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**ACTA STInG**

**Statistical Analysis Plan Template**

**June 2020**

ACTA gratefully acknowledges operational funding from the Australian Government’s Medical Research Future Fund

### PURPOSE OF DOCUMENT

This document provides a template for statistical analysis plans and will enable the user to develop a detailed and structured plan pre-specifying the analysis of a clinical trial.

### ROLE OF ACTA IN DEVELOPING STATISTICAL ANALYSIS PLAN

ACTA supports the Statisticians Interest Group (STInG) to promote professional standards of statistics in trials and where possible harmonise the practice of statistics in clinical trials settings within Australia. The generic advice provided by ACTA STInG should be considered while taking into account the specific individual circumstances and needs of the particular trial.

### ACKNOWLEDGEMENTS

We acknowledge the contributions of ACTA members and members of ACTA’s Statisticians Interest Group and Innovative Trial Design Reference Group in the preparation, development and review of this document. In particular, we would like to acknowledge the contribution by A/Prof Laurent Billot in the development of this template.

### DISCLAIMER

The information in this document is for general guidance only. ACTA does not make any representations or warranties (expressed or implied) as to the accuracy, currency or authenticity of the information provided.

**DOCUMENT HISTORY**

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| 1.0 | 24 April 2024 | First version | Dr Jean Spinks, Dr Esa Chen, Prof Dennis Petrie |
| 1.1 | 26 July 2024 | Second version | Dr Jean Spinks, Dr Esa Chen, Prof Dennis Petrie with oversight from Prof Rob Ware |

A logo for a medicine company

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Activating primary care for medicine safety:

The ACTMed stepped

wedge randomised controlled trial

Statistical Analysis Plan

Version 1.1

29 July 2024

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##### Study identifiers:

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### LIST OF ABBREVIATIONS

ACCHO Aboriginal Community Controlled Health Organisation

ACOS Asthma-COPD overlap syndrome

ACTMed Activating primary care for medicines safety

ANZCTR Australian and New Zealand Clinical Trials Registry

BMI Body mass index

CI Confidence interval

COPD Chronic obstructive pulmonary disease

CVD Cardiovascular disease

FHT Future Health Today

GP General practitioner

GPMP General practice management plan

HMR Home medicines review

ICD-10 International Classification of Diseases 10th Revision

MRFF Medical Research Future Fund

NACCHO National Aboriginal Community Controlled Health Organisation

PPMRH Potentially preventable medication-related hospitalisation

PHN Primary Health Network

RACGP Royal Australian College of General Practitioners

SEIFA Socio-economic index for areas

SPIRIT Standard Protocol Items: Recommendations for Interventional Trials

TCA Team care arrangement

UQ The University of Queensland

QI Quality improvement

### ADMINISTRATIVE INFORMATION

#### STUDY IDENTIFIERS

* UQ Ethics: 2022/HE002136 Protocol (SPIRIT) V11
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|  |  |  |  |

#### CONTRIBUTORS TO THE STATISTICAL ANALYSIS PLAN

The undersigned have reviewed this plan and approve it as final. They find it to be consistent with the requirements of the protocol as it applies to their respective areas. They also find it to be compliant with ICH-E9 principles and, in particular, confirm that this analysis plan was developed in a completely blinded manner (i.e., without knowledge of the effect of the intervention(s) being assessed).

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### STUDY SYNOPSIS

ACTMed (ACTivating primary care for MEDicine safety/Activating pharmacists[[1]](#footnote-1) to reduce medication-related problems) uses information technology and financial incentives to encourage pharmacists to work more closely with general practitioners to reduce the risk of medication-related harm, improve patients’ experience of care, streamline workflows, and increase the efficiency of medical care (1,2). Eligible general practices and Aboriginal Community Controlled Health Organisations (ACCHOs) will implement the ACTMed intervention. A practice pharmacist, already working in the practice or recruited for the trial, will use software (GRHANITE and Future Health Today (FHT)) to identify adults (18 years or older) at risk of serious medication-related problems and, in collaboration with general practitioners (GPs) and other practice staff, work within a quality improvement (QI) framework to resolve potential medication-related problems. The ACTMed trial will enrol 42 Queensland general practices in a stepped-wedge cluster randomised controlled trial to evaluate the effectiveness and cost-effectiveness of ACTMed. All practices will start without ACTMed. Each month 7 practices will be randomly assigned to have ACTMed introduced. 'Usual care' will be defined as practices not providing ACTMed, however this does not exclude practice patients using any of the existing medicine review arrangements available to them in primary or tertiary care (such as Home Medicines Review or MedCheck services from a community pharmacy). After a one-month on-boarding period, the intervention will be implemented for five additional months. Training and support for the pharmacists to implement ACTMed specifically, and quality improvement activities more generally, will be provided. The primary outcome is the proportion of people deemed *exposed* and who are identified as *at risk*, the definitions of which are determined by a pre-specified set of clinical indicators. At the end of the active intervention period and completion of data collection for the primary end point, data collection will continue for a period of five months to measure any persistence of effect.

#### STUDY OBJECTIVES

The aim of the ACTMed trial is to evaluate the effectiveness and cost-effectiveness of a general practice-based intervention (ACTMed) for reducing the risk of serious medication-related problems, and its impact on health care costs, health care efficiency and coordination, and patients’ experience of care. For the purposes of this study, we will restrict our analysis to serious medication-related problems, pre-specified by five clinical indicators that identify under-prescribing of condition-specific medications or monitoring tests (Table 1).

**Table 1:** Pre-specified clinical indicators of potentially serious medication-related problems

|  |  |  |  |
| --- | --- | --- | --- |
| **Indicator** | **Exposed population (denominator)** | **At-risk population (numerator)** | **Event to be avoided** |
| Atrial fibrillation | People with atrial fibrillation diagnosis AND  [(No diagnosis of stroke or transient ischaemic attack AND CHA2DS2-VA (3) score ≥ 1) OR  (History of stroke AND/OR transient ischaemic attack)] | Not taking anticoagulant therapy | Thrombo-embolic cerebrovascular event |
| Heart failure | People with heart failure diagnosis | Not taking angiotensin-converting enzyme inhibitor, angiotensin receptor blocker, or angiotensin receptor– neprilysin inhibitor | Congestive heart failure or fluid overload |
| Cardiovascular disease (a) | People with cardiovascular disease diagnosis | Not taking indicated statin | Ischaemic event |
| Cardiovascular disease (b) | People with cardiovascular disease diagnosis AND No diagnosis of atrial fibrillation | Not taking indicated antiplatelet medication | Ischaemic event |
| Tye 2 diabetes | People with type 2 diabetes diagnosis AND Prescribed at least one glucose-lowering medication | No glycated haemoglobin monitoring test result recorded during past six months | Diabetes-related complication |
| Asthma/chronic obstructive pulmonary disease | People with previous diagnosis of asthma or chronic obstructive pulmonary disease AND Frequent use of short-acting beta agonists or muscarinic antagonists (at least two prescriptions in the preceding twelve months) | No current use of maintenance therapy | Asthma or chronic obstructive pulmonary disease exacerbation |

Definitions: The *exposed population* meets the definition of the condition of interest. The *at-risk population* meets the definition of the condition of interest and the sub-optimal medication status. The *event to be avoided* is *the potentially preventable medication-related hospitalisation (PPMRH)* for the clinical indicator. *False positives* can occur due to discrepancies in the electronic medical record of patients, clinician judgment and/or the difference between prescribing and dispensing data. False positive cases are described as records of individuals who incorrectly meet the definition of either the exposed population and/or the at-risk population. Methods of accounting for false positive cases are detailed below.

* + 1. **PRIMARY OBJECTIVE**

The primary objective is to evaluate the effectiveness of the ACTMed intervention to reduce exposed population considered to be “at risk” of a pre-specified medication-related problem at the individual level.

H1: Implementation of the ACTMed intervention will significantly decrease the exposed population considered to be “at risk” of a pre-specified medication-related problem at the individual level.

* + 1. **SECONDARY OBJECTIVES**

Secondary objectives are to further test the effectiveness, but also feasibility and acceptability of the ACTMed intervention to health practitioners and consumers. Cost-effectiveness will also be evaluated.

H2: Implementation of the ACTMed intervention will significantly decrease the proportion of the exposed population considered to be “at risk” of a pre-specified medication-related problem at the practice level.

H3: The effectiveness of the ACTMed intervention in terms of the exposed population considered to be “at risk” of a pre-specified medication-related problem at the individual level will decrease once payment incentives and intensive quality improvement support are removed.

H4: Implementation of the ACTMed intervention will significantly decrease the number of potentially preventable medication-related hospitalisations (PPMRHs) in the exposed population. PPMRHs are defined as the type of hospitalisation that may be expected to be prevented for the five pre-specified clinical indicators by the ACTMed intervention (using a pre-specified list of ICD-10 codes, see Table 1).

H5: Implementation of the ACTMed intervention will significantly decrease deaths associated with serious medication-related problems in the exposed population. Deaths associated with serious medication problems are defined by set of pre-specified events (ICD-10 coded), considered to be potentially preventable by the ACTMed intervention. The deaths of interest relate to the five pre-specified clinical indicators by the ACTMed intervention.

H6: The effectiveness of the ACTMed intervention across practices will be associated with the activity level of pharmacists and general practitioners to resolve potential medication-related problems as recorded by actions in FHT.

H7: The ACTMed intervention will be acceptable to consumers.

H8: Delivering the ACTMed intervention will increase the job satisfaction of participating pharmacists and general practitioners.

H9: The ACTMed intervention will identify a greater number of false-positive cases than true positive cases.

H10: The ACTMed intervention will be cost-effective compared with usual care.

#### PRACTICE AND PATIENT POPULATION

* + 1. **INCLUSION CRITERIA – GENERAL PRACTICES AND ABORIGINAL AND TORRES STRAIT ISLANDER HEALTH SERVICES**
* General practices and Aboriginal and Torres Strait Islander Health Services located in Queensland, Australia;
* Services are required to have an estimated minimum of 5,000 active patients, except for up to 6 services included for reasons of equity of access, including smaller ACCHOs and culturally and linguistically diverse focused practices;
* Identification of at least one HMR credentialed pharmacist to lead the ACTMed intervention at the practice. The pharmacist could concurrently work in a community pharmacy or other practice setting as long as they can dedicate 5 hours per week on-site at the participating practice;
* Current users of Medical Director or Best Practice, both of which are compatible with GRHANITE® and FHT software;
* Meet the information technology requirements for installation and use of GRHANITE® and FHT; (1,2)
* Consent to provide de-identified individual level and aggregate practice level data for measurement of the primary and secondary outcomes as per the Service Agreement with The University of Queensland; and
* Have sufficient capacity to engage in the research project.
  + 1. **INCLUSION CRITERIA - PATIENTS**

Within recruited ACTMed practices, eligible patients include all adults (aged ≥18 years) who are considered active in the practice as defined by not being marked archived or deceased, are not pregnant or breastfeeding, or did not opt out of the ACTMed service.

* + 1. **EXCLUSION CRITERIA – PRACTICES**
* Practices and Aboriginal and Torres Strait Islander Health Services not located in Queensland, Australia;
* Use of an electronic medical record software that is not Medical Director or Best Practice;
* Practices and Aboriginal and Torres Strait Islander Health Services not willing to consent to the use of de-identified individual and practice level data.
  + 1. **EXCLUSION CRITERIA – PATIENTS**
* Patients who are under 18 years of age;
* Patients who withdraw their consent (opt-out) for their individual level data to be included in the trial;
* Patients who are pregnant and/or breastfeeding.

#### OUTCOMES

* + 1. **PRIMARY OUTCOME**
* The proportion of individuals from the *exposed* population (denominator) with any serious medication-related problem from the pre-specified clinical indicator (numerator = *at risk* population). The primary outcome will be measured at the end of each time period (month) from time period 0 until time period 7 (Figure 2). This will be determined by data extraction using the FHT software platform. The numerator and denominator will be adjusted to remove false positive cases identified (integration of medical records reveal that the patient is either not truly in the ‘exposed population’ and/or not truly in the ‘at risk’ population – Table 2). The date of false positive assignment is assumed to be at time period 0 (Figure 2).

False positive cases can occur due to discrepancies in the electronic medical record of patients and/or the difference between prescribing and dispensing data. Trial pharmacists will check clinical and dispense records (where possible) with My Health Record and record in the FHT software platform for any false positives, by marking and coding the reason for why a recommendation was deferred in the FHT software (Table 2). These records will be used to identify the false positive percentage.

**Table 2:** Reasons for false positive cases captured in the Future Health Today software

|  |  |  |  |
| --- | --- | --- | --- |
| **Reason** | **Description** | **Remove from numerator** | **Remove from denominator** |
| 1. **INCORRECTLY IDENTIFIED AS EXPOSED (Removed for primary and secondary outcome measurement)** | | | |
| Not at-risk diagnosis | Diagnosis for inclusion in the recommendation is incorrect | ✓ | ✓ |
| Preserved ejection fraction | Does not meet diagnostic criteria for ACTMed trial Heart Failure intervention. Ejection fraction >50% on echocardiogram | ✓ | ✓ |
| Ineligible due to age | Patient date of birth is incorrect and they are too young to be eligible for the trial | ✓ | ✓ |
| Ineligible due to pregnancy | Patient is pregnant and ineligible for the ACTMed trial but status has not been updated in patient history | ✓ | ✓ |
| Ineligible due to breastfeeding | Patient is breastfeeding and ineligible for the ACTMed clinical trial | ✓ | ✓ |
| Deceased | Patient deceased but status has not been updated in the patient profile | ✓ | ✓ |
| Inactive | Patient is no longer 'active' at the clinic | ✓ | ✓ |
| Other GP | Patient has a regular GP at another clinic and does not attend the clinic for usual care | ✓ | ✓ |
| 1. **INCORRECTLY DEFINED AS AT RISK (Removed for primary and secondary outcome measurement)** | | | |
| Medication reconciliation | Appropriate medication has been prescribed by external party (hospital, specialist) but not yet recorded correctly in the patient history | ✓ |  |
| Pathology reconciliation | Appropriate pathology test has been performed by external party (hospital, specialist) but not yet recorded correctly in the patient history | ✓ |  |
| Allergy | Patient is not suitable for medication due to recorded history of allergy | ✓ |  |
| Adverse drug reaction | Patient is not suitable for medication due to a recorded history of adverse drug reaction | ✓ |  |
| Intolerance | Patient is not suitable due to a recorded history of intolerance to the recommended medication | ✓ |  |
| 1. **IDENTIFIED AS ‘NOT AT RISK’ USING CLINICAL JUDGEMENT (Removed in robustness testing of primary and secondary outcome measurement)** | | | |
| Deprescribed | Patient has been appropriately deprescribed the medication, for example, older patient, bleeding risk, other comorbidities | ✓ | ✓ |
| Older age | Additional pharmacotherapy considered inappropriate due to age | ✓ | ✓ |
| Clinical opinion | Patient appears suitable for intervention but the GP deemed the intervention not to be appropriate at this time | ✓ | ✓ |
| Specialist opinion | Patient appears suitable for intervention, but the specialist deemed the intervention not to be appropriate at this time | ✓ | ✓ |
| Guideline query | Consensus guidelines not yet established or under debate. For example, CVD with no statin but patient has standalone Peripheral Vascular Disease; patient has exercise/allergy induced asthma | ✓ | ✓ |
| Individual circumstances | Patient is not considered appropriate for a particular recommendation due to individual circumstances. For example, unable to afford medication, lack of social supports, unlikely to comply | ✓ | ✓ |

For the primary and secondary outcome measures, the list of false positives in categories 1 and 2 (specific in Table 2) will be removed. A robustness analysis of the treatment effects for the primary and secondary outcome measures will be undertaken removing the list of false positives in category 3 from the numerator, and both the denominator and numerator.

* + 1. **SECONDARY OUTCOMES**

1. Practice level analysis: The proportion of individuals from the *exposed* population (denominator) with any serious medication-related problems (numerator = *at risk* population) in the intervention compared to the pre-intervention group. The secondary outcome will be measured at the end of each time period (month) from time period 0 until time period 7 (Figure 2). This will be determined by data extraction using the FHT software platform. The numerator and denominator will be adjusted to remove false positive cases identified (Tabel 2). This analysis is undertaken at the practice level.
2. Persistence of any treatment effect: The proportion of individuals from the exposed population with any serious medication-related problems once the intervention ceases (i.e. from one month post the first practice offboarded from the ACTMed intervention until 6 months post last practice implementing the intervention shown by time periods 8-12 in Figure 2). The analysis will be undertaken at the individual and practice levels.
3. The incidence rate of potentially preventable medication related hospitalisations (PPMRHs): defined as the number of PPMRHs per 10,000 person years at risk for the exposed population in the intervention compared to the pre-intervention group. The pre-intervention period for this objective is one year prior to the trial beginning in addition to the pre-intervention time during the trial period (practices not yet implementing the ACTMed intervention). This will be assessed by undertaking data linkage with data provided by Queensland Health to identify all PPMRHs related to the clinical indicators being measured (through a pre-specified list of ICD-10 codes).
4. Medication-related deaths: The proportion of medication-related deaths, identified by pre-specified ICD-10 codes, assessed by undertaking data linkage through Queensland Health (state death registry), in the intervention compared to the pre-intervention group.
5. Number and type of GP and pharmacist actions recorded: in FHT to review and resolve potential medication related problems (composite outcome), including the percentage of recommendations accepted.
6. Patient experience of the ACTMed service: A patient relevant experience measure ‘Consultation And Relational Empathy (CARE) Patient Feedback Measure’ will be used to measure aspects of the ACTMed service provision by pharmacists and GPs on the care experienced by consumers (4).
7. Health practitioner job satisfaction: the mean of health practitioner job satisfaction at baseline and 6 months post intervention implementation. Job satisfaction is measured using a 10-item question bank (5).
8. False positive percentage: the number of false positive cases (across each category type in Table 2, and combined) will be reported as a percentage of all cases identified.
9. Cost effectiveness analysis: We will estimate the cost per averted serious medication-related problem and the cost per averted potentially preventable medication-related hospitalisation in an in-trial and modelled economic evaluation. In addition, the cost savings associated with lower numbers of potentially preventable medication-related hospitalisations and emergency department visits will be estimated on the basis of Queensland hospitals registry data. The savings will be extrapolated to estimate the benefits were ACTMed introduced across Australia, and the cost of doing so will be estimated by extrapolating the costs associated with its implementation during the trial.

#### INTERVENTION

ACTMed is a co-designed population-based targeted, quality improvement, medicine safety service to identify individuals most at risk of MRPs within general practice. ACTMed uses specifically developed algorithms applied to routinely collected clinical records to identify and triage at risk individuals via an actionable dashboard. See Figure 1 for an overview of the proposed ACTMed intervention.

**Figure 1:** ACTMed intervention overview

Briefly, at-risk individuals will be identified through application of the clinical indicator data coding algorithms within the FHT system. ACTMed risk algorithms will be implemented nightly to query the database of participating general practices to maintain a current list of at-risk individuals. Utilizing the FHT dashboard, the trial pharmacist will screen the clinical record of identified at-risk individuals, check these records against the dispense information held in My Health Record (and any other clinical records held at the practice) to generate a consolidated list of at-risk patients ready to be triaged and actioned.

The FHT dashboard will record the results of the triage, including which practitioner is best suited to resolve the identified MRP risk. Triage will depend on the type of MRP, what action is required, and whether the client has any specific cultural or health needs requiring contact by a particular health practitioner involved in their care. Depending on the type of MRP risk, actions might include contacting the client directly, contacting the prescriber, or contacting the community pharmacist that regularly dispenses prescriptions for the client. Other potential actions could include ordering pathology or medical imaging services, patients being requested to visit their GP or pharmacist for review, or referral to a specialist or other allied health professional. If action has yet to be taken, a flag (in the form of a point of care pop-up warning) will appear in the medical records of a person identified at risk of MRP for when the person next visits the practice.

During the ACTMed trial, benchmarking reports of the included clinical indicators (number of individuals identified as at risk from a MRP as a proportion of the at-risk population) will be produced from aggregated FHT data held by the research team (based at the University of Melbourne) and reported to all practices for whom the intervention has started. Reports will be generated and circulated monthly. Additionally, the trial pharmacist will be encouraged to deliver feedback to the GP through a variety of channels including face to face meetings, practice meetings, and through dissemination of the latest dashboard results.

Specifically, the ACTMed intervention will involve:

* patients –a waiver of consent was provided to identify ‘at risk’ patients - will be contacted by their general practice or ACCHO if the pharmacist or GP thinks a medication review or monitoring is required. At that point, patients will choose to consent or not to be involved in the ACTMed intervention. This approach is consistent with the existing framework of continuous quality improvement that is commonly employed at general practices. As per usual care, patients can involve other people (for example, family members, carers, support workers or translators) in this process as they see fit;
* pharmacists – working within their usual scope of practice, pharmacists will be trained to triage and action potentially ‘at risk’ patients within a pre-specified practice protocol and workflow. For the ACTMed trial, they will be asked to undertake training, participate in at least three Community of Practice meetings facilitated by Brisbane South PHN, lead and document at least one quality improvement cycle and provide the ACTMed intervention for at least 5 hours per week;
* GPs – working within their usual scope of practice, GPs will work together with pharmacists to action potential medication-related problems according to current clinical guidelines. For the ACTMed trial, they will undertake training in the FHT software and at least one GP per practice will participate in the quality improvement cycle led by the pharmacist;
* Other health practitioners and practice support staff – will support implementation of the ACTMed intervention at the practice or ACCHO, including to provide information to patients who may be involved in the intervention.

**Clinical Indicators**

Five clinical indicators are used in the ACTMed trial. These indicators sit in the FHT software. The indicators are shown in Table 3.

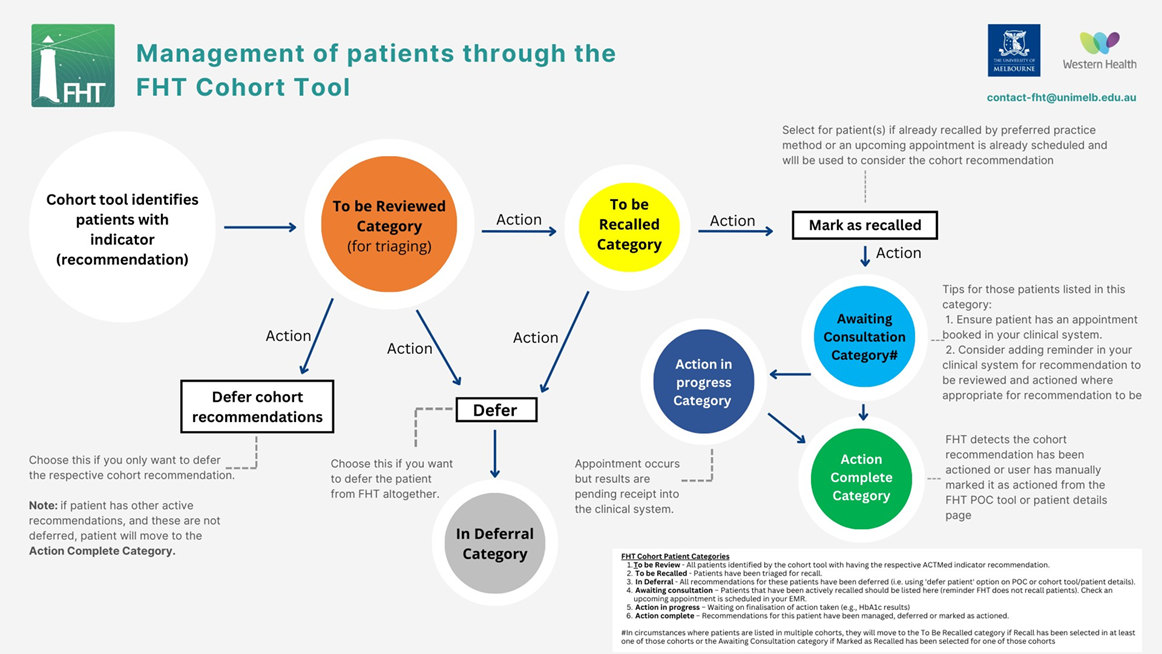
**Table 3:** ACTMed clinical indicators

|  |  |  |  |
| --- | --- | --- | --- |
| **Indicator** | **At risk population (denominator)** | **At risk population meeting definition of MRP (numerator)** | **Hospitalisation to avoid**  **(PPMRH)** |
| 1. Atrial fibrillation | * People with AF diagnosis AND * [(No diagnosis of stroke or TIA AND CHA2DS2-VA\* score ≥1) OR * (History of stroke AND/OR TIA)] | * Not taking anti-coagulant therapy | Thromboembolic cerebrovascular event |
| 1. Heart failure | * People with heart failure diagnosis | * Not taking ACE, ARB or ARNi | Congestive heart failure or fluid overload |
| 1. Cardiovascular disease (a) | * People with CVD diagnosis | * Not taking a statin when indicated | Ischaemic event |
| Cardiovascular disease (b) | * People with CVD diagnosis AND * No diagnosis of AF | * Not taking and anti-platelet when indicated | Ischaemic event |
| 1. Type 2 diabetes | * People with type 2 diabetes diagnosis AND   Prescribed >=1 glucose lowering medication | * No HbA1C monitoring test result recorded for >6 months | Diabetes-related complication |
| 1. Asthma/COPD | * People with previous diagnosis of asthma or COPD AND * Frequent use of SABA or SAMA (>=2 prescriptions in previous 12 months) | * No current use of maintenance therapy | Asthma or COPD exacerbation |

*MRP = medication-related problem; PPMRH=potentially preventable medication-related hospitalisation; AF=atrial fibrillation; TIA=transient ischaemic attack; ACE=angiotensin-converting enzyme (inhibitor); ARB=angiotensin receptor blocker; ARNi = angiotensin receptor-neprilysin inhibitor; CVD = cardiovascular disease; COPD = chronic obstructive pulmonary disease; SABA = short-acting beta agonists; SAMA= short acting muscarinic antagonists*

\* CHA2DS2-VA as measured by the Heart Foundation definition and points (3)

**Figure 2: Management of patients through the Future Health Today cohort tool**



#### RANDOMISATION AND BLINDING

Practices are randomised to one of six start dates in accordance with the stepped-wedge cluster randomised trial design (Figure 3). Forty-two practices were randomised on 4 August 2024, stratified as either “small” (<=6,000 active patients) or “large” (>600 patients), such that there are either 3 smaller and 4 larger or 4 small and 3 larger practices per step/tranche. Randomization was undertaken using a web-based interactive randomization service (Griffith University).

**Figure 3**: ACTMed trial design and timeframe



* + 1. **Deviations from randomisation protocol**

After five practices from one corporate group withdrew from the trial after enrolment (October 2023), an additional three practices were recruited and enrolled in late Oct/early November 2023 (herein called ‘booster practices’). These additional three practices were randomised (November 2023) to start in any of the remaining tranche start dates (tranches 4-6). The booster practices will be excluded from the ITT analysis of the primary outcome, but included in additional analyses.

#### SAMPLE SIZE

For an analysis of the primary outcome at the individual level and secondary outcome at the practice level, we estimated that 42 participating practices would be required to achieve 90% power for detecting a 10% practice-level absolute difference in the proportion of the exposed population at risk of a medication-related problem due to ACTMed (significance level, alpha = 0.05, inter-cluster correlation = 0.05), assuming a baseline proportion of those at risk of a medication-related problem among those people potentially exposed is 0.08, and that six practices will not complete the trial and therefore not deliver data.

For the key secondary outcome (proportion of exposed individuals in each practice with medication-related problem rates at the practice level), the sample size will be sufficient to achieve 80% statistical power for detecting a 19% practice-level absolute difference in medication-related problem rates. The anticipated difference was informed by the proportion of people at risk who had medication-related problems derived from an analysis of Patron data for 75 Victorian general practices (1,2).

We anticipate a total of 35 238 people exposed, based on an estimated 839 patients per practice across all indicators. This is comparable with estimates of the at-risk population and effect sizes of British intervention trials (6-9); one group that examined individual-level time series data found a 40% reduction in high-risk prescribing (7,8), but a later national study found an estimated 25% reduction at the more conservative practice level (10).

Stata 17 stepped-wedge command for sample size calculations was used to estimate the required sample size (11).

### STATISTICAL ANALYSIS

#### GENERAL PRINCIPLES

One change has been made to the planned statistical analysis from the study protocol (1,2). This is the addition of 3 practices randomised after five practices from one corporate group withdrew (detailed in 2.5.1 above).

The analysis plan described here includes all planned quantitative analyses for the ACTMed trial. A number of additional qualitative analyses are planned, including qualitative interviews with providers of the ACTMed service and recipients of the ACTMed service. Evaluation of the process of co-designing the ACTMed intervention by the Consumer Advisory Group, using mixed methods, will be undertaken. A qualitative analysis of de-identified Plan-Do-Study-Act cycles will also be undertaken.

All data for the quantitative analysis of the ACTMed trial, excluding the practitioner survey results, will be securely stored within the Patron data enclave, maintained by The University of Melbourne. All investigators involved in data analysis will adhere to the governance requirements of the Data for Decisions program, in additional to the data sharing agreement between The University of Queensland and The University of Melbourne. Data can only be accessed by virtual machine using multi-factorial authentication to the Patron environment. Queensland Health data (hospitalisation and death data) will also be stored in the Patron enclave.

Results will be reported according to the extension of the CONSORT 2010 Statement on the reporting of stepped-wedge cluster randomize trials (11). Prior to undertaking the analysis, the pre-intervention data will be tested for any time trend in the primary outcome to identify any potential risk of overestimation bias due to the stepped-wedge design.

#### 3.1.1 Statistical software

All statistical analyses will be performed using Stata v17 or above (StataCorp. Stata Statistical Software. College Station, TX: StataCorp LP)or R v 4.0.2 (Comprehensive R Archive Network) with Rstudio (v 2022.12.0+353 RStudio Team (2022). RStudio: Integrated Development for R. RStudio, PBC, Boston, MA URL http://www.rstudio.com/).

#### 3.1.2 Reporting conventions

P-values will be reported to 2 decimal places to p=0.01, then 3 decimal places to p=0.001. All smaller values will be reported as p<0.001.

#### 3.1.3 Data cleaning approach

Data cleaning and linking will be completed and documented within the Patron secure data environment, managed by the University of Melbourne. Raw data will be kept separate from analysis files. Data cleaning files will be documented and stored within the Patron secure data environment by an investigator who is blinded to when the ACTMed intervention was implemented at each practice. Quality checking and validation of the data cleaning approach will be undertaken by a second investigator who is blinded to when the ACTMed intervention was implemented at each practice.

#### 3.1.4 Confidence intervals and P-values

For each outcome variable, statistical significance will be assessed at the 0.05 level and 95% confidence intervals will be reported.

#### 3.1.5 Method for validating the results

Data analysis files will be documented and stored within the Patron secure data environment. Initial results will be prepared by data analysts in the research team without input of the statistician. Quality checking and validation of the data analysis and reporting of results will be undertaken by the statistician.

#### INTERIM ANALYSES

No interim analyses will be carried out for this study.

#### MULTIPLICITY ADJUSTMENT

No formal adjustments for multiplicity are planned, however significant test results will be interpreted considering any multiple comparisons made. To express uncertainty about the treatment effect, 95% confidence intervals will be used.

#### SUBJECT DISPOSITION

A waiver of consent for individual patients has been granted in the ACTMed Ethics application (The University of Queensland, Human Research Ethics (2022/HE002136)) to identify ‘at risk’ patients. If deemed clinically necessary by the practice team, any at risk patient will be contacted by their general practice or ACCHO if a consultation or review is required. For other at-risk patients, it may be decided to wait until their next scheduled appointment. Patients will choose to consent or not if recall is initiated by the practice, consistent with a framework of continuous quality improvement. As per usual care, patients will be encouraged to involve other people (for example, family members, carers, support workers or translators) in the recall process as appropriate. Patient flow through the ACTMed intervention will be recorded in the FHT software per Figure 2 above.

#### MISSING DATA

Loss to follow-up at an individual level is considered unlikely, as unless a patient actively withdraws their consent, individual-level data will be captured within the FHT software. However, practice withdrawal is considered possible (see 3.4 above). Any loss to follow-up will be reported by reason, alongside any resulting study amendments.

The primary analysis will be ‘intention-to-treat’ for all practices initially randomised where data is available (practices will be excluded if no data was available from that practice). For practices that withdraw, the dates and reasons for withdrawal will be documented along with the tranche they were randomized to. A secondary analysis will be undertaken which includes the booster practices, that is, the practices that were recruited following withdrawal of the five practices from one corporate entity. If some practices are missing data for some months, then a complete case analysis (only included practice with data for all months) will also be undertaken with appropriate sensitivity analyses, including best-case / worse-case scenario testing or best-case / worst-case carried forward.

Protocol deviations will be defined as a practice not onboarding within the specified month and/or not starting the intervention period as planned, missing data, inclusion of ineligible patients or any deviation from the protocol. All protocol violations will be reported by type, including a description of the deviation and the corrective action taken.

#### DATA SETS TO BE ANALYSED

Four key datasets will be linked and analysed. These include:

* De-identified data from the FHT software, which tracks individuals considered to be at risk and any actions undertaken by pharmacists, GPs and other practice staff to resolve potential medication-related problems;
* De-identified individual-level patient data from the electronic medical records of participating practices (including exposed and ‘at risk’ individuals);
* De-identified individual level hospitalisation data from Queensland Health (all exposed individuals). Where there is no linked data available for an exposed patient it is assumed they had no hospitalisation for the included date range; and
* De-identified individual level death data from Queensland Health (all exposed individuals). Where there is no linked data for an exposed patient, it is assumed they are still alive for the included date range.
  1. **COMPLIANCE TO STUDY INTERVENTION(S)**

Compliance to the study invention(s) includes:

1. The extent to which the intervention is implemented as intended (implementation fidelity), over time and across different sites.
2. How staff understand and respond to the intervention, over time and across different sites.
3. Context over time and across different sites and factors (including managerial, economic, organisational, and work level) that affect implementation.

Variables which will be used to define compliance during implementation include:

|  |  |
| --- | --- |
| **Time spent using training indicator** | Start date of the training indicator being activated until this indicator is switched off and the ACTMed indicators are switched on (start of active intervention) |
| **Duration of exposure** | Time from ACTMed indicators being switched on until offboarding date |
| **Delay in on-boarding** | Time from start of randomised step/tranche until ACTMed indicators switched (for practices with delayed start) |
| **Delay in start of activity** | Time from start of randomised step/tranche until “to be reviewed” cohort number first starts to decline from baseline value. |

#### PATIENT AND PRACTICE CHARACTERISTICS AND BASELINE COMPARISONS

The number of practices randomised to each tranche will be reported. The number of practices with data available in each tranche will be reported. Where practice data is available, patient and practice baseline statistics (pre-intervention) will be summarised in the following table for time period 0 (Figure 2). Mean and standard deviation (SD) or median and interquartile range (IQR) will be presented.

|  |  |
| --- | --- |
| **Patient characteristic** | **Categories** |
| Age - years | continuous |
| Sex | Male  Female  Other |
| Concession card status | No concession (general)  Concession or pension card  Repatriation/ veterans card |
| Socio-Economic Index for Areas (SEIFA) | deciles |
| Number of comorbidities  Number of medications  Number of visits last 12 months  GPMP or TCA arrangement in last 12 months  HMR in last 12 months | continuous  continuous  continuous  Yes  No  Yes  No |
| Bodyweight | Obese (BMI ≥30)  Overweight (BMI ≥25 to <30)  Normal weight (BMI ≥18.5 to <25)  Underweight (BMI <18.5) |
| Aboriginal and/or Torres Strait Islander person | Yes  No |
| Relationship status | Unknown  Single  Married  Divorced |
| Atrial fibrillation | Yes  No |
| Heart failure  Cardiovascular disease | Yes  No  Yes |
| Type 2 diabetes  Asthma  Chronic obstructive pulmonary disease (COPD) | No  Yes  No  Yes  No  Yes |
| Asthma-COPD overlap syndrome (ACOS) | No  Yes |
| Patient status at practice | EMR active (mean/SD of total patients at practice)  Inactive (mean/SD of total patients at practice)  Deceased (mean/SD of total patients at practice) |
| **Practice characteristic** | **Categories** |
| Number active patients (Patron definition- at least 3 visits to practice in last 3 years  Number of active patients (RACGP definition – at least 3 visits to practice in last 2 years)  Number of GPs at the practice  Number of practice nurses at the practice  Provision of bulk billing at the practice  Pharmacist previously employed in practice  Socio-Economic Index for Areas (SEIFA)  Urban  Regional/rural/remote | Continuous  Continuous  Continuous  Continuous  Yes  No  Yes  No  deciles  Yes  No  Yes  No |
| Medical record software | Medical Director  Best Practice |

EMR = electronic medical record; SD = standard deviation; BMI = body mass index; GPMP = GP management plan; TCA = team care arrangements; HMR = home medicines review; COPD = chronic obstructive pulmonary disease; ACOS = asthma COPD overlap syndrome; RACG = Royal Australian College of General Practice; GP = general practitioner

Summary statistics will be presented as frequency [percentage] for categorical variables, and chi-square tests will be used to determine between-group differences. Continuous variables will be summarised as mean [standard deviation (SD)] or median [interquartile range (IQR)] where appropriate, with t-tests (or Mann-Whitney U test) used to determine between-group differences.

#### ANALYSIS OF THE PRIMARY OUTCOME

Where data is available, we will undertake intention-to-treat (ITT) analysis of outcomes data for the primary outcome using the 42 randomised practices. Supplementary per protocol analyses will also be undertaken including the additional three booster practices.

* + 1. **MAIN ANALYSIS**

The main analysis of the primary outcome will be conducted at the individual level. The primary outcome is the proportion of individuals from the exposed population (denominator) with any serious medication-related problems (numerator) each month (time periods 0-7 in Figure 2) for all clinical indicators combined (composite measure). This will be determined by data extraction from the FHT software platform. Data from the training months when practices onboarded the ACTMed intervention will be treated as missing data for the primary outcome; therefore active intervention data will be available for a maximum of five months per practice, depending on the randomised start date of the ACTMed intervention. The effect of assuming no data available for the training month will be tested in a robustness analysis. The numerator and denominator will be adjusted to remove the category 1 and 2 pre-specified false positive cases identified (Table 2), with the date of false positive assumed have been recorded time period 0 (Figure 2). The treatment of category 3 false positive cases will be tested in robustness analyses, separately testing the removal of false positive cases on numerators, denominators and both on the treatment effect. Treatment effects for all clinical indicators will also be presented separately as a secondary analysis. The trial hypotheses will be evaluated through a framework of superiority.

For the primary outcome, we will use a mixed effects logistic regression model. The main fixed effect will be ACTMed exposure (intervention, pre-intervention). Calendar month will be included as a fixed covariable to account for time-dependent changes that may affect the primary outcome, such as change in GP prescribing behaviour. Practice will be included as a random effect to account for possible non-independence from observations from the same practice. Practice will be included as a random intercept by default, and as a random slope if the random slope model adds significantly more information than the random intercept model (using likelihood ratio test, P<0.05). Participants will be nested within practices. The effect estimate presented will be an odds ratio with 95% confidence interval. This will also be reported as an estimated marginal effect on the absolute proportion of exposed people at risk to provide a treatment estimate and 95% CI. The sensitivity of this finding will be investigated by re-running the analysis with stratification variable “practice size” (small/large, where large >=6,000 active patients) included as a fixed effect.

* + 1. **SUBGROUP ANALYSES**

We will analyse the primary outcome by practice and tranche (randomized start date) where sufficient data is available.

#### ANALYSIS OF SECONDARY OUTCOMES

* + 1. **SECONDARY OUTCOME 1** – Practice level analysis of the primary outcome

The analysis will be conducted at the practice level. The primary outcome is the monthly practice-level proportion of individuals from the at-risk population (denominator) with any serious medication-related problems (numerator) in the intervention compared to the pre-intervention group. This will be determined by data extraction from the FHT software platform. The numerator and denominator will be adjusted to remove false positive cases identified, with the date of false positive assumed have been recorded 6 months prior to the start of the intervention phase for that practice.

For secondary outcome 1, we will use a mixed effects linear regression model. Fixed effects will include ACTMed exposure (intervention, pre-intervention), calendar month and practice size (small/large). The effect estimate will be presented as mean difference and 95% CI.

* + 1. **SECONDARY OUTCOME 2** – Persistence of any treatment effect

The analysis will be conducted both at the individual level and the practice level. The persistence of any change in the proportion of individuals from the exposed population with any serious medication-related problems once the intervention ceases (i.e., end of the trial compared to 6 months post last practice implementing the intervention).

For secondary outcome 2, we will use a mixed effects logistic regression model (individual level) and linear regression (practice level). For the primary analysis, fixed effects will include ACTMed exposure (pre-intervention, intervention, post-intervention), calendar month and practice size (large/small); random effects will account for clustering at the practice level and patient level, with patients nested within practices. As a secondary analysis, the transition period will be added as a fixed-effect. For the logistic model we will report both odds-ratios, while for the linear model we will report mean difference

* + 1. **SECONDARY OUTCOME 3 –** Incidence rate ofpotentially preventable medication-related hospitalisations

Potentially preventable medication related hospital admissions will be analysed at the individual level. This outcome will be assessed by undertaking data linkage with data provided by Queensland Health to identify all hospitalisations related to the clinical indicators being measured (through a pre-specified list of ICD-10 codes – Table 4). All events will be summed for the pre-intervention period compared to the post intervention period and converted to rates by dividing the summed events by total person time of the *exposed* population.

For secondary outcome 3, we will use a mixed effects logistic regression model. Fixed effects will include ACTMed exposure (intervention, pre-intervention), calendar month and practice size (small/large); random effects will account for clustering (at the practice level) and repeated measures (at the patient level). Effect estimates will be reported as odds ratios and 95% CI.

**Table 4:** Pre-specified ICD-10 codes for hospital admissions (emergency department presentations and inpatient admissions)

|  |  |  |  |
| --- | --- | --- | --- |
| **Hospitalisation to avoid**  **(PPMRH)** | **ICD-10\_AM Codes** | **Description** | **Additional requirements** |
| Thromboembolic cerebrovascular event (13) | G45 | Transient cerebral ischaemic attacks and related syndromes | As principal or secondary diagnosis. |
|  | G46 | Vascular syndromes of brain in cerebrovascular diseases |
|  | I61 | Intracerebral haemorrhage |
|  | I62 | Other nontraumatic intracranial haemorrhage |
|  | I63 | Cerebral infarction |
|  | I64 | Stroke, not specified as haemorrhage or infarction |
|  | I65 | Occlusion and stenosis of precerebral arteries, not resulting in cerebral infarction |
|  | I66 | Occlusion and stenosis of cerebral arteries, not resulting in cerebral infarction |
|  | I67 | Other cerebrovascular diseases |
|  | I69 | Sequelae of cerebrovascular disease |
| Congestive heart failure or fluid overload (14) | I50 | Heart failure | As principal diagnosis.  Exclude cases with the following cardiac procedure codes:  Blocks [572], [600]–[606], [608]–[650], [653]–[657], [660]–[664], [666], [669]–[682], [684]–[691], [693], [705]–[707], [717] and codes 33172-00[715], 33827-01[733], 34800-00[726], 35412-00[11], 38721-01[733], 90217-02[734], 90215-02[732] |
|  | I11.0 | Hypertensive heart disease with (congestive) heart failure | As principal diagnosis.  Exclude cases with the following cardiac procedure codes:  Blocks [572], [600]–[606], [608]–[650], [653]–[657], [660]–[664], [666], [669]–[682], [684]–[691], [693], [705]–[707], [717] and codes 33172-00[715], 33827-01[733], 34800-00[726], 35412-00[11], 38721-01[733], 90217-02[734], 90215-02[732] |
|  | J81 | Pulmonary oedema | As principal diagnosis.  Exclude cases with the following cardiac procedure codes:  Blocks [572], [600]–[606], [608]–[650], [653]–[657], [660]–[664], [666], [669]–[682], [684]–[691], [693], [705]–[707], [717] and codes 33172-00[715], 33827-01[733], 34800-00[726], 35412-00[11], 38721-01[733], 90217-02[734], 90215-02[732] |
| Ischaemic event (13) | I20 | Angina pectoris | As principal or secondary diagnosis. |
|  | I121 | Acute myocardial infarction |
|  | I122 | Subsequent myocardial infarction |
|  | I123 | Certain current complications following acute myocardial infarction |
|  | I124 | Other acute ischaemic heart diseases |
|  | I125 | Chronic ischaemic heart disease |
|  | G45 | Transient cerebral ischaemic attacks and related syndromes | As principal or secondary diagnosis. |
|  | G46 | Vascular syndromes of brain in cerebrovascular diseases |
|  | I61 | Intracerebral haemorrhage |
|  | I62 | Other nontraumatic intracranial haemorrhage |
|  | I63 | Cerebral infarction |
|  | I64 | Stroke, not specified as haemorrhage or infarction |
|  | I65 | Occlusion and stenosis of precerebral arteries, not resulting in cerebral infarction |
|  | I66 | Occlusion and stenosis of cerebral arteries, not resulting in cerebral infarction |
|  | I67 | Other cerebrovascular diseases |
|  | I69 | Sequelae of cerebrovascular disease |
| Diabetes-related complication (14) | E10.0-E10.9 | Type 1 diabetes mellitus | Principal diagnosis only |
|  | E11.0-E11.9 | Type 2 diabetes mellitus |
|  | E13.0-E13.9 | Other specified diabetes mellitus |
|  | E14.0-E14.9 | Unspecified diabetes mellitus |
| Asthma or COPD exacerbation (14) | J45 | Asthma | As principal diagnosis. |
|  | J46 | Status asthmaticus | As principal diagnosis. |
|  | J20 | Acute bronchitis | As principal diagnosis.  Only with additional diagnoses of J41, J42, J43, J44 |
|  | J41 | Simple and mucopurulent chronic bronchitis | As principal diagnosis. |
|  | J42 | Unspecified chronic bronchitis | As principal diagnosis. |
|  | J43 | Emphysema | As principal diagnosis. |
|  | J44 | Other chronic obstructive pulmonary disease | As principal diagnosis. |

* + 1. **SECONDARY OUTCOME 4 –** Medication related deaths

Medication-related deaths will be analysed at the individual level. This outcome will be assessed by undertaking data linkage through Queensland Health (state death registry) for 12 months prior to the intervention compared to 12 months after the intervention.

For the secondary outcome 4, we will use a mixed effects logistic regression model. Fixed effects will include ACTMed exposure (intervention, pre-intervention), calendar month and practice size (small/large); random effects will account for clustering (at the practice level) and repeated measures (at the patient level). Effect estimates will be reported as odds ratios and 95% CI.

* + 1. **SECONDARY OUTCOME 5 –** Pharmacist and GP actions undertaken

Number and type of GP and pharmacist actions to resolve medication related problems (composite outcome). GP and pharmacist actions will be entered into the FHT software platform as part of the intervention (Figure 2).

* + 1. **SECONDARY OUTCOME 6 –** Client experience outcomes

A client relevant experience measure ‘Consultation And Relational Empathy (CARE) Patient Feedback Measure’ will be used to measure aspects of the ACTMed service provision by pharmacists and GPs (11). The CARE is measured by a 10-item question bank using a 5 point Likert scale (poor – excellent). Data analysis will be descriptive (mean and 95% CI), for each item as well as a global (summed) score, with pre-post difference tested using mixed-effects linear regression. Fixed effects will include ACTMed exposure (intervention, pre-intervention), calendar month and practice size (small/large); random effects will account for clustering (at the practice level) and repeated measures (at the patient level). Effect estimates will be reported as mean difference and 95% CI.

* + 1. **SECONDARY OUTCOME 7 –** Health practitioner job satisfaction

Health practitioner job satisfaction will be assessed at baseline and 6 months post intervention implementation. Job satisfaction is measured by a 10-item question bank using a 5-point Likert scale (extremely satisfied – extremely dissatisfied) (3). Data analysis will be descriptive (mean and 95% CI), for each item as well as a global (summed) score, with pre-post difference tested using mixed-effects linear regression. Fixed effects will include ACTMed exposure (intervention, pre-intervention), calendar month and practice size (small/large); random effects will account for clustering (at the practice level) and repeated measures (at the patient level). Effect estimates will be reported as mean difference and 95 % CI.

* + 1. **SECONDARY OUTCOME 8 –** False positive percentage

The false positive percentage of each clinical indicator used in the ACTMed trial will be reported. This will be measured by the number and type of “deferred” recommendations recorded in the FHT software. Deferred reason or type were coded by participating pharmacists. The data analysis will be descriptive (mean and 95% CI or median and interquartile range if data is skewed) for each deferred type (coded by participating pharmacists). False positive cases will be reported separately for each of the three categories identified in Table 2 and combined.

* + 1. **SECONDARY OUTCOME 9 –** Economic evaluation

The cost per averted serious medication-related problem and the cost per averted potentially preventable medication-related hospitalisation in an in-trial and modelled economic evaluation. In addition, any cost savings associated with lower numbers of potentially preventable medication-related hospitalisations and emergency department visits will be estimated on the basis of Queensland hospitals registry data. The savings will be extrapolated to estimate the benefits were ACTMed introduced across Australia, and the cost of doing so will be estimated by extrapolating the costs associated with its implementation during the trial.

#### ANALYSIS OF SAFETY OUTCOMES

A planned safety analysis will not be undertaken, given as how the primary outcome is a medication safety outcome. However, any adverse events reported by practices or Aboriginal and Torres Strait Islander Health Services will be reported.

### REFERENCES

1. Spinks J and the ACTMed Study Team (2022), Investigating the effect of ‘Activating pharmacists to reduce medication related problems’: The ACTMed stepped wedge cluster randomized trial (SW-CRT) protocol. The University of Queensland, UQ HREC #: 2022/HE002136
2. Spinks J, Violette R, Boyle DI, Petrie D, Fanning L, Hall KK, ... & Nissen, L. (2023). Activating pharmacists to reduce the frequency of medication‐related problems (ACTMed): a stepped wedge cluster randomised trial. Medical Journal of Australia, 219(7), 325-331.
3. National Heart Foundation of Australia, (2022). Clinical fact sheet - Stroke prevention in non-valvular atrial fibrillation using CHA2DS2-VA score. Available from: <https://www.heartfoundation.org.au/getmedia/eb9cefa4-c201-478b-a787-5402beaccc0a/Clinical_Fact_Sheet_-_Stroke_AF.pdf>
4. Mercer SW, Maxwell M, Heaney D, & Watt GC (2004). The consultation and relational empathy (CARE) measure: development and preliminary validation and reliability of an empathy-based consultation process measure. Family Practice, 21(6), 699-705.
5. Joyce CM, Schurer S, Scott A, Humphreys J, & Kalb G. (2011). Australian doctors’ satisfaction with their work: results from the MABEL longitudinal survey of doctors. Medical Journal of Australia, 194(1), 30-33.
6. Avery AJ, et al., (2012). A pharmacist-led information technology intervention for medication errors (PINCER): a multicentre, cluster randomised, controlled trial and cost-effectiveness analysis. Lancet, 379(9823): p. 1310-9.
7. Dreischulte, T., et al., (2016). Safer Prescribing--A Trial of Education, Informatics, and Financial Incentives. N Engl J Med, 374(11): p. 1053-64.
8. Dreischulte, T., et al., (2012). A cluster randomised stepped wedge trial to evaluate the effectiveness of a multifaceted information technology-based intervention in reducing high-risk prescribing of non-steroidal anti-inflammatory drugs and antiplatelets in primary medical care: the DQIP study protocol. Implement Sci, 7: p. 24.
9. Guthrie, B., et al., (2016). Data feedback and behavioural change intervention to improve primary care prescribing safety (EFIPPS): multicentre, three arm, cluster randomised controlled trial. British Medical Journal, 354: p. i4079
10. Rodgers S, Taylor AC, Roberts SA, Allen T, Ashcroft DM, Barrett J, ... & Avery, A. J. (2022). Scaling-up a pharmacist-led information technology intervention (PINCER) to reduce hazardous prescribing in general practices: Multiple interrupted time series study. PLoS medicine, 19(11), e1004133.
11. Hemming K, Girling A. A menu-driven facility for power and detectable-difference calculations in stepped-wedge cluster-randomized trials. *The Stata Journal*. 2014;14(2):363–380
12. Hemming K, Taljaard M, McKenzie JE, Hooper R, Copas A, Thompson JA, ... & Grimshaw JM. (2018). Reporting of stepped wedge cluster randomised trials: extension of the CONSORT 2010 statement with explanation and elaboration. British Medical Journal, 363.
13. Joshy G, Korda RJ, Abhayaratna WP, Soga K, Banks E. Categorising major cardiovascular disease hospitalisations from routinely collected data. Public Health Res Pract. 2015;25(3):e2531532
14. Australian Institute of Health and Welfare. National Healthcare Agreement: PI 18–Selected potentially preventable hospitalisations, 2022. Available at: [https://meteor.aihw.gov.au/content/740851#](https://meteor.aihw.gov.au/content/740851) Accessed 29/07/2024

### APPENDIX 1: PROPOSED TABLES AND FIGURES

Indicative figures and tables for the main analysis are presented below.

#### Figure 1: Consort flowchart

#### Table 1: Preintervention characteristics of patients and practices, by randomisation start date

|  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- |
| **Characteristic** | **Start date (tranche)** | | | | | |
|  | 1 | 2 | 3 | 4 | 5 | 6 |
| **Patients** | | | | | | |
| Age (mean, SD) |  |  |  |  |  |  |
| Female (#, %) |  |  |  |  |  |  |
| First nations (#, %) |  |  |  |  |  |  |
| Concession card (#, %) |  |  |  |  |  |  |
| SEIFA |  |  |  |  |  |  |
| **Practices** | | | | | | |
| Number practices # |  |  |  |  |  |  |
| Urban practices # |  |  |  |  |  |  |
| Patient number (mean, SD) |  |  |  |  |  |  |

#### Table 2: Primary outcome

|  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- |
|  | **Prevalence**  **No./total no. (%)** | | **Odds ratio (95% CI)** | | **Modelled adjusted mean prevalence of**  **at risk/exposed population** | | **Adjusted relative difference (95% CI)** | **p-value** |
| **Outcome** | **At start of ACTMed** | **At end of ACTMed** | **Pre-intervention period** | **Post-intervention period** | **Pre-intervention period** | **Post-intervention period** |  |  |
| Composite any at risk/any exposed |  |  |  |  |  |  |  |  |
| Small practices |  |  |  |  |  |  |  |  |
| Large practices |  |  |  |  |  |  |  |  |
| Indicator 1 |  |  |  |  |  |  |  |  |
| Indicator 2 |  |  |  |  |  |  |  |  |
| Indicator 3 |  |  |  |  |  |  |  |  |
| Indicator 4 |  |  |  |  |  |  |  |  |
| Indicator 5 |  |  |  |  |  |  |  |  |



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1. Activating pharmacists to reduce medication related problems was the name of the grant that was awarded under the Medical Research Future Fund (MRFF). Following consumer feedback during the co-design process, the name of the trial was changed to ACTivating primary care for Medicine Safety. [↑](#footnote-ref-1)