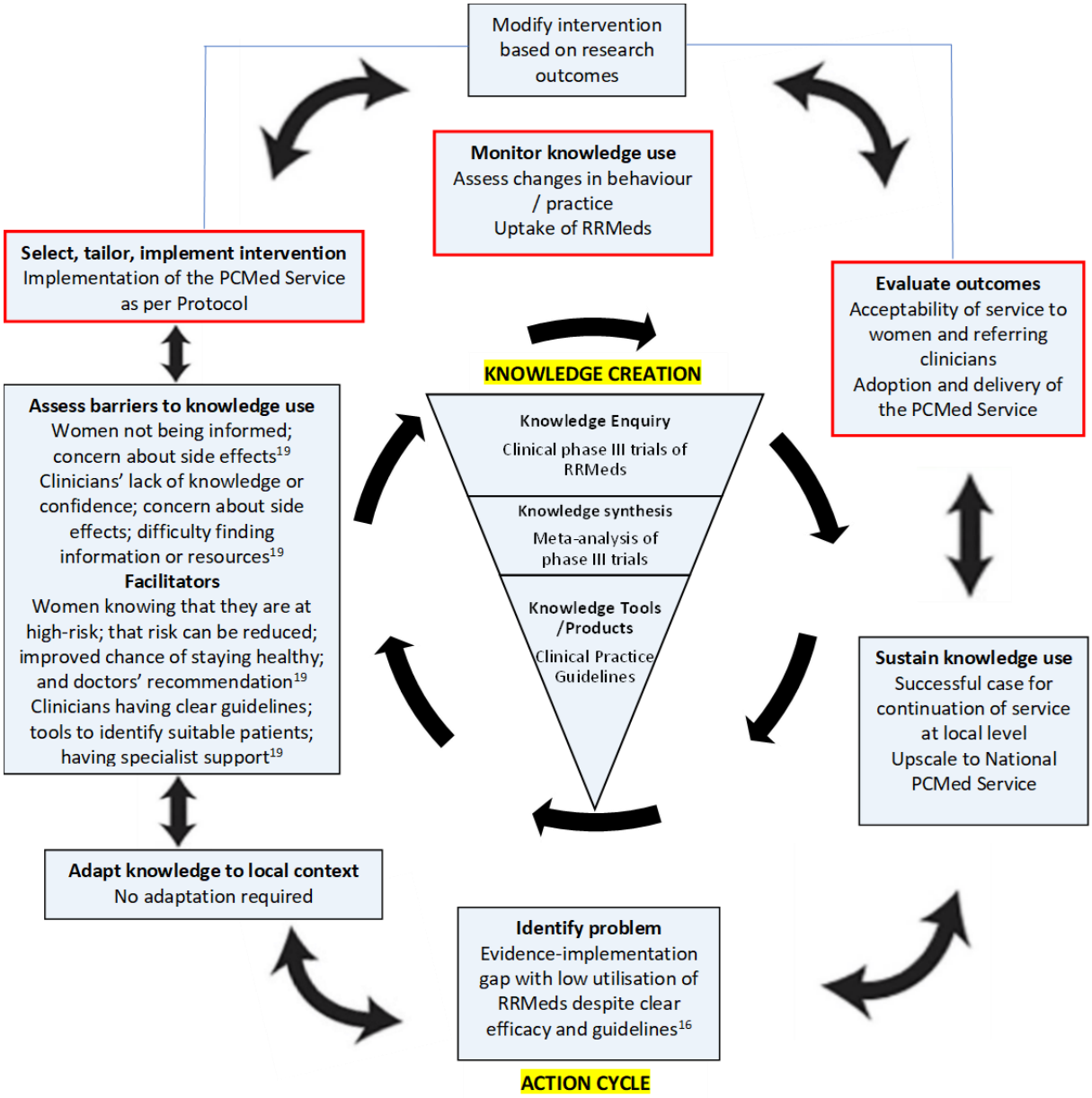

Figure 2: The Knowledge to Action Cycle adapted for Breast Cancer Risk Reducing Medications

The key research questions are whether the PCMed Service is associated with increased use of RRMeds, is well-adopted and is deliverable as planned, and is acceptable to clients and clinicians. The cost of the new Service will also be assessed.

The results of this research will be used internally within PMCC to provide an evidence-base for funding an ongoing clinical Service. However, it will also be used more broadly by key stakeholders to inform the planning of a potential scale-up phase of the PCMed Service. The ultimate vision is for scale-up to a national PCMed telehealth Service, potentially in partnership with other institutions and cancer peak bodies.

2.0 AIMS

2.1 Overarching Aim

The overarching aim is to explore the process and impact/effectiveness of implementing a new clinical service aimed at supporting the uptake of, and persistence with, breast cancer prevention medications.

2.2 Specific Aims

1) To determine whether the PCMed Service is associated with an increased use of RRMeds by women at increased risk of a 1st breast cancer who attended the RMH FCC, or the PMC clinics (FCC/BU/LEC) (hereafter referred to as the "Catchment Clinics", compared with the use of RRMeds in a historical cohort of similar women who attend the Catchment Clinics prior to the PCMed Service implementation. This will be assessed at approximately 12 months after the last Risk Management Consultation in the Catchment Clinic.

2) To describe the adoption of the PCMed intervention by women who attended the Catchment Clinics. Specifically, the proportion of eligible women that attend at least one PCMed consultation within 6 months of a Catchment Clinic Risk Management Consultation where the PCMed Service is discussed.

   To explore the characteristics associated with adoption of the PCMed intervention (age, socioeconomic status (SEIFA), marital status, indigenous status, country of birth (Australia/not Australia), need for interpreter, referral source (clinic i.e. FCC, LEC or BU and referring clinician type i.e. geneticist, medical oncologist, radiation oncologist, breast surgeon, other), estimated 10-year and 20-year breast cancer risk, estimated residual life-time breast cancer risk, history of breast biopsy, history of LCIS/AH, history of chest irradiation, parity, marital status, education level, number of 1st degree relatives with breast cancer).

Note aims 1 and 2 will only use data on women who attended the Catchment Clinics. It will not include data on women referred from other sources such as the RWH BU, the RMH BU or other doctors within or external to the Parkville Precinct. This is because the historical cohort data (needed for aim 1) will not be readily available nor will the number of potentially eligible women seen at those sites (needed for aim 2).

3) To determine the uptake of RRMeds 6 months after attendance at the PCMed Service in women who have no contraindications for prescription of RRMeds at the Initial or (if required) the Repeat Consultation.

   To explore the characteristics associated with uptake (age, socioeconomic status (SEIFA), indigenous status, country of birth (Australia/not Australia), need for interpreter, referral source (FCC/BU/LEC/external service etc), referring clinician

type, estimated 10-year breast cancer risk, estimated residual life-time breast cancer risk, history of breast biopsy, history of LCIS/AH, history of chest irradiation, parity, marital status, education level, and number of 1st degree relatives with breast cancer).

4) To explore the reasons for not taking up RRMeds in the 6 months after attending the PCMed Service in women (who had no contraindications for prescription of RRMeds at the Initial or Repeat Consultation(s). Their self-reported intention to take RRMeds in the future will also be explored.

5) To evaluate the acceptability of the Service:
    a. For woman who use the Service, and
    b. For clinicians working within the Catchment Clinics (regardless of whether or not they refer to the PCMed service) and for other referring clinicians (e.g. from RMH, RWH, GPs and other external sites).

6) To evaluate the delivery of the PCMed Service intervention (as described in Appendix A), and any adaptations required. Specifically:
    a. To determine the proportion of consultations that are conducted by telehealth rather than face to face or phone, and the reasons for requiring face to face consultations or phone if required.
    b. To describe the proportion of consultations conducted by the nurse practitioner (NP) versus a medical oncologist (MO) or the combination.
    c. To describe the approximate duration of the consultations (<15 minutes, 15-29 minutes, 30-44 minutes, 45-59 minutes, >1 hour).
    d. To describe the number of consultations required before a prescription is written, or the woman is discharged from the Service.
    e. To determine the number of women who do not attend the Post-Prescription Consultation and the reason why (e.g., no side-effects of concern; ceased the medication; did not take the medication).
    f. To determine the number and approximate duration (as per 6c. above) of additional Post-Prescription Consultations required and the reasons for them.
    g. To describe the number, approximate duration (<5 mins, 5-10 mins, 11-20 mins, >20 mins) and nature of patient, referrer, or GP calls to the hotline.
    h. To explore what factors, influence each of a-g (age, socioeconomic status (SEIFA), indigenous status, country of birth (Australia/not Australia), need for interpreter, referral source (FCC/BU/LEC/external service) and referring clinician type, marital status, education level, name of medication commenced (if any).
    i. To document any unintended consequences of the PCMed Service implementation.

7) To evaluate the cost to PMCC of delivering the PCMed Service by reporting:
    a. the amount of funding received per woman through activity-based funding,
    b. the cost of service-delivery per woman through micro-costing, and

the difference between funding (a) and cost (b).

8) To evaluate women's persistence with RRMeds at 2 years and 4.5 years (the latter only relevant for women having a 5 year planned course) after commencement. Reasons for ceasing RRMeds and characteristics associated with persistence with RRMeds will be explored.

Aims 3-8 will include data from all women who consent to this research and who attend the PCMed Service during the study timeframe (regardless of whether the referrals originated from Catchment Clinics or from doctors external to these sites).

3.0 METHODS

3.1 Study Design / Setting

The study is an implementation pilot of a new complex intervention (the PCMed Service) based in a specialist cancer centre.

3.2 Participants

This study will include 2 types of participants:

1) women at increased risk of breast cancer and
2) clinicians.

And 2 components

1) a retrospective component (historical controls - women only, no clinicians)
2) a prospective component – this component has four parts:
    i) data collection via EPIC and clinic database audit (under a waiver of consent) on all women from Catchment Clinics who are eligible to attend the PCMed Service but who do not attend the PCMed Service (this is required for Aims 1 and 2).
    ii) data collection via EPIC and clinic database audit (under an opt out consent process) on all women from Catchment Clinics who attend the PCMed Service (this is required for Aims 1 and 2).
    iii) Active follow-up of women who attend the PCMed Service and consent to this study (regardless of which referring clinic they came from). Women will be actively followed up after Service attendance with a questionnaire, telephone calls and an optional telephone interview. In regard to the telephone calls, the first call will occur at 6 months after the Initial or Repeat Consultation with the PCMed Service where a decision was made regarding RRMeds. All women regardless of whether they have commenced a RRMed will receive this phone call. For women who attended a Catchment Clinic a phone call will occur at 12 months after the Risk Management Consultation in the

Catchment Clinic (regardless of whether they have commenced a RRMed or not). All women who commence a RRMed will also be followed up with a telephone call at 2 years and (in the case of those having a planned 5 year course) at 4.5 years after RRMed commencement to assess persistence.

iv) clinicians at the referring clinics will receive a questionnaire and optional telephone interview.

3.2.1 Eligibility of Women

Note, eligibility criteria to attend the PCMed Service are outlined in Appendix A. The following criteria relate to inclusion in the research outlined in this study protocol.

For historical controls (retrospective component):

a. Assigned female at birth.
b. Attendee of a Catchment Clinic
c. Aged between 20 and 70 years at the time they have their most recent Risk Management Consultation.
d. Residual lifetime breast cancer risk at least 20%[26] or 10-year risk of at least 5%[27], or history of LCIS or atypical hyperplasia[28], or prior thoracic irradiation before the age of 35 and the radiation was given at least 5 years prior[29].
e. Does not require germline genetic testing to further clarify risk.
f. Not eligible for the PMCC or RMH Breast and Ovarian Cancer Risk Management Clinic (i.e., those with a pathogenic variant in a major breast cancer predisposition gene and those who are untested 1st degree relatives of carriers).
g. No history of invasive breast cancer or ductal carcinoma in situ (DCIS).
h. No history of bilateral mastectomy.
i. No prior or current use of RRMeds at the time of the Risk Management Consultation.

For prospective component:

a. Assigned female at birth.
b. Age between 20 and 70 years.
c. Residual lifetime breast cancer risk at least 20%[26] or 10-year risk of at least 5%[27], or history of LCIS or atypical hyperplasia[28], or prior thoracic irradiation before the age of 35 and the radiation was given at least 5 years prior[29].
d. Does not require germline genetic testing to further clarify risk.
e. Not eligible for the PMCC or RMH Breast and Ovarian Cancer Risk Management Clinic (i.e., those with a pathogenic variant in a major breast cancer predisposition gene and those who are untested 1st degree relatives of carriers).
f. No history of invasive breast cancer or ductal carcinoma in situ (DCIS).
g. No history of bilateral mastectomy.
h. No prior or current use of RRMeds.
i. Written informed consent (for attendees of the PCMed Service).

3.2.2 Eligibility of Clinicians

- All clinicians who saw eligible women in the Catchment Clinics during the prospective study period (whether or not they referred any women to the PCMed Service).
- All clinicians external to Catchment Clinics (e.g., RMH, RWH, GPs) who referred women to the PCMed Service during the prospective study period.

3.3 Identification of Eligible Women and Clinicians

3.3.1 Historical Controls (retrospective component) for Aim 1

Historical controls will be consecutive eligible women who attended any of the Catchment Clinics. They will have attended those clinics in the same months of the year (but in the year prior) as the women who are included in the prospective component to ensure study results are not biased by any seasonal variation in uptake of RRMeds. They will be identified using the FCC database and EPIC. Data will be abstracted from EPIC and the FCC database (waiver of consent).

3.3.2 Prospective Data Collection for Aim 1 and 2 for Women Who do not Attend the PCMed Service

Only women attending Catchment Clinics will be relevant to these aims. Data will be collected on consecutive women attending the Catchment Clinics from the study commencement date (14/11/2023). The Catchment Clinics will be actively encouraged to refer women to the PCMed Service. Clinics will be pre-screened for eligible women and clinicians reminded about the new PCMed Service, and a pamphlet provided (see Appendix B) so they can introduce the Service to potentially eligible women. Reasons for declining a referral to the PCMed Service will be recorded if this information is readily available.

"Recruitment" of these consecutive women will cease when the sample size of consenting women who do attend the PCMed Service has been reached (see 5.1 Sample Size). These women will be identified using the EPIC database and data will be abstracted from EPIC and the FCC database where relevant (waiver of consent).

3.3.3 Recruitment for Women who Attend the PCMed Service

All women who attend the PCMed Service will be invited to participate in this research. They will have the option of opting out of having their data abstracted (for Aims 1 and 2) from EPIC and the FCC database. They will be specifically invited to provide written informed consent for active follow-up, i.e., a questionnaire, follow-up phone calls and an optional telephone interview as outlined below in section 3.6.2. Only women who provide consent for this active follow-up will be included in aims 3-8. They will be identified as they are referred to the PCMed Service. They will be invited to participate by email/post at least 2 weeks prior to their attendance at the PCMed Service.

3.3.3.1 Recruitment of women for the PCMed Service Acceptability Interview

A subset of consenting women will be invited to participate in interviews regarding their experience of the Service (Aim 5). Women will be contacted by phone following their last

planned PCMed consultation and invited to participate in an interview regarding their experience of the Service (see Appendix C). A purposive sampling framework, using quota sampling,[30] has been devised, to ensure a representative cross section of the sample population is recruited for the interview. Quota sampling will allow for a minimum number of cases to be recruited to each of the pre-specified demographic categories:

- Age: (20-39 years); (40-55years); (>55years).
- Residence (Metro/Regional/Rural)
    - Residence will be defined using the Accessibility/Remoteness Index of Australia Plus (ARIA+) Remoteness Area Categories 0-4,[31] whereby:
        - Metropolitan areas are Remoteness Area Category 0;
        - Regional areas are Remoteness Area Category 1; and
        - Rural areas are Remoteness area category 2-4.

Referring Clinic: Familial Cancer Clinic, Breast Unit, Late-Effects Clinic, General Practice, Other.

Women will be recruited until saturation is reached. Based on the expertise of the research group, the sample size estimated to achieve "theoretical saturation" is approximately 15-20 women.[32,33] As such, the minimum quota to be recruited to each category will be attempted as outlined below, noting that each single woman will contribute to the quotas of all of the pre-specified demographic categories. It is prospectively acknowledged that it may not be possible for all quotas to be met.

- Age:
    - At least 3 woman who are 20-39 years;
    - At least 3 woman who are 40-55 years;
    - At least 3 woman who are >55 years.
- Residence:
    - At least 3 woman who are from a metropolitan area (ARIA 0);
    - At least 3 woman who are from a regional area (ARIA 1);
    - At least 3 woman who are from a rural area (ARIA 2-4[31]).
- Referring clinic:
    - At least 2 women are referred by the LEC;
    - At least 2 women are referred by the FCC;
    - At least 2 women are referred by Breast Unit;
    - At least 2 women are referred by GPs;
    - At least 2 women are referred from "other" sources.

As the women are being invited to interview, these quotas will be monitored to establish whether they are being met. By using these minimum quotas, this strategy will ensure that key groups are represented in the sample, whilst still providing flexibility in the final sample composition. To start with, 2 women from each referring clinic (FCC, LEC, Breast Unit, GP and other) will be recruited. After these 10 women are recruited, the quotas for age and residence categories will also be monitored for subsequent participants. Subsequent sampling will aim to ensure that as many of the pre-specified quotas across all categories are met.

3.3.3.2 Recruitment of Women to participate in Aim 8.

Given that Aim 8 was added to the protocol in 2025 (i.e. after study commencement), additional advice regarding recruitment of women to allow for the evaluation of persistence with RRMeds is provided here.

Women who were recruited to this study prior to the addition of "Aim 8", and who have commenced RRMeds, will be invited to reconsent using the amended PICF to allow them to receive follow-up phone calls at 2 years and (for those having a planned 5 year course) at 4.5 years after medication commencement. This invitation will be made using the telephone script (Appendix G) at the time the 6 or 12 month follow-up phone call (whichever is first). Women who provide verbal consent for the additional call(s) will be sent (emailed or mailed) the revised Patient Information and Consent Form (PICF v2) to sign. Any woman who has additional questions regarding this consent process will be offered an additional telehealth appointment to discuss.

Women who were recruited to this study prior to the addition of "Aim 8", and who have already received their final planned follow-up phone call (at 6 or 12 months), will not be contacted and will not be invited to participate in the collection of data for "Aim 8".

3.3.4 Recruitment of Clinicians (Aim 5)
Eligible clinicians will be identified from i) RMH or PMCC FCC, PMCC BU (surgeons only) and PMCC LEC and ii) from referrals received from RMH BU, RWH and external doctors. A subset of these will be invited to participate in interviews regarding their experience of the Service (Aim 5). Recruitment will be stratified using a purposive sampling framework that has been devised, using quota sampling[30], to ensure a representative cross section of clinicians including clinic type (Familial Cancer Clinic, Breast Unit, Late Effects Clinic, General Practice, other), speciality (medical oncology, radiation oncology, breast surgery, haematology, geneticist, genetic counsellor or general practice, and sex (male/female) are included.

Recruitment will commence once sufficient clinicians have made referrals to the PCMed Service, such that it is feasible for the sample size to be met. Clinicians will then be recruited until saturation is reached. Based on the expertise of the research group, the sample size estimated to achieve "theoretical saturation" is approximately 15-20 clinicians.[32,33] As such, the minimum quota to be recruited to each category will be attempted as outlined below, noting that each clinician will contribute to the quotas of all of the pre-specified demographic categories. It is prospectively acknowledged that it may not be possible for all quotas to be met.

- Sex:
    - At least 5 women;
    - At least 5 men.
- Clinic Type:
    - At least 3 clinicians from Breast Unit;
    - At least 3 clinicians from the Late Effects Clinic;

  - At least 3 clinicians from the FCC;
  - There is no prespecified quota from General Practice and “other”, given these clinicians were not specifically targeted for referrals.
- Specialty:
  - At least 1 Medical Oncologist;
  - At least 1 Radiation Oncologist;
  - At least 1 Breast Surgeon;
  - At least 1 Haematologist;
  - At least 1 Geneticist/genetic counsellor;
  - There is no prespecified quota of GPs or External Specialists, given that these clinicians were not clinician groups targeted for referrals.

As clinicians are selected for interview, these quotas will be monitored to establish whether they are being met. To start with, 1 clinician from each specialty will be recruited. After 5 clinicians are recruited, the quotas for sex and clinic type categories will also be monitored when recruiting subsequent clinicians. Subsequent sampling will aim to ensure that as many as possible of the pre-specified quotas across all categories are met.

3.4 The Intervention

The PCMed Service will be a consultative, telehealth Service co-led by a nurse practitioner and a medical oncologist. It is described in detail in Appendix A.

Eligible women attending the PCMed Service will be offered an Initial Consultation with either a nurse practitioner or a medical oncologist (see Appendix D). In the Initial Consultation women will be offered a discussion about their personal breast cancer risk and personalised information regarding the risks and benefits of RRMeds.

Women who do not want to take RRMeds or for whom RRMeds are not appropriate, will be referred back to their referring clinician or GP.

For women who want to commence RRMeds a prescription will be provided at the Initial Consultation or at a Repeat Consultation (as needed). All women supplied with a prescription for RRMeds will be booked for an 8-to10-week Post-Prescription Consultation to assess toxicities.

A hotline telephone Service will be provided for emergent concerns for referring clinicians, GPs and the women attending the Service. Further ad hoc Post-Prescription Consultations will be allowed if requested by the woman or her referring doctor or GP.

The PCMed Service intervention is illustrated in a flow chart below (Figure 3).

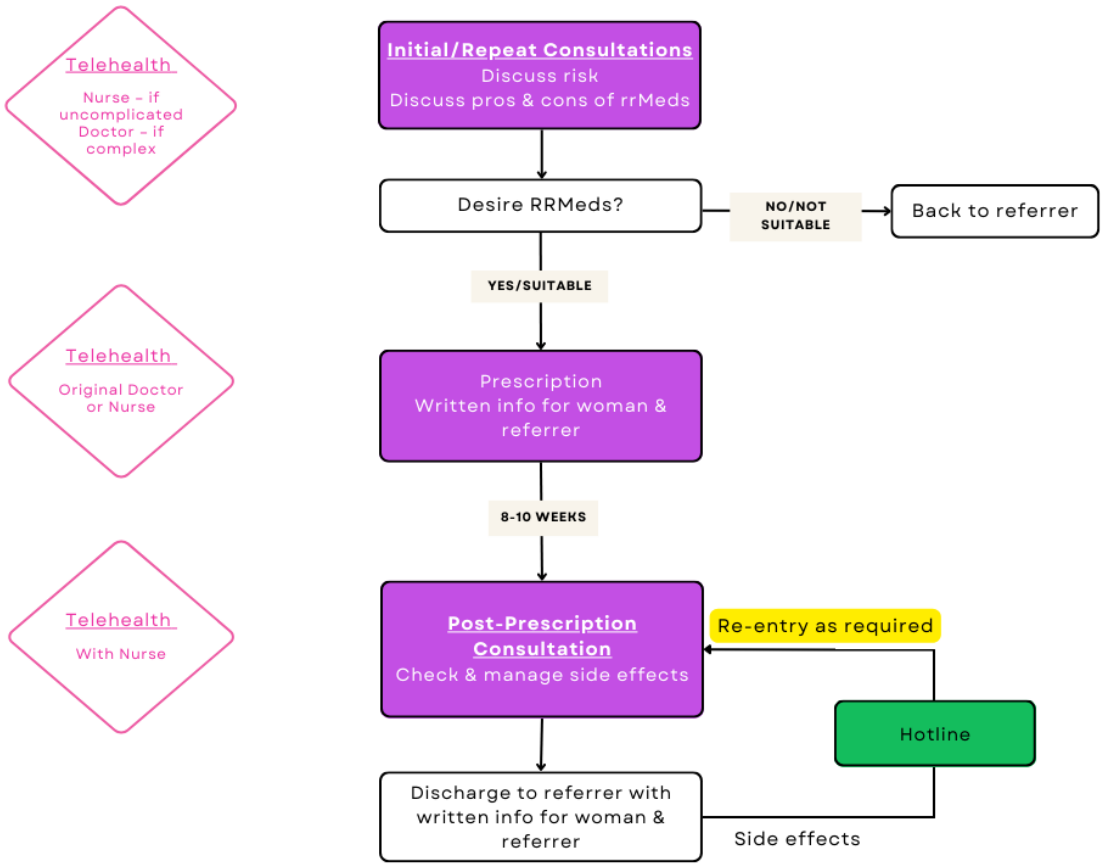

Figure 3: PCMed Service Intervention

3.5 Study Consent Process

3.5.1 Waiver of Consent for Historical Controls and Prospective Women who do not Attend the PCMed Service

A waiver of consent is requested to collect and analyse both prospective and historical control chart data on women attending the Catchment Clinics who meet eligibility for the PCMed Service. It is essential for aim 2 of this study that the denominator of eligible women coming through the Catchment Clinics is known so that we can determine the adoption of the new Intervention. It is impractical to consent these women, there is little risk of harm and there is no reason to believe that they would not consent if asked. There is sufficient protection of their privacy and confidentiality as names will not be used and reporting of the study results will not allow individuals to be identified, the benefits of the research in terms of optimising development of a new breast cancer prevention service (which if successful will reduce breast cancer incidence in the population) outweighs any harm associated with not seeking consent.

3.5.2 Dual Opt-out and Opt-In Consent for Women who attend the PCMed Service

Women who do not attend the PCMed Service will have their data collected and analysed for aims 1 and 2 under a consent waiver. This approach is not appropriate for women who do attend the PCMed Service, as it is not viable to argue that it is impractical to consent these women. Thus, women who do attend the PCMed Service will have the option of opting out (see Appendix D) of having their data abstracted from EPIC and the FCC database. If they do not opt out the data will be collected and analysed as per this protocol.

Conversely, an opt-in consent process will be used for the prospective active follow-up data collection for the women in this study who attend PCMed Service (Aims 3-8). That is, they will be invited to consent via a Participant Information and Consent Form (PICF) to a questionnaire, follow-up phone calls at 6 and 12 months, as well as at 2 years and (for those having a planned 5 year course) at 4.5 years if they choose to commence an RRMed. They will also be invited to consent to an optional telephone interview. If they consent, they can still change their mind and decline the interview when contacted about it.

Women who do not require an interpreter and who have a valid personal email address will be emailed a PICF in the form of an e-Consent. Women who do not have a personal email address will have the PICF posted to them.

Women who require an interpreter will have the PICF explained to them in their own language by a certified interpreter at the time of their Initial Consultation at the PCMed Service. The circumstances around the use of an interpreter, if required, will be documented in the electronic medical record (EMR).

Those who do not return the PICF will receive an email reminder, and/or a telephone call unless they have opted out of having their data abstracted from EPIC and the FCC database (for Aims 1 and 2).

3.5.3 Clinicians

The Theoretical Framework of Acceptability[34] (TFA) questionnaire, along with an explanatory email (see Appendix E), will be emailed to all eligible clinicians. Completion of the TFA questionnaire will be considered implied consent to use the TFA data. Clinicians will have the option to email the researchers to say they are not interested in participating. For those who do not opt out or respond, a reminder will be emailed at 1 week and again 3 weeks after the first invitation was sent.

All eligible clinicians will be invited to participate in a semi-structured telephone interview (Appendix F). Clinicians will be asked to provide a contact telephone number and suggest an interview time if they are willing to participate. Consent to use the data will be implied if they participate in the interview. Clinicians can indicate if they do not wish to participate via reply email. If no response is received, a reminder email will be sent.

3.6 Data Collection

3.6.1 Historical Cohort (retrospective component) for Aim 1

Historical data will be sourced from EPIC and the RMH and PMCC FCC database. Data collected will include: patient unit record number (PURN), initials, date of birth, Indigenous status, country of birth, postcode, marital status, parity, education level, whether interpreter required, clinic where last Risk Management Consultation took place, type of clinician seen (e.g. geneticist, medical oncologist etc.), date of last Risk Management Consultation, whether RRMeds were discussed and whether at 12 months after the last Risk Management Consultation there was documentation that the woman had commenced RRMeds. If there was no discussion of RRMeds and there is no documentation of use, it will be assumed the woman did not use RRMeds. If RRMeds were discussed but there is no documentation regarding whether they were used by the woman at 12 months after the last Risk Management Consultation, staff from the clinic in which they were seen for Risk Management will contact the woman to ask this. This follow-up of the actions taken after consultation, although admittedly rarely done due to resource limitations, can be considered a standard of care rather than specifically for research purposes. The relevant Units have agreed to this approach.

3.6.2 Prospective Data Collection

From EPIC and during Consultations:

Data on all eligible women who attend a Catchment Clinic and receive a Risk Management Consultation will be sourced from EPIC, and the RMH or PMCC FCC database (where relevant). Data collected at the time of the last Risk Management Consultation will include: patient unit record number (PURN), initials, date of birth, Indigenous status, country of birth, postcode, marital status, parity, education level, whether interpreter required, clinic where last Risk Management Consultation took place, type of clinician seen (e.g. geneticist, medical oncologist etc.), date of last Risk Management Consultation, whether RRMeds were discussed and whether the PCMed Service was discussed (or a pamphlet about the Service given).

For women in this group who subsequently attend the PCMed Service, further information will be collected during the consultations and from EPIC, including name and email address for the purposes of emailing electronic questionnaires (or name and postal address for the purposes of mailing hard-copy questionnaires), referring clinician name and type, date of referral, clinic from which they were referred, appointment type (e.g., Initial Consultation, Repeat Consultation, date of appointment, mode of consultation (i.e., telehealth, telephone, face-to-face) education level, menopausal status, hormone level results (if done), family history, history of LCIS or AH, history of chest irradiation (if so age at irradiation, dose, whether alkylating chemotherapy has been received, whether pelvic radiation has been received), 10 year, 20 year and residual lifetime risk of breast cancer, risk assessment tool used, use of hormonal contraception at time of clinic visit, use of menopausal hormone therapy at time of clinic visit, use of anti-coagulants (current and ever), current use of CYP2D6 inhibitors, other concomitant medications, history of osteoporosis, bone density scan results (if done), history of thrombosis (including deep venous thrombosis, pulmonary

embolism, stroke), history of other cancers (type and presumed prognosis), smoking status, currently trying to conceive, pregnant or lactating or planning pregnancy within the next 3 years, any difficulty swallowing or taking tablets, lactose intolerance, whether eligible for RRMeds (which ones and if not why not), whether woman indicated interest in taking RRMeds, whether prescription for RRMeds was accepted, RRMed type recommended, type prescribed, and duration of consultations (which will be manually recorded by the attending clinician).

If telephone calls were received via the 'Hotline', additional data will include who the caller was (e.g., woman, carer, referring clinician, GP), reason for the call (e.g., concerns related to treatment, general information needed), and outcome of the call (e.g., interruption of RRMeds, cessation of RRMeds, change in RRMeds).

Data Collection at 6 months
At 6 months after the Initial or Repeat Consultation, women will receive a telephone call (see Appendix G). Data collected will include whether RRMeds were commenced (Y/N), the date of commencement (if not previously recorded), whether RRMeds were ceased (Y/N), reason for ceasing RRMeds (if applicable), intent to use RRMeds in the future (Y/N), if no intention to use RRMeds then the reason for not intending to use RRMeds, and factors that would facilitate use of RRMeds.

Data Collection at 12 months
Data will be collected at 12 months after the Risk Management Consultation in the Catchment Clinic at which the woman was deemed suitable for referral to the PCMed Service (regardless of whether she was referred or not).

For women who aren't consented to active follow-up, and who do not attend PCMed Service, this data will be collected under a waiver of consent from EPIC as per section 3.6.1. Data collected will include uptake of RRMeds (Y/N).

For women who do consent to active follow-up, this data will be collected via a telephone call (Appendix G). Data collected at this telephone call will include uptake of RRMeds (Y/N), the date of commencement (if not previously recorded), were RRMeds ceased (Y/N), reason for ceasing RRMeds (if applicable), intent to use RRMeds in the future (Y/N), if no intention to use RRMeds then the reason for not intending to use RRMeds (as applicable).

Data Collection at 2 years
Data collection at this time point is only relevant to women who have commenced a RRMed. Data will be collected 2 years after the woman has commenced a RRMed and will include whether the RRMeds were permanently ceased (Y/N), if so, when they were ceased, reason(s) for ceasing the RRMed (if applicable), whether they sought medical advice regarding the reason for ceasing, and if so with whom (GP/PCMed Service/breast specialist/other), whether they would consider re-starting the same or a different RRMed in the future and if so what factors would facilitate that.

Data Collection at 4.5 years
Data collection at this time point is only relevant to women who have commenced a RRMed with a planned 5 year course. Data will be collected approximately 4.5 years after the woman has commenced a RRMed and will include whether RRMeds were permanently ceased (Y/N), if so, when they were ceased, reason(s) for ceasing RRMeds (if applicable) whether they sought medical advice regarding the reason for ceasing, and if so with whom (GP/PCMed Service/breast specialist/other), whether they would consider re-starting the same or a different RRMed in the future and if so what factors would facilitate that.

Theoretical Framework for Acceptability (TFA) Questionnaire
Consenting women participating in the research will receive a Cover Letter and TFA questionnaire (see Appendix H) via email or post after their PCMed Initial or Repeat Consultations. This questionnaire will take less than 5 minutes to complete. If no response received, 2 reminders will be sent out at 1 to 2 weeks and then 3 to 4 weeks after the initial invitation sent.

Eligible Clinicians will also receive a Cover Letter and TFA Questionnaire (see Appendix E) by email. This questionnaire will take less than 5 minutes to complete.

The number of clinicians who do not participate, their sex, clinic type and specialty will be collected and reported as part of the study.

Interviews with Women
An interview guide, consisting of a list of semi-structured questions has been developed by study investigators including medical oncologists, a nurse practitioner, and an implementation scientist (Appendix I). The interview guide aims to explore the acceptability of the PC Med Service for women, including their perception of the clinic before, during and after attendance. The interview guide was formulated with the Theoretical Framework of Acceptability (TFA) in mind.[34] The TFA comprises seven constructs that guide the assessment of acceptability of an intervention from the perspective of participants (and those delivering the intervention).[34] In formulating the guide, only the constructs felt to be relevant to the participant's experience of the PCMed Service were used to formulate questions – these included affective attitude, self-efficacy, burden, intervention coherence and perceived effectiveness. The ethicality and opportunity cost constructs were not perceived as being relevant to the intervention being assessed.

The interview guide will be pilot tested with the first two women. Refinement of research questions will be made based on the pilot test. Interviews will be conducted by telephone. The interviewer will highlight the purpose of the interview, address the terms of confidentiality, and provide contact details for the participant to contact, if they wish, on completion of the interview. Interviews will be audio recorded, transcribed professionally and de-identified, and analysed thematically using NVIVO[35] software. We will recruit participants until saturation of themes is reached.

Data analysis will occur simultaneously with data collection. Data analysis is described in Section 5.2.3 “Specific Aim Analyses – Aim 5”.

Interviews with Clinicians
A separate interview guide with semi-structured questions for clinicians has also been developed by study investigators including medical oncologists, a nurse practitioner and an implementation scientist (Appendix J). The interview guide aims to explore the acceptability of the PC Med Service for referring clinicians, including the referral process and any interactions they had with the Service (regardless of whether they actually referred any women to the service or not). The interview guide will be pilot tested with the first clinician. Refinement of research questions will be made based on the pilot test. Interviews will be conducted via telephone, and will be audio recorded, transcribed, and analysed thematically using NVIVO[35] software. Interviews will be de-identified after transcription. Recruitment of clinicians will stop once saturation of themes is reached.

Data analysis will occur simultaneously with data collection. Data analysis is described in Section 5.2.3. “Specific Aim Analyses – Aim 5”

Data Collection to evaluate Cost of PCMed Delivery (Aim 7)
Micro-costing entails making an inventory of all resources needed for service delivery. The data to calculate the cost of service-delivery over the study duration will not require additional data collection to that described above. Data used will include the number and duration of all consultations, type of consultation, who provided the service (nurse practitioner or medical oncologist), involvement of interpreter during consultation as well as the duration of calls received via the ‘Hotline’.

Data on the time spent by the administration officer to support the activities of the PCMed Service (making appointments, taking hotline telephone calls to direct to nurse practitioner, mailing notifications) will not be collected because the time spent per woman is expected to be negligible. A reasonable estimate will be used instead. The hourly cost of the administration officer, nurse practitioner, medical oncologist/s and interpreter(s) will be determined by the recorded activity and salaries as per Awards and Enterprise Agreements.

The data to calculate the level of funding received per women will be extracted from EPIC records. As the PCMed Service will use Activity Based Funding[36], all consultations (including type and mode) and the person undertaking the consultation (nurse practitioner or medical oncologist) will be recorded in EPIC. All consultations that meet the funding requirements are considered ‘Service Events’ with each ‘Service Event’ allocated a National Weighted Activity Unit (NWAU). Data on those ‘Service Events’ for all individuals participating in the study will be extracted by the PMCC Reporting System (DASH). By assigning a monetary figure assigned to each NWAU the amount of funding can be calculated.

Research Journal
A formal research journal (see Appendix G) will be kept by the nurse practitioner informed by the FRAME fidelity framework and the COM-B behaviour change framework. Influences

on the Service and the nurse practitioner role will be recorded alongside changes to the PCMed Service Process and rationale for the change. Any unintended consequences of the implementation of the PCMed Service will be documented.

3.7 Data Storage and Security

Data will be kept strictly confidential according to the National Statement on Ethical Conduct in Human Research 2007 and the Australian Code for Responsible Conduct of Research 2007.

Patient research data will be stored electronically where possible, on a specialised, secure web-based database (REDCap) or in secure folders in the Peter MacCallum Cancer Centre network drives.

Audio recordings from the interviews will be transcribed and de-identified. The de-identified transcriptions and audio files will be kept on a password-protected computer and stored in secure folders in the Peter MacCallum Cancer Centre network drive.

Any laptop or desktop computer used for this study will be password-protected with no data stored on an external hard drive, CD or USB. Any paper records will be kept in a locked cabinet in a room with controlled access at the Peter MacCallum Cancer Centre.

Research data will only be visible to and accessed by members of the Research Team who are directly involved with the administration, collection, or analysis of the data.

Patient data, including transcriptions will only be analysed in a coded form. Individual patients will not be identifiable from the presented or published material.

Per the Australian Code for Responsible Conduct of Research 2018, research data, including audio files and transcriptions, will be stored for a minimum period of 5 years from the date of the last publication. Once this date is reached, these files will be destroyed by erasure unless further approval for retention is obtained.

4.0 ENDPOINTS

1) Primary Endpoint: Use of RRMeds at 12 months after a Risk Management Consultation in a Catchment Clinic.
2) Attendance by women at PCMed Service at 6 months following documented discussion on PCMed Service at Risk Management Consultation.
3) Use of RRMeds at 6 months after the Initial Consultation at PCMed Service or Repeat Consultation if required.
4) Reason for non-use of RRMeds at 6 months after first consultation at PCMed Service (or after Repeat Consultation if required).
5) Acceptability:
    a. Acceptability of the PCMed Service (as per the Theoretical Framework of Acceptability (TFA) questionnaire) for woman 2 to 3 weeks after the Initial of Repeat Consultation/s if a Repeat Consultation required.
    b. Acceptability of the PCMed Service for clinicians as assessed by the TFA questionnaire.

   c. Acceptability of the PCMed Service for women who use the service, assessed via a semi-structured qualitative interview following their last planned PCMed consultation.
   d. Acceptability of the PCMed Service to clinicians, assessed via semi-structured interview.
6) Evaluation of service delivery will be assessed using the following variables at the end of the study period:
   a. Number of consultations conducted by telehealth, face-to-face, or Reason for consultation not being conducted by telehealth.
   b. Number of consultations undertaken by nurse practitioner and/or medical oncologist.
   c. Duration of every consultation.
   d. Number of consultations required before a prescription is written for RRMeds.
   e.
      i. Number of failures to attend (FTA) the post-prescription consultation.
      ii. Reason for failure to attend the post-prescription consultation.
   f. Number of ad hoc Post-Prescription Consultations required after the 1st post-prescription consultation.
   g.
      i. Number of calls to Hotline over a period of 6 months.
      ii. Duration of call.
      iii. Reason for call.
   h. Factors that influence delivery of service as per protocol.
   i. Unintended consequences of PCMed Service.
7) Evaluation of the cost-of-service delivery:
   a. Funding received by the PCMed Service per woman who uses RRMeds.
   b. Funding received by the PCMed Service per woman attending the Service.
   c. Cost of the PCMed Service per woman who uses RRMeds.
   d. Cost of the PCMed Service per woman attending the Service.
   e. Difference between (a) and (c).
   f. Difference between (b) and (d).
8) Persistence with RRMeds
   a. At 2 years after commencement of the RRMed
   b. At 4.5 years after commencement of the RRMed (only relevant for women having a 5 year planned course).

5.0 STATISTICAL ANALYSIS AND SAMPLE SIZE CONSIDERATIONS

5.1 Sample Size

Aim 1

Based on national data[17] we expect that 2% of women who attended the Catchment Clinics prior to the commencement of the PCMed intervention (i.e., the historical controls) will

have used RRMeds. We consider an increase in use from 2% to 20% to be clinically significant, given the PCMed Service is a complex intervention. A prospective sample size of 57 women attending the PCMed Service will provide 80% power to detect a minimum change from 2% to 20% at a 5% significance level. The sample size of consecutive consented women attending the PCMed Service will be 63 for this study, to account for a 10% drop out/loss to follow-up.

Table 1: Sample size scenarios* - sample size per arm

	Post-implementation uptake				
Pre-implementation uptake	**10%**	**15%**	**20%**	**25%**	**30%**
1.0%	121	72	50	38	30
2.0%	162	86	57	42	33
2.5%	189	95	61	45	34
5.0%	474	160	88	59	43
7.5%	2084	304	134	80	55
10.0%	N/A	726	219	113	72

*Minimum sample size required in each of the prospective and historical cohorts presuming 80% power at the 5% significance level.

If the use of RRMeds in the historical controls is > 2%, a larger sample size may be needed as per table 1 above. For example, if the historical use is 5%, a sample size of 59 + 10%, i.e., 65 will be required to show an increase from 5% to 25%. A protocol amendment will be submitted if a change in sample size is required once the historical control data are available.

We will identify 100 consecutive historical controls. If 0% of these use RRMeds, we will extend the sample to a total of 150.

Aim 2

For aim 2 (adoption of the PCMed Service) we will prospectively collect data on eligible women attending the Catchment Clinics until we have 63 consented women that actually attended the PCMed Service. Thus, the sample size is not fixed. We will have collected some data on other women after that time, but we will not use that in the analysis.

Aim 5 interviews

To investigate findings from the TFA questionnaire, follow-up interviews will be conducted. (n≈15-20 for each of women and clinicians). This number should allow for reaching concept density. The clinician sample is expected to include geneticists, genetic counsellors, oncologists, breast surgeons, haematologists, and radiation oncologists.

5.1.1 Analysis sets

The primary analysis set will consist of all eligible women who attend the PCMed Service and the historical controls. The secondary analysis set will consist of all eligible women attending Catchment Clinics (regardless of whether they subsequently attend the PCMed Service), and the historical controls.

5.1.2 Interim analysis

An interim analysis may be conducted to ensure both the prospective and historical cohorts are sufficiently powered to permit comparison of the primary endpoint. Additional sample may be recruited as required.

5.2 Statistical Analyses

All statistical analyses will be undertaken in Stata version 17 (StataCorp. 2021. *Stata Statistical Software: Release 17*. College Station, TX: StataCorp LLC.) and R version 4.0.5 (The R Foundation for Statistical Computing, Vienna, Austria).

5.2.1 General – descriptive statistics

Categorical variables will be summarised using frequency and percentage. Continuous variables will be summarised using mean and standard deviation (SD) or median and interquartile range (IQR) as appropriate. Incidence rates will be expressed as the count of events divided by the number of subjects and/or per unit time as appropriate and expressed as point estimates with associated 95% confidence intervals and presuming an underlying Poisson or negative binomial distribution.

5.2.2 General – inferential statistics

Comparisons of event proportions between the prospective cohort and historical controls will be conducted using a chi-square test or Fisher's exact test as appropriate. Associations between participant characteristics and study outcomes will be explored using univariable and multivariable logistic, Poisson and/or negative binomial regression as indicated. Multivariable models will be assessed for collinearity and interactions between explanatory covariates. Adjustment for clinic effects will be conducted by including the clinic ID as a random effect in the aforementioned models. The final selection of test or model type will be confirmed upon initial review of the collected data with consideration given to the number of available events for each outcome. For all analyses, $p<0.05$ will be considered significant.

5.2.3 Aim specific analyses

Aim 1

The proportion of women who start RRMeds within 12 months of a cancer Risk Management Consultation in the Catchment Clinic will be summarised pre- and post-implementation of the PCMed Service using descriptive statistics as detailed in section 5.2.1. Proportions will be compared using a chi-square or Fisher's exact test. Differences in the distribution of confounders between the historical and prospective cohorts will be managed using adjusted regression as described in section 5.2.2. This analysis will use the primary analysis set as described in 5.1.1.

Aim 2
The proportion of women who attended each Catchment Clinic for a Risk Management Consultation and received a discussion and / or information about the PCMed Service and who subsequently attended the PCMed Service within 6 months of a Risk Management Consultation will be summarised using descriptive statistics as per section 5.2.1. Associations between participant characteristics and the likelihood of adoption will be analysed using logistic regression as described in section 5.2.2. This analysis will use the secondary analysis set as described in section 5.1.1. Descriptive statistics will be used to summarise reason/s for declining a referral to the PCMed Service as an exploratory endpoint.

Aim 3
The proportion of women (without contraindications) who had used RRMeds within 6 months of their Repeat Consultation will be summarised using descriptive statistics as per section 5.2.1.

Aim 4
Reason for non-use of RRMeds at 6 months after the Initial Consultation at PCMed Service (or after Repeat Consultation if required) will be summarised using descriptive statistics as per section 5.2.1.

Aim 5
Acceptability – Theoretical Framework for Acceptability (TFA) Questionnaire metrics will be summarised using descriptive statistics as per section 5.2.1.

Semi-structured interview data will be analysed both inductively and deductively. The Theoretical Framework for Acceptability will act as the coding framework for deductive analysis.

Interviews will be transcribed in full and de-identified. All transcripts will be read in conjunction with the original audio recording to check for accuracy. Two authors (SL and WC) will independently code several interviews and determine the level of agreement on coding the data. After 6 interviews with women, and 5 interviews with clinicians (one with each referring specialty), a summary of the themes with supporting quotes will be generated. Themes will be reviewed by co-investigators for feedback regarding the themes and any refinements required for the interviews. After 15 interviews (with women and clinicians respectively), the coding framework capturing the full range of comments will be developed and reviewed by co-authors. After interview 15 (with women and clinicians respectively), new interviews will be reviewed in light of the coding framework to determine whether saturation of the main themes has been achieved. The final coding framework will be reviewed by all authors. Regular research meetings will continue where analysis will be discussed with the research team, particularly any areas of complex coding.

Aim 6
Evaluation of service delivery will be summarised using descriptive statistics as per section 5.2.1.

Aim 7
Associated costs and funding received through Activity Based Funding will be summarised using descriptive statistics as per section 5.2.1.

Aim 8
The proportion of women who commence a RRMed and persist with taking it at 2 years and 4.5 years will be summarised using descriptive statistics as per section 5.2.1. Reasons for non-persistence will also be summarised using descriptive statistics.

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