Statistical Analysis Plan for Future Health Today: A pragmatic stratified 12-month cluster randomised control trial of quality improvement activities for Chronic Kidney Disease in general practice

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Abbreviations

ACEI – Angiotensin-Converting Enzyme Inhibitor

ARB – Angiotensin Receptor Blocker

CKD – Chronic Kidney Disease

CSV – Comma Separated Values

CVD – Cardiovascular Disease

EGFR – Estimated Glomerular Filtration Rate

EMR – Electronic Medical Record

FHT – Future Health Today

FTE – Full-Time Equivalent

GLM – Generalised Linear Model

GP – General Practitioner/General Practice

GRHANITE – Generic Health Network Information Technology for Enterprise

HABIC R^2 - Health and Biomedical Informatics Centre

HDL – High-density lipoprotein

ICC - Intra-Cluster Correlation

IQR – Interquartile Range

IRSD – Index of Relative Socioeconomic Disadvantage

ITT – Intention To Treat

LDL – Low-density lipoprotein

MBS - Medicare Benefits Schedule

QI – Quality Improvement

SAP – Statistical Analysis Plan

SQL – Structured Query Language

SEIFA – Socio-Economic Indexes for Areas

uACR – Urine Albumin-Creatinine Ratio

VicREN – Victorian Research and Education Network

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1. Introduction

1.1 Synopsis

Future Health Today (FHT) is a stratified head-to-head cluster randomised controlled trial (RCT) of quality improvement (QI) activities in general practice in Australia. The QI program that forms the intervention consists of a new technology platform (FHT, with audit, recall, clinical decision support and monitoring of QI activity capability) and case-based learning series for specific clinical areas. For the FHT trial we have focused on QI programs for two common conditions managed in general practice, chronic kidney disease (CKD) and cancer-risk. The QI CKD program focuses on reducing cardiovascular disease (CVD) risk for individuals with a recorded diagnosis or pathology results consistent with a diagnosis of CKD. The QI cancer-risk program focuses on the appropriate investigation and follow-up of people at increased risk of an undiagnosed cancer among general practice patients. General practices will be randomly assigned equally to either the QI CKD program or the QI cancer-risk program, with different target populations and outcomes measured for each QI program. Thus, practices randomised to the QI cancer-risk program will act as an active control for the QI CKD program, and vice versa.

This Statistical Analysis Plan (SAP) will focus on the CKD intervention and a separate SAP will be developed documenting the statistical analysis for the cancer-risk intervention. The analysis and findings for each study (CKD and cancer-risk) will be published as separate manuscripts following the CONSORT (Consolidated Standards of Reporting Trials) guidelines.[1] The background and rationale for the FHT trial are described in the trial protocol, including the setting, recruitment, eligibility criteria, randomisation, and sample size calculations. This document elaborates on the statistical analysis for the primary and secondary outcomes of the CKD intervention, including sensitivity and pre-planned explanatory analyses, non-adherence adjusted analyses, and handling of missing outcome data where appropriate. This SAP also describes the analysis for the immediate outcomes for the health economic evaluation related to costs of the intervention and health services utilisation. Whereas the study trial protocol describes the simulation study investigating the longer-term health economics impacts of implementing FHT QI program on the incidence of CVD and renal replacement events in patients with CKD. The process evaluation to identify the barriers and facilitators to successful implementation of FHT in daily practice will be described in a separate document.

1.2 Primary Hypothesis

The null hypothesis is that there is no difference in the proportion of patients with a recorded diagnosis or pathology results consistent with a diagnosis of CKD who attend general practice participating in FHT CKD QI program (intervention arm) who receive guideline concordant care to reduce CVD risk, within the 12 months period post-randomisation, compared with patients attending general practice providing usual care for CKD (active control arm). The alternative hypothesis is that there is a difference.

1.3 Study Aims/Objectives

The primary objective of the CKD trial component is to determine the effectiveness of the FHT QI program for CKD compared to usual care for patients with a recorded diagnosis or pathology results consistent with a diagnosis of CKD receive guideline concordant care[2-4] within 12-months post-randomisation to reduce CVD risk.

The secondary objectives of the trial are to determine the effectiveness of FHT QI program for CKD compared to usual care for patients with a recorded diagnosis or pathology results consistent with a diagnosis of CKD regarding the:

a) proportion of patients that are prescribed an angiotensin-converting enzyme inhibitor (ACEI) or angiotensin receptor blockers (ARB) consistent with guidelines to reduce CVD risk[2-4], prescribed during the 12-month follow-up period post-randomisation.
b) proportion of patients who are prescribed statins consistent with guidelines to reduce CVD risk[4,5], prescribed during the 12-month follow-up period post-randomisation.
c) mean systolic blood pressure (mmHg) using the most recent recorded reading at 12-months post-randomisation
d) mean lipid results (total cholesterol, low-density lipoprotein (LDL) cholesterol, high-density lipoprotein (HDL) cholesterol and triglycerides - all mmol/L) using the most recent recorded results at 12-months post-randomisation
e) mean urine albumin:creatinine ratio (uACR) based on most recently recorded results at 12-months post-randomisation
f) proportion of patients with a reduction in uACR of at least 30% from baseline measurement
g) proportion of patients classified as being at low, moderate, or high cardiovascular disease risk at 12-months post-randomisation
h) mean eGFR (ml/min/1.73^2) between baseline at 12-months post-randomisation
i) rate of general practice encounters per patient over the 12 months post-randomisation.

For the health economics analysis, the aim is to quantify the costs of the delivery of the FHT QI program and the health care service costs. Specifically, the objectives are:

j) to estimate the cost of the FHT software program installation for QI and cost of training for general practitioners to use the software
k) to examine the primary health service utilisation and cost incurred by patients in the intervention arm compared to control arm over the 12-month period post-randomisation.

2. Trial Design

The FHT trial is a stratified head-to-head cluster randomised controlled trial. The unit of randomisation is the general practice, where practices are randomly allocated concurrently on 1:1 ratio to either participate in the FHT CKD QI module (intervention arm) or the FHT Cancer-risk module (active control arm for the CKD study). All general practices will be provided access to the respective QI programs at the commencement of the trial (October 4th, 2021). Please refer to the trial protocol for a detailed description of the intervention and comparator.

2.1 Study population

The trial will be conducted in general practices in Victoria and Tasmania. Full details of the eligibility and exclusion criteria for general practices are provided in the trial protocol.

Patients attending general are eligible if at the commencement of the trial (4th of October 2021) they:

- Are aged 18-80 years (inclusive)
- Have a recorded diagnosis of CKD or pathology results consistent with CKD[6] and that may benefit from pharmacological therapy to reduce CVD risk consistent with Kidney Health Australia[3], RACGP Red Book[2] and National Vascular Disease Prevention Alliance Guidelines[4]

Eligible patients will be excluded if they:

- Have a recorded history of renal transplant or chronic dialysis
- Are pregnant
- Are recorded as no longer active in the general practice or deceased in the EMR

2.2 Framework

The framework for the statistical analysis will utilise a superiority framework.

2.3 Interim Analyses and Stopping Guidelines

No formal interim statistical analyses are planned for this trial. As the data used in the study is EMR data extracted from general practices, no formal data monitoring and no stopping guidelines were required.

2.4 Data Management and Workflow

General practice and practice staff characteristics will be collected via survey before randomisation.

Patient characteristics, baseline measures and outcome data will be measured using patient data extracted from general practice EMRs and stored in the Patron database. Patient data will be extracted from each practice using the GHRANITE tool at each data collection period namely, 4th October 2021 (baseline), 4th April 2022 (6 months), 4th July 2022 (9 months) and 30th September 2022 (12 months). The extracted data will be processed and curated by Patron data team members and stored within the Patron enclave using a separate database for each data collection period. This process takes at least two weeks.

The FHT QI module installed within practices as part of the FHT intervention interacts with the practice EMR system, running the FHT algorithms over patient data to identify patients with CKD or pathology consistent with CKD who could benefit from initiation of statins and/or ACEI/ARBs. The criteria used to identify the eligible patients with a recorded diagnosis or pathology results consistent with a diagnosis of CKD who attend general practice and the creation of the recommendations for guideline concordant care to consider (flags) are outlined in the Future Health Today business requirements document which was used to develop the FHT algorithms embedded in the technology platform. Within participating general practices individual patient level recommendations can be viewed. However, only aggregate level data is extracted by Future Health Today platform and available to the research team. As a result, these data are not linked with Patron database used for the trial statistical analysis.

Therefore, part of this curation process is the replication of the eligible patients and flags generated by FHT algorithms in the practices, patient outcomes and baseline measures, using identical algorithms to those embedded within, and executed by, FHT platform within the Patron dataset. These algorithms were independently validated by the biostatistician using baseline data. Limitation of this approach is that we will only be able to derive the action taken by clinicians if they were recorded in an extractable field in the EMR that is included in the Patron dataset, such as, medication prescriptions ordered, pathology results and observations.

All data within the Patron enclave is deidentified with patient and practice identifiers replaced by a unique hashed code prior to the data leaving the general practice. Data managers and analysts can access the databases for the project and utilise Structured Query Language (SQL) queries to create Comma Separated Values (CSV) files containing the data required for the trial analysis. Files downloaded from the Patron databases will be saved within a secure virtual machine accessible only by the study biostatisticians, health economists and the data manager. The virtual machine requires multifactor authentication to access. Within the secure virtual environment, the data manager or biostatistician will then import the CSV data files into Stata Statistical Software v17 [7] for data processing and statistical analysis. Data will be checked for errors, resolving them where possible. Labelling, recoding, and the creation of composite variables will be carried out, where required. Data from each data collection period will be collated using the unique patient identifier.

The statistical analysis for the CKD study will be conducted by the biostatistician, with oversight from the senior biostatistician. The senior biostatistician will review the statistical analyses and will explicitly check the Stata programming code for the statistical analysis, reporting and interpretation of the results. Health economists will be responsible for the analyses related to the health economics component of the trial. The files for the final analysis will be stored within the secure virtual environment, as well as all subsequent outputs including (but not limited to) Stata Statistical software Do files (*.do), data sets (*.dta), log (*.log) and graph (*.gph) files.

The biostatistician conducting the analysis and study investigators not involved in practice support and engagement will remain masked to the allocation of practices. Masking will be maintained as general practices are de-identified by the GRHANITE data extraction tool and assigns a unique code to the general practice records and patient codes. The study arm codes made available to the biostatistician conducting the analysis will be uninformative. The results for the primary outcome for the CKD study will initially be presented to the FHT investigators using the uninformative study code to maintain masking and will be revealed after the results have been interpreted.

2.5 Timing of final analysis and outcomes assessment

Statistical analyses for the CKD study are planned to commence when the final data set is received late October 2022 and after the Statistical Analysis Plan has been uploaded to the Australian and New Zealand Clinical Trials Registry. Analysis for the cancer-risk study described in a separate SAP is planned to commence in 2023.

Primary and secondary outcomes will be assessed at the trial end date, 30th September 2022, approximately 12-months after the trial start date, 4th October 2021. Subsequent references to the trial period refer to this 12-month period. The outcomes at end of the trial will be based on their most recent

recorded medication prescribed, observations and/or pathology test results in the EMR within the trial period.

Baseline measures of the outcome and patient characteristics will be assessed at the trial start date (4th October 2021). The baseline measures of the outcomes for eligible patients will be based on the history of observations and/or pathology test results in the EMR in the preceding 12 months from the 4th of October 2021, except for systolic blood pressure which will be based on the preceding 6 months, and current medication status, which considers the entire history of prescribed medications.

3. Statistical Principles

3.1 Level of statistical significance and confidence intervals

Estimates of the intervention effect will be reported with 95% confidence intervals and two sided-p-values.

3.2 Adjustment for multiple tests including description of controlling for type I error

No adjustments will be made for multiplicity. Separate sample sizes were determined for the respective primary outcomes for the CKD and cancer-risk studies and different samples will be drawn from the respective populations for the two studies. The total number of practices recruited in the trial were based on the sample size required for the CKD arm of the trial.

3.3 Adherence and protocol deviations

Protocol deviations include technical issues resulting in FHT being inaccessible for periods throughout the trial and preventing the extraction of data to the Patron system. Technical issues with FHT, practice computers/servers (preventing upload of data or function of FHT) or other technical issues that prevent staff from accessing FHT could negatively impact on the ability of GPs to participate in quality improvement program and to receive recommendations to facilitate delivery of guideline concordant care to patients within their cohort and may attenuate the effect of the intervention. Practices allocated to the active control arm will only have access the QI cancer-risk program.

4. Trial Population and Statistical Analysis

4.1 Outcomes

The **primary outcome** is the proportion of eligible patients with a diagnosis or pathology results consistent with CKD at baseline subsequently prescribed ACEI/ARB, or/and statins consistent with Kidney Health Australia[3], RACGP Red Book[2] and National Vascular Disease Prevention Alliance Guidelines[4] within the 12 months trial period , and will be considered to have received guideline concordant care. The absence of any recorded prescription for an ACEI/ARB and/or statins during the trial period will be considered equivalent to the patient not being prescribed the medications.

Secondary outcomes will include the individual indicators for guideline concordant care, including recorded medication prescribed, observations and/or pathology test results and number of encounters of patients that attended during the 12-month trial period.

(1) The proportion of eligible patients with a diagnosis or pathology results consistent with CKD at baseline subsequently prescribed ACEIs or ARBs consistent with Kidney Health Australia[3], RACGP Red Book[2] and National Vascular Disease Prevention Alliance Guidelines[4] within the 12 month trial period. The absence of any recorded prescription for an ACEI/ARB during the trial period will be considered equivalent to the patient not being prescribed an ACEI or ARB.

(2) The proportion of eligible patients with a diagnosis or pathology results consistent with CKD at baseline subsequently prescribed statins consistent with the National Vascular Disease Prevention Alliance Guidelines[4] and ACC/AHA Guideline on the Primary Prevention of Cardiovascular Disease[5] within the 12 month trial period. The absence of any recorded prescription for a statin will be considered equivalent to the patient not being prescribed a statin.

(3) Change in mean systolic blood pressure (mmHg) between baseline and the end of the trial. Patients' most recent systolic blood pressure measurement at baseline, up to six-months pre-trial (4th April 2021) from the trial start date will be compared to the most recently recorded measurement occurring within the trial period at the end of the trial. The timing of blood pressure measurements may vary within and between study arms.

(4) Change in mean lipid results (mmol/L) between baseline and the end of the trial. Patients' most recent lipid measurement at baseline, up to 12-months pre-trial (4th October 2020) will be compared to the most recently recorded measurement occurring within the trial period, at the end of the trial. The timing of lipid measurements may vary within and between study arms. Four types of lipids will be investigated:

- Total cholesterol
- LDL cholesterol
- HDL cholesterol
- Triglycerides

(5) Change in mean uACR between baseline and the end of the trial. Patients' most recent uACR measurement at baseline ($uACR_{baseline}$), up to 12 months before the trial start date (4th October 2020) will be compared to the most recently recorded measurement occurring within the trial period ($uACR_{12mth}$), at the end of the trial. The timing of uACR measurements may vary within and between study arms.

(6) The proportion of eligible patients whose uACR decreases by ≥ 30%, defined as follows:

$$\frac{(uACR_{baseline} - uACR_{12mth})}{uACR_{baseline}} \geq 0.3$$

(7) The proportion of patients categorised as low (<10%), moderate (10 to 15%), and high risk (>15%) of CVD within the next 5-years based on the Framingham Risk Equation used by the Australian

management guidelines[4]. Patients will automatically be classified as being at high risk of CVD regardless of their Framingham 5-year risk if they have at least one of the following clinically conditions:

- Diabetes and age > 60 years
- Diabetes with microalbuminuria (> 20 mcg/min or uACR > 2.5 mg/mmol for males, > 3.5 mg/mmol for females)
- Moderate or severe chronic kidney disease (persistent proteinuria or eGFR< 45 mL/min/1.73 m2)
- A previous diagnosis of familial hypercholesterolaemia
- Systolic blood pressure ≥ 180 mmHg or diastolic blood pressure ≥ 110 mmHg
- Serum total cholesterol > 7.5 mmol

(8) The change in mean eGFR (ml/min/1.73^2) between baseline and the end of the trial. Patients' most recent eGFR measurement at baseline, up to 12 months prior to the beginning of the trial (4th October 2021) will be compared to the most recently recorded eGFR measurement occurring within the trial period, at the end of the trial. The timing of eGFR measurements may vary within and between study arms.

(9) The rate of general practice encounters per patient over the trial period. This will be calculated using total number of general practice encounters in the 12-month trial period of all eligible patients with a diagnosis or pathology results consistent with CKD at baseline divided by the total time they were observed in the trial. For each patient, time will be one year, calculated from the date the trial commenced (4th October 2021) to the end of the trial (30th September 2022), except for patients/practices that discontinued during the trial period, where time observed will be calculated from the 4th October 2021 to the date the patient(s) discontinued/withdrew.

Health economics outcomes are:

(10) The cost of the installation for the software program for QI, training, QI support and education. This will be calculated at the general practice level, using cost data collected by Health and Biomedical Informatics Centre (HABIC R^2) who developed and provided technical support for the FHT software and the FHT investigators and research team who liaised with practices and facilitated the education sessions.

(11) Cost of primary care service utilisation per patient per year. These will be calculated based on Medicare items, Provider Charge, Schedule Fee, Patient Out of Pocket in the Medicare Benefits Schedule (MBS) data linked to patients in the Patron for the FHT evaluation.

4.2 Baseline practice, practice staff, and patient characteristics

Baseline practice and practice staff characteristics include:

- State (Victoria, Tasmania)
- IRSD terciles based on the Index of Relative Socio-Economic Disadvantage (IRSD) [8] using the practice postcode. The first tercile represents relatively disadvantaged sociodemographic geographic areas compared to geographic areas with higher ranks (Tercile 3).
- Practice participation in a formalised QI program in the past 6 months (yes, no)

- Practice size based on the GP full-time equivalent (FTE) of 4 or less FTE or greater than 4 FTE as reported by the practice. FTE will be defined as the total number of full-time GPs plus the total number of part time GPs multiplied by 0.5FTE.
- GPs sex (male, female)
- GPs age group (<35 years; 35 to 50 years; >50 years)
- Number of FTE registered nurses. FTE will be defined as the total number of full-time nurses plus the total number of part time nurses multiplied by 0.5FTE.
- Registered nurses' sex (male, female)
- Registered nurses age group (<35 years; 35 to 50 years; >50 years)
- Number of FTE practice managers and administrative staff. FTE will be defined as the total number of full-time practice managers/administrative staff plus the total number of part time practice managers/administrative staff multiplied by 0.5FTE.
- Practice managers/administrative staff sex (male, female)
- Practice managers/administrative staff age group (<35 years; 35 to 50 years; >50 years)

Patient characteristics and medication prescribed, observations and/or pathology test results recorded at baseline (4th October 2021) extracted from the EMR include:

- Sex (male, female, other)
- Age (years)
- ACEI/ARB prescription status (ACEI only, ARB only, both ACEI/ARB, None)
- Statin prescription status (yes/no)
- Recommendation for guideline concordant care to consider initiating medications (Statin only; ACEI/ARB only; Both statin and ACEI/ARB)
- Systolic blood pressure (mmHg)
- Total cholesterol (mmol/L)
- LDL cholesterol (mmol/L)
- HDL cholesterol (mmol/L)
- Triglycerides (mmol/L)
- uACR (mg/g)
- eGFR (ml/min/1.73^2)
- CVD risk category (low, medium, and high)
- Recorded diagnosis of type 2 diabetes prior to baseline (yes/no)

4.3 Other information extracted from the EMR that occur during the trial period

- Patient experienced ischemic stroke, heart attack, peripheral vascular disease, and/or kidney dialysis
- Pregnancy
- Patient deceased
- Time between most recent reported measurement at end of the trial in the EMR compared to baseline for secondary outcomes (1 to 8)

4.4 Withdrawal and Follow-up

Staff within practices and/or the practice may withdraw at any time. If a practice withdraws then no further patient data will be extracted from the EMR system. However, existing data (prior to notice of withdrawal) will be used in the final analysis unless the practice requests existing data also be excluded. Individual patients can also withdraw their data by notifying their general practice that they no longer consent to their data being used for research purposes. As the intervention is applied at the general practice level within the EMR system this means that no further patient data will be extracted. However, existing data (prior to notice of withdrawal) will be used in the final analysis unless the participant requests existing data also be excluded.

4.5 Descriptive analysis

The flow of practices and eligible patients from recruitment to trial end, will be shown in a CONSORT diagram[1], see Appendix Figure 1 for the template. The report will include the number of practices approached for involvement in the trial, the number of practices that met study eligibility criteria, the number practices consented and randomised by their allocated study arm, together with the total number and the mean number of eligible patients per practice and number that were included in the intention to treat analysis. The number of practices and/or patients who withdraw or discontinue will also be summarised by study arm and period that the withdrawal/discontinuation occurred (0-6 months, 7-9 months, 10-12 months). When such information is available, the reason a practice/patient withdrew or discontinued the intervention will be reported by study arm.

Descriptive statistics will be used to describe general practice and patients' baseline characteristics and baseline outcome measures overall and by study arm as outlined in Appendix B Table 1 and Table 2. Descriptive statistics will also be used to summarise other information extracted from the EMR that occur during the trial period by study arm and overall. Categorical data will be summarised using counts and percentages, according to the number of eligible patients with available data. Continuous data will be summarised using arithmetic mean, standard deviation if the data have a symmetric distribution. When appropriate, continuous outcome data with a right skewed distribution may be presented as a geometric mean instead of an arithmetic mean. Otherwise, if the distribution if the data is non-symmetrical, the median and interquartile range (25^{th} and 75 percentiles) will be presented instead. The intra-cluster correlation coefficient with 95% intervals will also be reported for baseline patient measurements estimated using one-way analysis of variance.

4.6 Primary Analyses

The primary analyses will use an intention to treat (ITT) approach, where all practices randomised will be included in the analysis by their allocated study arm status, regardless of whether they received all, part, or none of the intended intervention.

4.6.1 Primary outcome

For the primary outcome, the odds ratio (relative measure) and the difference in proportions between the intervention and control arms (absolute measure) will be estimated using a generalised linear model (GLM) with the logit link and identity link functions, respectively, and binomial distribution for both models. Both models will include randomisation stratification factors, GP FTE and IRSD terciles as covariates, and use Generalised Estimating Equations with an exchangeable correlation structure and robust standard errors to allow for correlation of outcomes within general practice. If the model used to

estimate the risk difference fails to converge, the risk difference will be derived from the GLM with the logit link function.[9,10]

Absolute (difference in proportions between the intervention and control arms), and relative (odds ratio) estimated intervention effects for the primary outcome will be reported with 95% confidence intervals and p-values.

4.6.2 Secondary outcomes

Statistical methods described for the primary outcome will be used for the **binary secondary outcomes 1, 2, and 6.** For each outcome, an additional covariate will be fitted in the regression model. For outcome 1, we will adjust for whether a recommendation would have been made to consider initiating ACEIs or ARBs for the patient (yes/no). Similarly for outcome 2, we will adjust for whether the recommendation would have been received to consider initiating statins (yes/no). For outcome 6, we will include uACR at baseline as a covariate.

For the analysis of continuous secondary **outcomes 3, 4, 5 and 8**, a mixed effects linear model with study arm, baseline measure of the outcome (where appropriate), randomisation stratification factors (GP FTE and IRSD terciles) will be fitted as fixed effects and general practice as a random effect. The estimated intervention effects will be reported as the difference in means between the intervention and active control arms with 95% confidence intervals and p-values.

Outcomes with a skewed distribution may be log-transformed, in which case, the estimated intervention effect will be reported as a ratio of the geometric means between study arms, with their respective 95% confidence interval and p-value.

Secondary outcome 7 will be analysed using the proportional odds logistic regression model with randomisation stratification factors (GP FTE and IRSD terciles) and baseline CVD risk group included as fixed effects. Generalised Estimating Equations with an exchangeable correlation structure and robust standard errors will be used to allow for correlation of outcomes within general practice. An alternative model will be considered if the assumption of proportional odds is not met.[11]

The estimated intervention effect will be reported as a cumulative odds ratio with their respective 95% confidence interval and p-value.

Secondary outcome 9 will utilise a Poisson mixed effects model (or a Negative Binomial mixed effects model if overdispersion is detected), with fixed effects for study arm and the randomisation stratification factors (GP FTE and IRSD terciles), and random effect for general practice. The estimated intervention effect will be reported as differences in rate between the intervention and control arms and rate ratios with 95% confidence intervals and p-values.

4.6.3 Health economic outcomes

Costs of the installation of the software program and training of the general practice staff to use the software (**Outcome 10**) will be summarised using descriptive statistics.

Health care service costs (**Outcome 11**) will be compared between the intervention and control arms using a GLM with a log link and gamma distribution, two-part model or mixtures model depending on the distribution of costs.

4.7 Supplementary Analysis

4.7.1.1 Sensitivity analysis 1: Adjustment of additional covariates

Sensitivity analysis of primary and secondary outcomes will additionally adjust for three confounders measured at baseline: prior practice participation in a formalised quality improvement program (yes, no), patient's age at baseline, sex (male, female, other). These variables will be added as covariates to the regression models described for the primary analysis.

4.7.1.2 Sensitivity analysis 2: Intercurrent events

All eligible patients will be included in the primary ITT analysis, including any patients who die during the trial period. Patients who become pregnant during the trial will also be included in the ITT analysis, although treatment is likely to be deferred for these patients by the general practitioner as these medications are not recommended during pregnancy. We expect the numbers who die over the 12 months of the trial period or become pregnant to be less than 10% of the sample size and similar in the two arms. However, if they do exceed 10% of the sample size, we will conduct a sensitivity analysis for the primary outcome excluding these patients from the ITT analysis.

4.7.1.3 Sensitivity analysis 3: Missing outcome data

1) A sensitivity analysis will be conducted to assess the robustness of the missing data assumption using a pattern-mixture model for the primary outcome if more than 10% of the eligible patients have missing responses either because of patient and/or practices withdraw from the trial.
2) For the secondary outcomes related to pathology test results and observations (outcome 3 to 8), there may be missing data at baseline and/or the end of the trial for various reasons. For instance: (1) the pathology test was not ordered, or blood pressure not measured; (2) pathology test was ordered/blood pressure measured but the results were either incorrectly recorded (e.g., non-sensical beyond physiological belief), or not recorded in the EMR; (3) general practitioners may have recorded a prescription or an observation such as blood pressure, but they might not have been recorded in a field that is extracted by GRHANITE and stored in the Patron dataset; (4) the patient did not attend the practice during the trial period. Given the complexity of the EMR data and different reasons for the missing data, it is difficult to determine at this stage the most appropriate statistical methods to handle the missing data. [12,13] The approach will be determined after a blinded review of the missing data patterns, the reason for missing data and their corresponding mechanism, and the SAP will be updated accordingly. The techniques that may be used to handle incomplete data include adding additional covariates associated with missing data to the mixed effects linear model for continuous outcomes, multiple imputation approach and/or using a pattern-mixture model.

4.7.2 Adherence-adjusted analysis

The effects of incomplete adherence on the estimated intervention effects will be investigated using a complier average casual effect (CACE) analysis[14-16] for the primary outcome only. Prior to conducting the data analysis, study investigators and the data management team, masked to the practice's study arm allocation and informed by the process evaluation, will meet to review adherence with the intervention protocol and construct the indicators for incomplete adherence based on the level of FHT QI program integration within each practice. These will be:

1) the number of days that the QI module is active within each practice that will take into consideration whether practices experienced technical issues during the trial period, such as

delayed initiation of the intervention or the FHT QI program was available for intermittent periods of time during the trial period. We will consider practices to have adhered to the intervention if the FHT QI program was accessible for at least 75% of the time during the 12 months of the trial duration. Other cut-points may be considered after a masked review of the process evaluation measures.

2) the number of FTE general practitioners and FTE nurses compared to the number of computers where the FHT QI module is installed/accessible by general practice clinicians as a proxy measure of the degree of access to the point of care clinical decision support tool. FHT QI platform was not installed on all the computers in some general practices. Thus, some general practitioners/nurses within these practices may not have been exposed to the FHT platform or may have had limited access to the platform, specifically the point of care clinical decision support tool. The cut-point for non-adherence will be defined after masked review of the process evaluation measures.
3) the degree of engagement of general practices with the different components of the intervention (e.g., ECHO series, use of the FHT tool to create cohorts) which will be informed by the process evaluation.

A separate CACE analysis will be conducted for each of the nominated adherence indicators above. A two-stage least squares instrumental variable regression will be undertaken where the adherence variables are binary indicator variables and study arm used as the instrumental variable for adherence to the intervention. We will use robust estimation for the variance to account for clustering by general practice and adjust for the stratification factors (practice size and IRSD terciles). Sensitivity analyses using other statistical methods for incomplete adherence may also be conducted to assess the robustness of underlying assumptions.[16]

4.7.3 Subgroup Analysis

Three sub-group analyses will be conducted, regardless of the trial findings of the primary analyses.

1. Patients that had a recommendation to consider initiation of a statin may have been prescribed ACEI/ARB or did not require this class of medications at baseline. Thus, we will conduct a sub-group analysis using the same regression models described above for the secondary outcomes 1, 5 and 6 by whether patients receive a recommendation to consider initiation of ACEIs/ARBs at baseline. For patients that receive a recommendation to consider initiation of ACE Is/ARBs at baseline and receive a prescription for the class of medications during the trial period, we will investigate the effect of the time between receiving their first prescription to the most recent measure of the pathology measure at the end of the trial period (<3 months; >=3-6 months; >=6 months) for the secondary outcomes 5 and 6, as appropriate. These findings may be reported in part with the primary analysis or in a separate publication.

2. Patients that had a recommendation to consider initiation of an ACEI/ARB may have been prescribed statins or may not require statins at baseline. Thus, we will conduct a sub-group analysis using the same regression models described above for the secondary outcome 2 and 4 by whether patients would receive a recommendation to consider initiation of statins at baseline. For patients that receive a recommendation to consider initiation of statins and

receive a prescription for statin during the trial period, we will investigate the effect of the time between receiving their first statin prescription to the most recent measure of the pathology measure at the end of the trial period (<3 months; >=3-6 months; >=6 months) for outcome 4, as appropriate. These findings may be reported in part with the primary analysis or in a separate publication.

3. The statistical analyses described for the primary and secondary outcomes will be repeated for eligible patients with and without a recorded diagnosis of type 2 diabetes at baseline. This sub-group analysis will be reported in a separate paper to the primary analysis.

The statistical analysis for each subgroup will be conducted by including the subgroup variable and its interaction with the intervention as fixed effects to the regression models. Summary statistics will be presented for each sub-group within each study arm, as well as estimates for the intervention effects (appropriate to the outcome type) with a 95% confidence interval and a p-value corresponding to the interaction term between the study arm and the subgroup variable. The estimates may also be displayed on a forest plot.

4.8 Statistical Software, Reporting and Technical details

All analyses will be conducted using Stata Statistical software (v17)[7] or later. Appendix B Table 3 provides the proposed template for the statistical analysis of the primary and secondary outcomes. These results may also be presented graphically, where appropriate. Any post-hoc explanatory analyses not identified in the SAP will be clearly identified in the final statistical report. Any deviations from the planned analyses detailed in the SAP will be documented and reported in a revised version of this SAP.

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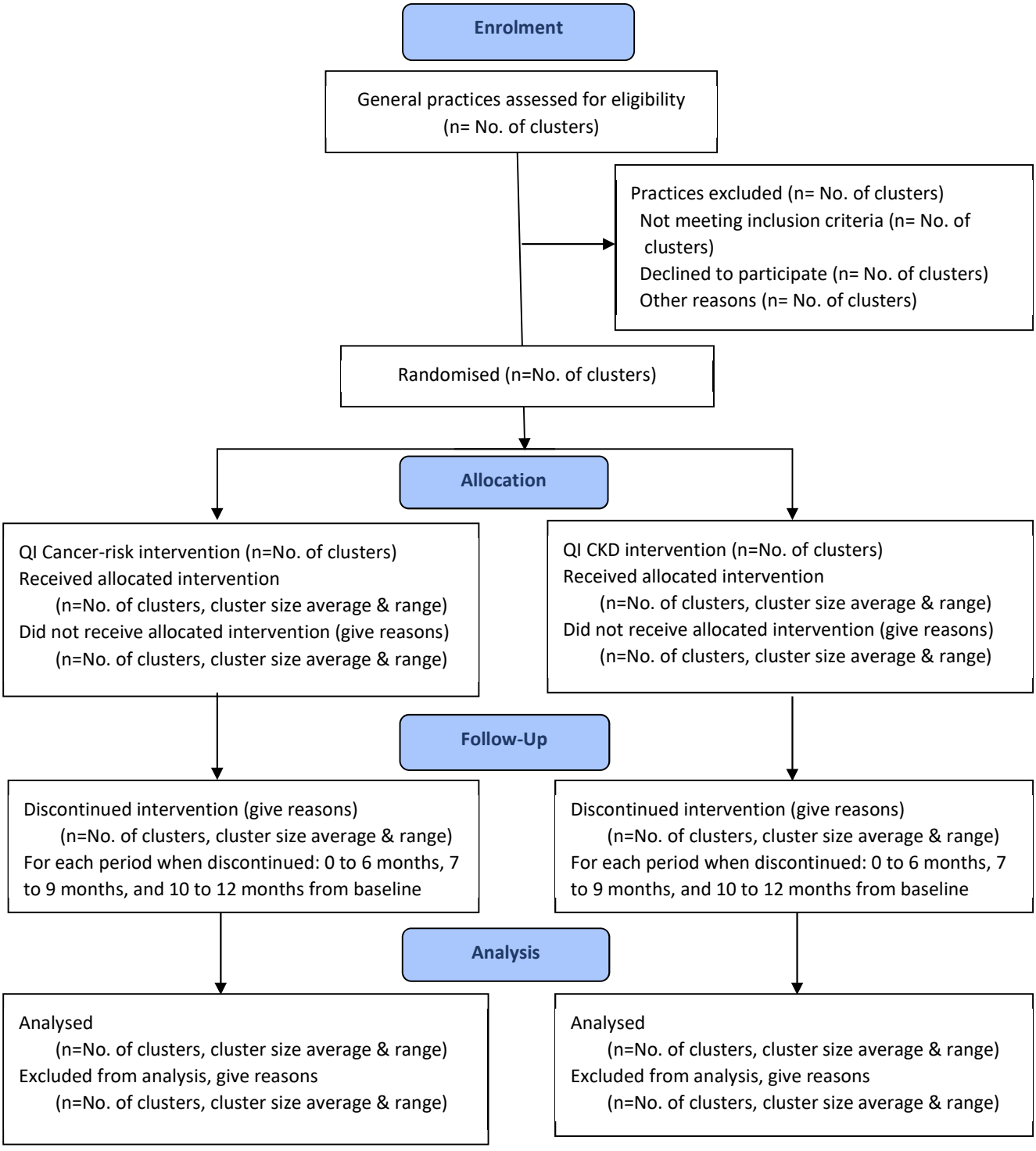
Appendix A – CONSORT diagram



Appendix B – Proposed tables for Baseline Participant Characteristics and Outcomes

Table 1. Baseline characteristics of practices and practice staff for all participants and by study arm

	All participants	Intervention arm	Active control arm
Practice Characteristics	N	N	N
State			
Victoria	n(%)	n(%)	n(%)
Tasmania	n(%)	n(%)	n(%)
Relative Socio-Economic Disadvantage Index (Terciles)			
1 Most disadvantaged	n(%)	n(%)	n(%)
2	n(%)	n(%)	n(%)
3 Least disadvantaged	n(%)	n(%)	n(%)
Previously participated in QI Program	n(%)	n(%)	n(%)
Practice Size			
4 or fewer FTE GPs	n(%)	n(%)	n(%)
Greater than 4 FTE GPs	n(%)	n(%)	n(%)
Number of FTE GPs	Median (IQR)	Median (IQR)	Median (IQR)
Number of FTE Nurses	Median (IQR)	Median (IQR)	Median (IQR)
Number of FTE Practice Managers/Administrative staff	Median (IQR)	Median (IQR)	Median (IQR)
General practitioners	N	N	N
Sex			
Male	n(%)	n(%)	n(%)
Female	n(%)	n(%)	n(%)
Age			
< 35 years	n(%)	n(%)	n(%)
35 to 50 years	n(%)	n(%)	n(%)
> 50 years	n(%)	n(%)	n(%)
Registered nurses	N	N	N
Sex			
Male	n(%)	n(%)	n(%)
Female	n(%)	n(%)	n(%)
Age			
< 35 years	n(%)	n(%)	n(%)
35 to 50 years	n(%)	n(%)	n(%)
> 50 years	n(%)	n(%)	n(%)
Practice managers/ Administrative staff	N	N	N
Sex			
Male	n(%)	n(%)	n(%)
Female	n(%)	n(%)	n(%)
Age			
< 35 years	n(%)	n(%)	n(%)
35 to 50 years	n(%)	n(%)	n(%)
> 50 years	n(%)	n(%)	n(%)

N – number of practices/practice staff; % - Column percentage; IQR – Interquartile range; FTE – Full-time equivalent; GP - general practitioner. **Note**: Continuous variables may be categorised and sub-categories may also be collapsed in final table published.

Table 2. Baseline characteristics of patients for all participants and by study arm

Patient Characteristics	**All participants**	**Intervention arm**	**Control arm**
	N	N	N
Sex			
Male	n(%)	n(%)	n(%)
Female	n(%)	n(%)	n(%)
Other	n(%)	n(%)	n(%)
Age (years)	mean (SD)	mean (SD)	mean (SD)
Prescribed ACEI/ARB			
ACEI only	n(%)	n(%)	n(%)
ARB only	n(%)	n(%)	n(%)
ACEI and ARB	n(%)	n(%)	n(%)
None	n(%)	n(%)	n(%)
Prescribed Statins			
Yes	n(%)	n(%)	n(%)
No	n(%)	n(%)	n(%)
Recommendation for guideline concordant care to consider initiating:			
Both ACEI/ARB & statins	n(%)	n(%)	n(%)
ACEI/ARBs only	n(%)	n(%)	n(%)
Statin only	n(%)	n(%)	n(%)
CVD Risk Category			
Low	n(%)	n(%)	n(%)
Moderate	n(%)	n(%)	n(%)
High	n(%)	n(%)	n(%)
SBP (mmHg)	N mean (SD)	N mean(SD)	N mean(SD)
Lipids (all mmol/L)			
Total	N mean(SD)	N mean(SD)	N mean(SD)
LDL	N mean(SD)	N mean(SD)	N mean(SD)
HDL	N mean(SD)	N mean(SD)	N mean(Sd)
Triglycerides	N mean(SD)	N mean(SD)	N mean(SD)
uACR (mg/g)	N mean(SD)	N mean(SD)	N mean(SD)
eGFR (ml/min/1.73^2)	N mean(SD)	N mean(SD)	N mean(SD)

N – number of patients; % - Column percentage; SD – standard deviation

Note: Continuous variables may be categorised and sub-categories may also be collapsed in final table published.

Table 3. Analyses for Primary and Secondary Outcomes

	All participants	Intervention arm	Active control arm	Estimated effect size Coefficient (95%CI)		
Primary Outcome	N	N	N			
Primary analysis	n (%)	n (%)	n (%)	Difference (95% CI)	Odds ratio (95% CI)	p-value
Sensitivity Analysis[1]				Difference (95% CI)	Odds ratio (95% CI)	p-value
Sensitivity Analysis[2]				Difference (95% CI)	Odds ratio (95% CI)	p-value
Adherence adjusted analysis[3]				Difference (95% CI)	Odds ratio (95% CI)	p-value
Secondary outcomes (1, 2, and 6)	N	N	N			
Primary analysis	n (%)	n (%)	n (%)	Difference (95% CI)	Odds ratio (95% CI)	p-value
Sensitivity Analysis[1]				Difference (95% CI)	Odds ratio (95% CI)	p-value
Sensitivity Analysis[2]				Difference (95% CI)	Odds ratio (95% CI)	p-value
Secondary Outcomes (3, 4, 5 and 8)	N	N	N			
Primary analysis	mean (SD)	mean (SD)	mean (SD)	Difference in means (95% CI)		p-value
Sensitivity Analysis[1]				Difference in means (95% CI)		p-value
Sensitivity Analysis[2]				Difference in means (95% CI)		p-value
Secondary Outcome 7	N	N	N			
Primary analysis				Cumulative Odds ratio (95% CI)		p-value
Low CVD risk	n (%)	n (%)	n (%)			
Medium CVD risk	n (%)	n (%)	n (%)			
High CVD risk	n (%)	n (%)	n (%)			
Sensitivity Analysis[1]				Cumulative Odds ratio (95% CI)		p-value
Sensitivity Analysis[2]				Cumulative Odds ratio (95% CI)		p-value
Secondary Outcome 9	N	N	N			
Primary analysis	n (rate)	n (rate)	n (rate)	Difference in rates (95% CI)	Rate ratio (95% CI)	p-value
Sensitivity Analysis[1]				Difference in rates (95% CI)	Rate ratio (95% CI)	p-value
Sensitivity Analysis[2]				Difference in rates (95% CI)	Rate ratio (95% CI)	p-value

N – number of patients; Difference – Difference in percentages between the arms, unless otherwise stated; SD - Standard deviation; % - column percentages; CI -Confidence interval.

[1] Sensitivity analysis adjusted for the practice participation in formalised QI program, patients age in year, and patient's sex

[2] Sensitivity analysis for intercurrent events

[3] Adherence adjusted analysis repeated for each of the nominated adherence indicator

Note: The table may be split to separate tables for the different outcomes.

Statistical Analysis Plan for Future Health Today: A pragmatic stratified 12-month cluster randomised controlled trial of quality improvement activities in general practice for patients at risk of undiagnosed cancer.

TRIAL FULL TITLE	Statistical Analysis Plan for Future Health Today: A pragmatic 12-month cluster randomised controlled trial of quality improvement activities in general practice for patients at risk of undiagnosed cancer.
TRIAL SHORT TITLE	FHT trial: Cancer-risk Statistical Analysis Plan
TRIAL REGISTRATION	This trial is registered with the Australian and New Zealand Clinical Trial Registry (www.anzctr.org.au) (ACTRN): ACTRN12620000993998. Date registered: 02 October 2020.
ETHICS APPROVAL	Trial protocol was approved by the Faculty of Medicine, Dentistry and Health Sciences Human Ethics Sub-Committee at the University of Melbourne (ID: 2056564).
PROTOCOL VERSION	Manski-Nankervis, J.-A., Hunter, B., Hallinan, C. M., Lumsden, N., Martinez Gutierrez, J., Chima, S., Nelson, C., Tran, A. D., Jesudason, S., Boyle, D., Chondros, P., McMorrow, R., Radford, J., Prictor, M., and Emery, J. (2022), "Future Health Today: Protocol for a pragmatic stratified cluster randomised head-to-head trial of quality improvement activities in general practice compared to active control.", University of Melbourne. https://doi.org/10.26188/21342891.v2.

SAP Revision History

Version	Reason(s) for change	Date

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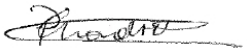
A/Prof. Patty Chondros	Senior Biostatistician	Department of General Practice, University of Melbourne	
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The design, management, analysis, and reporting of the study are entirely independent of the funders.

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Abbreviations

ABBREVIATION	DEFINITION
AE	Adverse Event
CKD	Chronic Kidney Disease
CSV	Comma Separated Values
CV	Coefficient of variation
CVD	Cardiovascular Disease
EMR	Electronic Medical Record
FHT	Future Health Today
FOBT	Faecal Occult Blood Test
FTE	Full-Time Equivalent
GI	Gastro-Intestinal
GLM	Generalised Linear Model
GP	General Practitioner
GRHANITE	Generic Health Network Information Technology for Enterprise
HABIC R^2	Health and Biomedical Informatics Centre
Hb	Haemoglobin
ICC	Intra-cluster correlation
IQR	Interquartile Range
IRSD	Index of Relative Socio-economic Disadvantage
ITT	Intention-to-treat
MBS	Medicare Benefits Schedule
MCH	Mean Corpuscular Haemoglobin
MCV	Mean Corpuscular Volume
NICE	National Institute for Health and Care Excellence
PAT	Practice Assessment Tool
PSA	Prostate-Specific Antigen
QI	Quality Improvement
RCT	Randomised controlled trial
SAP	Statistical Analysis Plan
SEIFA	Socio-Economic Indexes for Areas
SQL	Structured Query Language
VicREN	Victorian Research and Education Network

1 Introduction

1.1 Synopsis

Future Health Today (FHT) is a stratified head-to-head cluster randomised controlled trial (RCT) of quality improvement (QI) activities in general practice in Australia. The QI program that forms the intervention consists of a new technology platform (FHT, with audit, recall, clinical decision support and monitoring of QI activity capability) and case-based learning series for specific clinical areas. For the FHT trial we have focused on QI programs for two common conditions managed in general practice, cancer-risk and chronic kidney disease (CKD). The QI cancer-risk program focuses on the appropriate investigation and follow-up of people at increased risk of an undiagnosed cancer among general practice patients. The QI CKD program focuses on reducing cardiovascular disease (CVD) risk for individuals with a recorded diagnosis or pathology results consistent with a diagnosis of CKD. General practices will be randomly assigned equally to either the QI CKD program or the QI cancer-risk program, with different target populations and outcomes measured for each QI program. Thus, practices randomised to the QI cancer-risk program will act as an active control for the QI CKD program, and vice versa.

This statistical analysis plan (SAP) will focus on the cancer-risk intervention and a separate SAP was developed documenting the statistical analysis for the CKD intervention. The analysis and findings for each study (CKD and cancer-risk) will be published as separate manuscripts following the CONSORT (Consolidated Standards of Reporting Trials) guidelines.[1] The background and rationale for the FHT trial are described in the trial protocol, including the setting, recruitment, eligibility criteria, randomisation, and sample size calculations.

This document elaborates on the statistical analysis for the primary and secondary outcomes of the cancer-risk intervention, including sensitivity and pre-planned explanatory analyses, health economic analyses and handling of missing outcome data where appropriate. The process evaluation to identify the barriers and facilitators to successful implementation of FHT in daily practice will be described in a separate document.

1.2 Primary hypothesis

The null hypothesis is that there is no difference in the proportion of patients, identified as at risk of an undiagnosed cancer, who receive guideline concordant follow-up at 12 months post-intervention compared with patients attending general practice providing usual care (active control arm) The alternative hypothesis is that there is a difference in the primary outcome between the two trial arms.

1.3 Study objectives

The cancer-risk trial component will evaluate the effectiveness of the FHT QI intervention on the appropriate investigation and follow-up of people at increased risk of an undiagnosed cancer in general practice.[2-5] The primary objective is to determine if patients with abnormal test results and additional clinical features placing them at risk of an undiagnosed cancer who attend general practice clinics participating in FHT QI for cancer-risk (intervention arm) are more likely than similar patients attending general practices that provide usual care (control arm) to be assessed and investigated within 12 months post-randomisation.

Secondary objectives of the trial are to determine the effectiveness of the FHT QI program for cancer risk compared to usual care for patients by evaluating the:

1. proportion of patients with markers of anaemia ((Haemoglobin <130g/L in men and <115g/L in women) or MCV <80fl or MCH <27pg or ferritin<30µg/L) that have been assessed for upper and lower GI symptoms and/or haematuria or who have had at least one of the following investigations ordered during the 12-month follow-up period post-randomisation: a repeat full blood count, iron studies, coeliac disease serology, faecal occult blood test (FOBT), transvaginal ultrasound or a referral for further investigation.[2,6]

2. proportion of patients with markers of anaemia that have a prescription of oral supplements and/or had an iron infusion recorded in the general practice electronic medical record (EMR) during the 12-month follow-up period post-randomisation.[7]

3. proportion of patients with a raised platelet count that have been assessed for symptoms (defined in Victorian Department of Health[3], NICE[2], and Cancer Council[4] guidelines as indicative of oesophageal, gastric, colorectal, endometrial, lung or ovarian cancer) or who have been followed up with one or more of the following during the 12-month follow-up period post-randomisation: a repeat platelet count, chest x-ray, chest CT, FOBT, transvaginal ultrasound, CA125, or a referral for further investigation.

4. proportion of patients with one raised PSA that have been followed up with a second PSA and/or free-to-total PSA percentage (as per Cancer Council Australia guidelines[4]) or a referral for further investigation, during the 12-month follow-up period post-randomisation.[5,8]

5. proportion of patients with an altered test result placing them at risk of an undiagnosed cancer (iron-deficiency anaemia, raised platelets or raised PSA) who have a diagnosis of prostate, oesophageal, gastric, colorectal, endometrial, lung or ovarian cancer during the 12-month follow-up period post-randomisation.

6. rate of encounters per patient identified as at risk of undiagnosed prostate, oesophageal, gastric, colorectal, endometrial, lung or ovarian cancer over the 12 months post-randomisation.

7. time to investigation for patients who have an altered test result placing them as at increased risk of an undiagnosed cancer during the trial period, using the first relevant investigation to occur between the patient's entry into the trial and 12-months post-randomisation.

For the health economic analysis, the objective is to quantify the costs of the delivery of the FHT QI program and the health care service costs. Specifically, the objectives are:

8. to estimate the cost of the FHT software program installation for QI and cost of training for general practitioners to use the software.
9. examine primary health service utilisation and cost incurred by patients identified as at risk of cancer in the intervention arm compared to at risk patients in the active control arm over the 12-month period post-randomisation.

2 Trial design

The FHT trial is a stratified head-to-head cluster randomised controlled trial. The unit of randomisation is the general practice, where practices are randomly allocated concurrently on 1:1 ratio to either participate in the FHT Cancer-risk module (intervention arm) or FHT CKD QI module (active control arm). All general practices will be provided access to the respective QI programs at the commencement of the trial (October 4th, 2021). The active control arm described in this SAP will receive a QI program aimed at optimising pharmacological management in people with CKD to reduce cardiovascular disease (CVD) risk. Please refer to the trial protocol for a detailed description of the intervention and comparator.

2.1 Study Population

The trial will be conducted in general practices in Victoria and Tasmania. For full details of the eligibility and exclusion criteria for general practices, please refer to the study protocol.

2.2 Patient eligibility and exclusion criteria

Eligible patients will be identified as at risk of cancer by applying at least one or more of the following criteria:

At baseline – 4th October (**closed cohort**):

1. Patients aged 50 to 80 years (inclusive) without a recorded GI, unspecified or metastatic cancer in the last 5 years who have one marker of anaemia (defined as Hb <130g/L in men and <115g/L in women or MCV <80fl or MCH <27pg or ferritin<30µg/L) in the past 6 months or two consecutive markers of anaemia in the past 12 months.
2. Males aged 40 to 80 years (inclusive) without a recorded diagnosis of lung, colorectal, gastro-oesophageal or unspecific cancer in the previous 5 years or females aged 40 to 80 years old without a diagnosis of lung, colorectal, gastro-oesophageal, ovarian, endometrial or unspecific cancer in the previous 5 years who have one elevated plated count (defined as platelet count > 400 x 10^9/L) in the past 6 months or two consecutive elevated platelets counts in the past 12 months.
3. Males, aged 40-80, without a recorded diagnosis of prostate cancer with a raised PSA (defined as male aged 40-49 PSA > 2.0 ng/ml; male aged 50+ PSA> 3.0 ng/ml) in the past 6 months.

4th Oct 2021 - 4th April 2022 (**open cohort**):

4. Eligible patients not captured at baseline, with one or more markers of anaemia between October 4, 2021, and April 4, 2022.
5. Eligible patients not captured at baseline with an elevated platelet count between October 4, 2021, and April 4, 2022.
6. Eligible patients not captured at baseline with an elevated PSA between October 4, 2021, and April 4, 2022.

The terms closed and open cohort refer to when the patients were identified as at risk of cancer: at baseline, or during the first 6-months of the trial, respectively. Subsequent references to the closed and open cohorts refer to these eligibility criteria and the timeframes used to identify these patients.

Exclusions:

1. Patients that are recorded as no longer active in the general practice or deceased in the EMR.
2. Patients that are pregnant at baseline.

2.3 Framework

The framework for the statistical analysis will test for superiority: the primary objective is to determine whether the FHT QI program increases appropriate follow-up in patients identified as at risk of an undiagnosed cancer.

2.4 Interim analyses and stopping guidelines

No formal interim analyses are planned for this trial. As the data used in this study is EMR data extracted from general practice, no formal data monitoring was required and there are no stopping guidelines in place.

2.5 Data management and workflow

General practice and practice staff characteristics will be collected via survey before randomisation.

Patient characteristics, baseline measures and outcome data will be measured using patient data extracted from general practice EMRs and stored in the Patron database. Patient and practice data will be extracted from each practice using the GHRANITE tool at each data collection period (4th October 2021 (baseline), 4th April 2022 (6 months), 4th July 2022 (9 months) and 30th September 2022 (12 months). The extracted data will be processed and curated by Patron data team members and stored within the Patron enclave using a separate database for each data collection period. This process takes approximately two weeks.

The FHT QI module installed within practices as part of the FHT intervention interacts with the practice EMR system, running the FHT algorithms over patient data to identify patients at risk of an unidentified cancer that may benefit from further follow up. The criteria used to identify the eligible patients at risk of an unidentified cancer who attend general practice and the creation of the recommendations for guideline concordant care to consider (flags) are outlined in the Future Health Today business requirements document which was used to develop the FHT algorithms embedded in the technology platform. Within participating general practices individual patient level recommendations can be viewed. However, only aggregate level data are extracted by Future Health Today platform and available to the research team. As a result, these data are not linked with Patron database used for the trial statistical analysis. Therefore, part of this curation process is the replication of the eligible patients and flags generated by FHT algorithms in the practices, patient outcomes and baseline measures, using identical algorithms to those embedded within, and executed by, FHT platform within the Patron dataset. These algorithms were independently validated by the biostatistician using baseline data. A limitation of this approach is that we will only be able to derive the action taken by clinicians if they were recorded in an extractable field in the EMR that is included in the Patron dataset, such as pathology results, medication prescriptions written, and observations.

All data within the Patron enclave is deidentified with patient and practice identifiers replaced by a unique hashed code prior to the data leaving the general practice. Data managers and analysts can access the databases for the project and utilise Structured Query Language (SQL) queries to create Comma Separated Values (CSV) files containing the data required for the trial analysis. Files downloaded from the Patron databases will be saved within a secure virtual machine accessible only by the study biostatisticians, health economists and the data manager. The virtual machine requires multifactor authentication to access. Within the secure virtual environment, the data manager or statisticians will then import the CSV data files into Stata Statistical Software[9] for data processing and statistical analysis. Data will be checked for errors, resolving them where possible. Labelling, recoding,

and the creation of composite variables will be carried out, where required. Data from each data collection period will be collated using the unique patient identifier.

The statistical analysis for the cancer-risk study will be conducted by a PhD Candidate and the study biostatistician, with oversight from the senior biostatistician. The senior biostatistician will review the statistical analyses and will explicitly check the Stata programming code for the statistical analysis, reporting and interpretation of the results. Health economists will be responsible for the analyses related to the health economics component of the trial. The files for the final analysis will be stored within the secure virtual environment, as well as all subsequent outputs including (but not limited to) Stata .do, .dta, .log and .gph files.

The data analysts conducting the analysis and study investigators not involved in practice support and engagement will remain masked to the allocation of practices. Masking will be maintained as general practices are de-identified by the GRHANITE data extraction tool and assigns a unique code to the general practice records and patient codes. The study arm codes made available to the biostatistician conducting the analysis will be uninformative. The results for the primary outcome for the cancer-risk study will initially be presented to the FHT investigators using the uninformative study code to maintain masking and will be revealed after the results have been interpreted.

2.6 Timing of final analysis and outcome assessments

Statistical analyses for the cancer-risk study will commence in September 2023 after the Statistical Analysis Plan has been uploaded to the Australian and New Zealand Clinical Trials Registry.

Primary and secondary outcomes will be assessed at the trial end date, 30th September 2022, approximately 12-months after the trial start date, 4th October 2021. Subsequent references to the trial period refer to this 12-month period. The outcomes will reflect the status of each patient at the trial end date, based on their recorded observations, investigations and/or pathology test results in the EMR.

Baseline measures of the outcome and patient characteristics will be assessed at the trial start date (4th October 2021). The baseline measures for eligible patients will be based on the history of pathology test results in the EMR, in the preceding 6 months from the 4th of October 2021 for raised PSA, and the preceding 12-months for markers of anaemia and raised platelets.

3 Statistical principles

3.1 Level of statistical significance and confidence intervals

Estimates of the intervention effect will be reported with 95% confidence intervals and two sided-p-values.

3.2 Adjustment for multiple tests

No adjustments will be made for multiplicity. Separate sample sizes were determined for the respective primary outcomes for the cancer-risk and CKD studies and different samples will be drawn from the respective populations for the two studies. The total number of practices recruited in the trial were based on the sample size required for the CKD arm of the trial.

3.3 Adherence and protocol deviations

Protocol deviations include technical issues resulting in FHT being inaccessible for periods throughout the trial and preventing the extraction of data to the Patron system. Technical issues with FHT, practice

computers/servers (preventing upload of data or function of FHT) or other technical issues that prevent staff from accessing FHT could negatively impact on the ability of GPs to participate in the quality improvement program and to receive recommendations to facilitate delivery of guideline concordant care to patients within their cohort and may attenuate the effect of the intervention. Practices allocated to the control arm will only have access to the QI CKD program.

4 Trial population and Statistical Analyses

4.1 Primary outcome

The **primary outcome** is the proportion of eligible patients identified as at risk of undiagnosed prostate, oesophageal, gastric, colorectal, endometrial, lung or ovarian cancer that have been assessed and investigated according to NICE[2], Cancer Council Victoria[4], Victorian Government Department of Health and Human Services[8], Prostate Cancer Foundation of Australia guidelines[5], within the 12-month trial period. The absence of any relevant recorded investigation, prescription, observation, or diagnosis during the trial period will be considered equivalent to the patient not being assessed or investigated.

The primary outcome will include any relevant investigation, dependent on whether patients were identified as at risk of cancer for iron deficiency anaemia, raised platelets or raised PSA. The relevant investigation must occur between being identified as at risk of an undiagnosed cancer (either at baseline or within the following 6 months), and the trial end date (30th Sept 2022).

For each patient identified as at risk of cancer with one or more markers of anaemia, a relevant investigation includes a repeat full blood count, iron studies, coeliac disease serology, FOBT, transvaginal ultrasound, referral to gastroenterologist, assessment of upper or lower GI symptoms and/or haematuria, prescription of an oral supplement and/or record of an iron infusion.

For each patient identified as at risk of cancer with a raised platelet count, a relevant investigation includes a repeat platelet count, chest x-ray, chest CT, FOBT, CA-125, transvaginal ultrasound, assessment for symptoms for lung, colorectal, gastro-oesophageal, ovarian or endometrial cancer, referral to a gastroenterologist, respiratory physician, or gynaecologist.

For each patient identified at risk of cancer with a raised PSA, a relevant investigation includes a repeat PSA test, free to total PSA percentage and/or referral to a urologist.

For any patient identified as at risk of cancer with more than one altered test result (e.g., anaemia and raised platelets), we will consider a relevant investigation from either marker as the equivalent of being assessed and investigated according to guidelines. In usual care, it is expected that the GP would prioritise care or use a sequential manner in responding to multiple possible investigations.

EMR data will be used to determine if an investigation has occurred. The reason for encounter, reason for prescription and diagnosis fields will be reviewed for relevant symptoms. Documents in, documents out and the diagnosis fields will be reviewed for specialist referrals. For other investigations, the requests, results, investigations, prescription and prescription reason fields will be explored.

4.2 Secondary outcomes

Secondary outcomes will include the individual indicators for guideline concordant care, including pathology test results, investigations, prescriptions, referrals, diagnosis, time to investigation and

number of encounters of patients that attended included general practices during the 12-month period.

(1) The proportion of eligible patients identified in the closed and open cohorts with markers of anaemia, that have subsequently been followed-up according to guidelines[2,6] within the 12-month trial period. Relevant investigations include a repeat full blood count, iron studies, coeliac disease serology, FOBT, transvaginal ultrasound, referral to gastroenterologist and/or assessment of upper or lower GI symptoms and/or haematuria. The absence of any of recorded investigation during the trial period will be considered equivalent to not being investigated.

(2) The proportion of eligible patients identified in the closed and open cohorts with markers of anaemia, that have subsequently been prescribed an oral supplement and/or have a record of an iron infusion in the 12-month trial period. The absence of any recorded prescription for an oral supplement or iron infusion will be considered equivalent of the patient not being prescribed an oral supplement or iron infusion.

(3) The proportion of eligible patients identified in the closed and open cohorts with raised platelet count, that have subsequently been followed-up according to Victorian Department of Health[4], NICE[2] and Cancer Council[4] within the 12-month trial period. Relevant investigations include a repeat platelet count, chest x-ray, chest CT, FOBT, CA-125, transvaginal ultrasound, assessment for symptoms for lung, colorectal, gastro-oesophageal, ovarian or endometrial cancer and/or referral to a gastroenterologist, respiratory physician, or gynaecologist. The absence of any of relevant recorded investigation during the trial period will be considered equivalent to not being investigated.

(4) Proportion of eligible patients whose sex at birth is coded as male in the EMR in the closed and open cohort with one raised PSA that have been followed up according to Cancer Council Australia guidelines[4] within the 12-month trial period. Relevant investigations include a repeat PSA test, free to total PSA percentage and/or referral to a urologist[5,8]. The absence of any of relevant recorded investigation during the trial period will be considered equivalent to not being investigated.

(5) Proportion of eligible patients in the closed and open cohorts that have a new recorded diagnosis of prostate, oesophageal, gastric, colorectal, endometrial, lung or ovarian cancer recorded in the general practice EMR within the 12-month trial period. The absence of any of recorded diagnosis during the trial period will be considered equivalent of no diagnosis being made.

(6) The rate of general practice encounters per eligible patient over the 12-month trial period. This will be calculated using total number of general practice visits over the trial period of all eligible patients identified as at risk of an undiagnosed cancer in the closed cohort divided by the total time they were observed in the trial. For each patient, time will be calculated from the date the trial commenced (4th Oct 2021) to the end of the trial (30th September 2022). If the patient was in the open cohort, the time observed will be calculated from the date they the patient enters the trial to the end of the trial (30th September 2022). For patients/practices that discontinue during the trial period, time observed will be calculated from they entered the (namely, the 4th October 2021 for the closed cohort or date they first report of an abnormal test result for the open cohort) to the date the patient(s) discontinued/withdrew from the trial.

(7) Time to investigation for patients with abnormal pathology results identified as at risk of an undiagnosed cancer in the open cohort. This includes any investigation, treatment, review of symptoms or referrals as described in the primary outcome. Time to investigation will be defined as the number of days between the initial altered test result date and the first investigation (re-testing, investigations, treatments, referrals and review of symptoms). Outcomes will be assessed at 12 months from baseline and patient records without follow-up action by this time will be censored.

Health economics outcomes are:

(8) The cost of the installation for the software program for QI, training, QI support and education. This will be calculated at the general practice level, using cost data collected by Health and Biomedical Informatics Centre (HABIC R^2) who developed and provided technical support for the FHT software and the FHT investigators and research team who liaised with practices and facilitated the education sessions.

(9) Cost of primary care service utilisation per patient per year. These will be calculated based on Medicare items, Provider Charge, Schedule Fee, Patient Out of Pocket in the Medicare Benefits Schedule (MBS) data linked to patients in the Patron for the FHT evaluation.

4.3 Baseline practice, practice staff and patient characteristics

Baseline practice and practice staff characteristics include:

- State (Victoria, Tasmania)
- IRSD terciles based on the Index of Relative Socio-Economic Disadvantage (IRSD) [10] using the practice postcode. The first tercile represents relatively disadvantaged sociodemographic geographic areas compared to geographic areas with higher ranks (Tercile 3).
- Practice participation in a formalized QI program in the past 6 months (yes, no)
- Practice size based on the GP full-time equivalent (FTE) of 4 or less FTE or greater than 4 FTE as reported by the practice. FTE will be defined as the total number of full-time GPs plus the total number of part time GPs multiplied by 0.5FTE.
- GPs sex (male, female)
- GPs age group (<35 years; 35 to 50 years; >50 years)
- Number of FTE registered nurses. FTE will be defined as the total number of full-time nurses plus the total number of part time nurses multiplied by 0.5FTE.
- Registered nurses' sex (male, female)
- Registered nurses age group (<35 years; 35 to 50 years; >50 years)
- Number of FTE practice managers and administrative staff. FTE will be defined as the total number of full-time practice managers/administrative staff plus the total number of part time practice managers/administrative staff multiplied by 0.5FTE.
- Practice managers/administrative staff sex (male, female)
- Practice managers/administrative staff age group (<35 years; 35 to 50 years; >50 years)

Patient characteristics and pathology tests, medications prescribed, referrals and observations recorded at baseline (4th October 2021) for the closed cohort and at time of entry into the study for the open cohort, that will be extracted from the EMR include:

- Age (years)
- Sex (male, female, other)

- Hb (g/L)
- MCH (fL)
- MCV (pg)
- Ferritin (µg/L)
- Platelets (UI/ml)
- PSA (ng/ml)
- Free to total PSA (%)
- Recorded diagnosis of relevant cancer in the 5 years prior to baseline (yes/no)

Other information extracted from the EMR that occur during the trial period:

- Pregnancy
- Patient deceased

4.4 Analysis methods

4.4.1 Withdrawal/follow-up

Staff within practices and/or the practice may withdraw from the study. If a practice withdraws, then no further patient data will be extracted from the EMR system. However, existing data (prior to notice of withdrawal) will be used in the final analysis unless the practice requests existing data also be excluded. Individual patients can also withdraw their data by notifying their general practice that they no longer consent to their data being used for research purposes. As the intervention is applied at the general practice level within the EMR system this means that no further patient data will be extracted. However, existing data (prior to notice of withdrawal) will be used in the final analysis unless the participant requests existing data also be excluded.

4.4.2 Descriptive analysis

The flow of practices and eligible patients from recruitment to trial end will be shown in a CONSORT diagram,[1] see Appendix A for the template. The report will include the number of practices approached for involvement in the trial, the number of eligible practices, the number of practices consented, the number of eligible practices randomised by their study arm, together with the total number and the mean number of eligible patients per practice and number that were included in the intention to treat analysis. The number of practices and/or patients who withdraw or discontinue will also be summarised by study arm and period that the withdrawal/discontinuation occurred (0-6 months, 7-9 months, 10-12 months). When such information is available, the reason a practice withdrew or discontinued the intervention will be reported by study arm.

Descriptive statistics will be used to describe general practice and patients' baseline characteristics and baseline outcome measures overall and by study arm as outlined in Appendix B Table 1 and Table 2. Descriptive statistics will also be used to summarise other information extracted from the EMR that occur during the trial period by study arm, for the closed and open cohort separately and overall. Categorical data will be summarised using counts and percentages, according to the number of eligible patients with available data. Continuous data will be summarised using arithmetic mean, standard deviation if the data have a symmetric distribution. When appropriate, continuous outcome data with a right skewed distribution may be presented as a geometric mean instead of an arithmetic mean. Otherwise, if the distribution if the data is non-symmetrical, the median and interquartile range (25^{th} and 75^{th} percentiles) will be presented instead. The intra-cluster correlation coefficient with 95%

intervals will also be reported for baseline patient measurements estimated using one-way analysis of variance.

4.4.3 Primary analysis

The primary analysis will use an intention to treat (ITT) approach, where all practices randomised will be included in the analysis by their allocated study arm status, regardless of whether they received all, part or none of the intended intervention.

4.4.4 Primary outcome

For the primary outcome, the odds ratio (relative measure) and the difference in proportions between the intervention and control arms (absolute measure) will be estimated using a generalised linear model (GLM) with the logit link and identity link functions, respectively, and binomial distribution for both models. Both models will include randomisation stratification factors, GP FTE and IRSD terciles as covariates, and use Generalised Estimating Equations with an exchangeable correlation structure and robust standard errors to allow for correlation of outcomes within general practice. If the model used to estimate the risk difference fails to converge, the risk difference will be derived from the GLM with the logit link function.[11,12]

The absolute (difference in proportions between the intervention and control arms) and relative (odds ratio) estimated intervention effects for the primary outcome will be reported with 95% confidence intervals and p-values.

4.4.5 Secondary outcomes analysis

Statistical methods described in the primary outcome will be used for the **binary secondary outcomes 1-5.**

Secondary outcome 6 will utilise a Poisson mixed effects model (or a Negative Binomial mixed effects model if overdispersion is detected), with fixed effects for study arm and the randomisation stratification factors (GP FTE and IRSD terciles), and random effect for general practice. The estimated intervention effect will be reported as differences in rate between the intervention and control arms and rate ratios with 95% confidence intervals and p-values.

Secondary outcome 7 will be analysed using a time to event analysis to compare the time to investigation for patients in the open cohort with an altered test results identified as at risk of an undiagnosed cancer between the study arms using a Cox proportional hazards model, adjusted for the randomisation stratification factors (GP FTE and IRSD terciles). Robust standard errors will be used to adjust for clustering effect by general practice. The proportional hazards assumption will be assessed following a two-step procedure: (1) calculate covariate specific tests and (2) plot the scaled and smoothed scaled Schoenfeld residuals obtained from the model.[13] Kaplan-Meier survival curves will also be used to present time to event by study arm[14], and the overall survival data will be summarised following good practice guidelines.[15] If the proportional hazards assumption is not met, we will use consider using a stratified proportional hazards model or a parametric model as appropriate.[13] A sensitivity analysis using a competing risk analysis will be considered if patients at risk of undiagnosed cancer have died prior to an investigation/end of the trial follow-up period.

Estimates of the intervention effect will be reported as hazard ratios and 95% confidence intervals and p-value.

4.4.6 Health economic outcomes

Costs of the installation of the software program and training of the general practice staff to use the software (**Outcome 8**) will be summarised using descriptive statistics.

Health care service costs (**Outcome 9**) will be compared between the intervention and control arms using a GLM with a log link and gamma distribution, two-part model or mixtures model depending on the distribution of costs.

4.5 Supplementary analyses

4.5.1 Sensitivity analyses 1: Adjustment of additional covariates

Sensitivity analysis of primary and secondary outcomes will additionally adjust for four confounders measured at baseline: prior practice participation in a formalised quality improvement program (yes, no), patient's' age at entry into the cohort, sex (male, female, other) and whether they were identified in the open or closed cohort. These variables will be added as covariates to the regression models described for the primary analysis.

4.5.2 Sensitivity analysis 2: Intercurrent events

All eligible patients will be included in the primary ITT analysis, including any patients who die during the trial period. Patients who become pregnant during the trial will also be included in the ITT analysis, as the clinical management of this sub-group of patients should not change. We expect the numbers who die over the 12 months of the trial period or become pregnant to be less than 10% of the sample size and similar in the two arms. However, if they do exceed 10% of the sample size, we will conduct a sensitivity analysis for the primary outcome excluding these patients from the ITT analysis.

4.5.3 Sensitivity analysis 3: Referral data

We will conduct a sensitivity analysis for outcomes relating to referrals (primary outcome and secondary outcome 4) for investigations regarding a possible prostate cancer. The sensitivity analysis will focus on prostate cancer as a referral to a urologist is one of the primary recommendations for follow-up delivered in the intervention. We expect that referral information will be difficult to capture in the EMR extracted data and not well recorded, leading to an underestimation of referrals to a specialist. Therefore, we will include diagnosis of prostate cancer, prostatitis or benign prostatic hyperplasia as a proxy for receiving a referral to a specialist (when the referral to the specialist was not reported in the EMR). For instance, for patients with one raised PSA who have no recorded referral to a urologist, will be coded for the sensitivity analysis as receiving a referral if they had a prostate diagnosis made by a urologist after they were identified as at risk of cancer. Same analysis outlined for the binary outcomes will be used for the sensitivity analysis. Other forms of cancer may be subject to this sensitivity analysis pending inspection of the data.

4.5.4 Sensitivity analysis 4: Symptoms

The outcome definition of appropriate follow-up includes any guideline concordant action taken by the GP including pathology tests, investigations, prescriptions, referrals and recording of relevant symptoms in the EMR. Due to the non-specific nature of some symptoms associated with cancer, we will conduct a sensitivity analysis for the primary outcome excluding symptoms as a measure of appropriate follow-up. The same analysis outlined for the binary outcomes will be used for the sensitivity analysis.

4.5.5 Sensitivity analysis 5: Missing outcome data

Due to the definition used to determine the study cohorts (i.e., patients determined to be at risk of an undiagnosed cancer) and the use of EMR data to determine outcomes, except for patients withdrawing from having their data for use in the Patron repository, we do not expect missing data and all eligible patients will be included. For the primary outcome and secondary outcomes 1-5 and 7, at the conclusion of the trial, anyone with a relevant follow-up or investigation will be considered to

have received guideline concordant care. If a relevant investigation or follow-up is not in the patient record, then they will be considered to not have received guideline concordant care.

1) We expect the number of individual patients who withdraw their data from the study to be small. A sensitivity analysis will be conducted to assess the robustness of the missing data assumption using a pattern-mixture model if more than 10% of the eligible patients have missing responses either because of patient and/or practices withdraw from the trial.

4.5.6 Adherence-adjusted analysis

In the SAP for the CKD study we outlined a sensitivity analysis for incomplete adherence on the estimated intervention effects using a complier average casual effect (CACE) analysis[16-18] for the primary outcome only. However, after the study investigators and data management team reviewed the data for adherence with the intervention protocol, we were unable to construct the indicators for incomplete adherence based on the level of FHT QI program integration within each practice. Thus, adherence-adjusted analysis will not be conducted. Three types of data were to be used as measures of adherence:

1) the number of practitioners actively engaged in the FHT trial compared to the number of computers with the FHT QI module installed/accessible by general practice clinicians as a proxy measure of the degree of access to the point of care clinical decision support tool.
2) the number of days that the QI module is active within each practice, that will take into consideration whether practices have experienced technical issues during the trial period.
3) the degree of engagement of general practices with the different components of the intervention (e.g., ECHO series, use of the FHT tool to create cohorts).

During data review, a series of observations were made that resulted in removal of adherence-adjusted analysis from the suite of analyses planned for the trial. Regarding the number of practitioners actively engaged in the FHT trial compared to the number of computers with the FHT QI module installed, the completeness and quality of the data collected was not considered to be of sufficient completeness, quality and/or reliability to use it as a proxy measure of access or engagement. Regarding the number of days that the QI module was active, the gathered data was incomplete and did not capture the range of technical issues experienced within practices. Data on major technical issues was available but such issues were rare, indicating that no practices experienced severe technical issues to a degree that indicated incomplete adherence. Finally, data collected regarding degree of engagement with intervention components was also considered to be insufficient for use as a proxy of adherence.

4.5.7 Exploratory/sub-group analyses

To evaluate the shorter time for follow-up in the open cohort, we will conduct a sub-group analysis in patients identified as at risk of an undiagnosed cancer, using the sub-groups of those identified at baseline (closed cohort), compared with those identified in the first 6 months after the trial start date (open cohort). Further sub-group analyses will be conducted for the primary outcome, such as the appropriate investigation for sex (male, female, other) and age at entry into the cohort. These exploratory analyses may be reported in part with the primary analysis or in a separate publication.

The statistical analysis for each subgroup will be conducted by including the subgroup variable and its interaction with the intervention as fixed effects to the regression models. Summary statistics will be presented for each sub-group within each study arm, as well as estimates for the intervention effects (appropriate to the outcome type) with a 95% confidence interval and a p-value corresponding to the

interaction term between the study arm and the subgroup variable. The estimates may also be displayed graphically using forest plots.

4.6 Statistical software and technical details

All analyses will be conducted using Stata Statistical software (v17).[9] Appendix B Table 1, 2 and 3 provide the proposed template for the statistical analysis of the primary and secondary outcomes. These results may also be presented graphically, where appropriate. Any post-hoc explanatory analyses not identified in the SAP will be clearly identified in the final statistical report. Any deviations from the planned analyses detailed in the SAP will be documented and reported in a revised version of this SAP.

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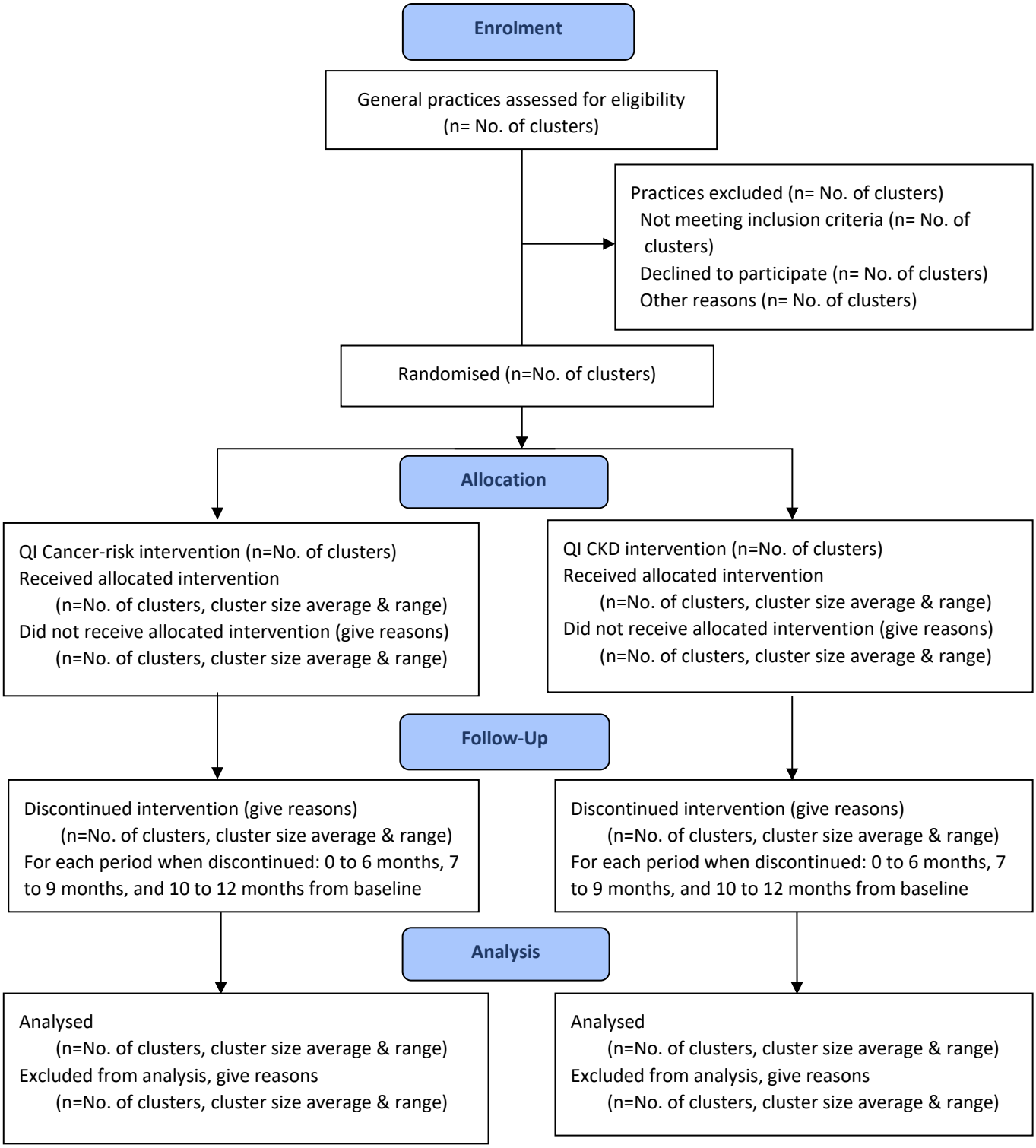
Appendix A: CONSORT diagram



Appendix B: Proposed tables for Baseline Participant Characteristics and Outcomes

Table 1. Baseline characteristics of practices and practice staff for all participants and by study arm

	All participants	Intervention arm	Active control arm
Practice Characteristics	N	N	N
State			
Victoria	n(%)	n(%)	n(%)
Tasmania	n(%)	n(%)	n(%)
Relative Socio-Economic Disadvantage Index (Terciles)			
1 Most disadvantaged	n(%)	n(%)	n(%)
2	n(%)	n(%)	n(%)
3 Least disadvantaged	n(%)	n(%)	n(%)
Previously participated in QI Program	n(%)	n(%)	n(%)
Practice Size			
4 or fewer FTE GPs	n(%)	n(%)	n(%)
Greater than 4 FTE GPs	n(%)	n(%)	n(%)
Number of FTE GPs	Median (IQR)	Median (IQR)	Median (IQR)
Number of FTE Nurses	Median (IQR)	Median (IQR)	Median (IQR)
Number of FTE Practice Managers/Administrative staff	Median (IQR)	Median (IQR)	Median (IQR)
General practitioners	N	N	N
Sex			
Male	n(%)	n(%)	n(%)
Female	n(%)	n(%)	n(%)
Age			
< 35 years	n(%)	n(%)	n(%)
35 to 50 years	n(%)	n(%)	n(%)
> 50 years	n(%)	n(%)	n(%)
Registered nurses	N	N	N
Sex			
Male	n(%)	n(%)	n(%)
Female	n(%)	n(%)	n(%)
Age			
< 35 years	n(%)	n(%)	n(%)
35 to 50 years	n(%)	n(%)	n(%)
> 50 years	n(%)	n(%)	n(%)
Practice managers/ Administrative staff	N	N	N
Sex			
Male	n(%)	n(%)	n(%)
Female	n(%)	n(%)	n(%)
Age			
< 35 years	n(%)	n(%)	n(%)
35 to 50 years	n(%)	n(%)	n(%)
> 50 years	n(%)	n(%)	n(%)

N – number of practices/practice staff; % - Column percentage; IQR – Interquartile range; FTE – Full-time equivalent; GP - general practitioner. **Note**: Continuous variables may be categorised and sub-categories may also be collapsed in final table published.

Table 2. Baseline characteristics of patients by study arm

Patient Characteristics	**All participants**		**Closed cohort**		**Open cohort**	
	Intervention N	Control N	Intervention N	Control N	Intervention N	Control N
Sex						
Male	n(%)	n(%)	n(%)	n(%)	n(%)	n(%)
Female	n(%)	n(%)	n(%)	n(%)	n(%)	n(%)
Other	n(%)	n(%)	n(%)	n(%)	n(%)	n(%)
Age (years)	mean (SD)	mean (SD)	mean (SD)	mean (SD)	mean (SD)	mean (SD)
Markers of anaemia						
Hb (g/L)[a]	n(%)	n(%)	n(%)	n(%)	n(%)	n(%)
MCH (<80fL)	n(%)	n(%)	n(%)	n(%)	n(%)	n(%)
MCV (<27 pg)	n(%)	n(%)	n(%)	n(%)	n(%)	n(%)
Ferritin (<30 µg/L)	n(%)	n(%)	n(%)	n(%)	n(%)	n(%)
Raised platelets						
>400mmol/L	n(%)	n(%)	n(%)	n(%)	n(%)	n(%)
Altered PSA						
(ng/ml)[b]	n(%)	n(%)	n(%)	n(%)	n(%)	n(%)
Two altered tests	n(%)	n(%)	n(%)	n(%)	n(%)	n(%)
Three altered tests	n(%)	n(%)	n(%)	n(%)	n(%)	n(%)

N – number of patients; % - Column percentage; SD – standard deviation

[a] Hb<130g/L for males, <115g/L for females

[b] PSA>2.0ng/ml aged 40-49, >3.0ng/ml aged 50+

Note: Continuous variables may be categorised and sub-categories may also be collapsed in final table published.

Table 3. Analyses for Primary and Secondary Outcomes

	All participants	**Intervention**	**Control**	**Estimated effect size Coefficient (95%CI)**		
Primary Outcome	N	N	N			
Primary analysis	n (%)	n (%)	n (%)	Difference (95% CI)	Odds ratio (95% CI)	p-value
Sensitivity Analysis[1]				Difference (95% CI)	Odds ratio (95% CI)	p-value
Sensitivity Analysis[2]				Difference (95% CI)	Odds ratio (95% CI)	p-value
Secondary outcomes (1 to 5)	N	N	N			
Primary analysis	n (%)	n (%)	n (%)	Difference (95% CI)	Odds ratio (95% CI)	p-value
Sensitivity Analysis[1]				Difference (95% CI)	Odds ratio (95% CI)	p-value
Sensitivity Analysis[2]				Difference (95% CI)	Odds ratio (95% CI)	p-value
Secondary Outcome 6	N	N	N			
Primary analysis	n (rate)	n (rate)	n (rate)	Difference in rates (95% CI)	Rate ratio (95% CI)	p-value
Sensitivity Analysis[1]				Difference in rates (95% CI)	Rate ratio (95% CI)	p-value
Sensitivity Analysis[2]				Difference in rates (95% CI)	Rate ratio (95% CI)	p-value
Secondary Outcome 7	n[3]/N	n[3]/N	n[3]/N			
Primary analysis	Median time[4] (95% CI)	Median time[4] (95% CI)	Median time[4] (95% CI)		Hazard ratio (95% CI)	p-value
Sensitivity Analysis[1]					Hazard ratio (95% CI)	p-value
Sensitivity Analysis[2]					Hazard ratio (95% CI)	p-value

N – number of patients; Difference – Difference in percentages between the arms, unless otherwise stated; % - column percentages; CI -Confidence interval.

[1] Sensitivity analysis adjusted for the practice participation in formalised QI program, patients age in year, and patient's sex

[2] Sensitivity analysis for intercurrent events

[3] n is the number of investigations

[4] Median time to investigation estimated using the Kaplan-Meier estimator

Note: The table may be split to separate tables for the different outcomes.