**Protocol for Ethics**

**Timely post-discharge medication reviews to Improve Continuity – the Transitions Of Care stewardship (TIC TOC) study in rural and regional Australia**

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**Grantee/Sponsor:** The University of Sydney.

**Table 1. PROJECT TEAM MEMBERS - ROLES AND RESPONSIBILITIES**

|  |  |  |
| --- | --- | --- |
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| Dr Manya Angley | Director Manya Angley Research and Consulting | Chief Investigator B, Quality use of medicines, medication management expert  |
| Professor Rebekah Jane Moles | Professor, Sydney Pharmacy School, The University of Sydney, Pharmacist | Chief Investigator C, Pharmacy and Transitions of care, Medication management services and safety expert |
| Ms Deirdre Thelma Criddle | Complex Care Clinical Pharmacist, South Metropolitan Health Service Murdoch | Chief Investigator D, predictive risk modelling, medication management |
| Associate Professor Rohan Andrew Elliott | Senior Clinician, Austin Health; Adjunct Associate Professor, Monash University | Chief Investigator E, Medication safety, transitions of care, geriatric medicine expert |
| Ms Deborah Rigby | Adjunct Associate Professor, School of Pharmacy, University of Queensland | Chief Investigator F, Medication safety, transitions of care, geriatric medicine expert |
| Prof Sepehr Shakib | Professor Clinical Pharmacology, University of Adelaide | Chief Investigator G, Medication safety, transitions of care, geriatric medicine expert |
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| Dr Stephen Carter | Senior Lecturer, Sydney Pharmacy School, University of Sydney, Pharmacist | Chief Investigator I, Medication safety, transitions of care, geriatric medicine expert |
| Dr Charley Ann Budgeon | Lecturer, Biostatistician, School of Population and Global Health, University of Western Australia  | Chief Investigator J, Statistical Expert, proficiency in SAS, R, and M-Plus programs. |
| Dr Kim-Huong Nguyen | Senior Research Fellow, Faculty of Medicine, University of Queensland | Chief Investigator K, Economics, Econometrics, Economic evaluation expert |
| Dr Paul Andrew Yates | Geriatrician, Austin Hospital, Heidelberg, Victoria | Chief Investigator L, Medication safety and Transitions of Care expert |
| Ms Katie Maree Phillips | Hospital Outreach Pharmacist, The Royal Melbourne Hospital | Chief Investigator M, Transition of care and medication review expert |
| Mr Jerry Yik | Head of Policy and Advocacy, The Society of Hospital Pharmacists of Australia, Collingwood, Victoria | Chief Investigator N, Pharmacy Policy, Medication safety, quality use of medication expert  |
| Prof Faye McMillan | Professor of Indigenous Health, University of Technology Sydney; Deputy National Rural Health Commissioner. | Chief Investigator O, Strait Islander people, Medication and Pharmacy practice expert |
| Mrs Deborah Hawthorne | Consultant pharmacist, South Wangaratta Medical Clinic, Victoria | Chief Investigator P, Health services research, Medication safety, Pain, and Primary care expert |
| Ms Cristen Fleming | Rural Health Manager and Clinical Pharmacist at Western NSW Local Health District  | Chief Investigator Q, Principal Investigator for WNSWLHD sites, Virtual Clinical Pharmacist, Clinical medication and management expert |
| Ms Anna Louise Packer | Virtual Clinical Pharmacist at Western NSW Local Health District | Chief Investigator R, Clinical medication and management, Telehealth expert |
| Ms Linda Krogh | Virtual Clinical Pharmacist at Orange Health Service | Chief Investigator S,Clinical medication and management expert |
| Associate Professor Simon Poon | Associate Professor, School of Computer Science, Faculty of Engineering, University of Sydney | Chief Investigator T,Health Information and Evaluation expert |
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1. **SUMMARY**

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| Study Title | Timely post-discharge medication reviews to Improve Continuity – the Transitions Of Care stewardship (TIC TOC) study in rural and regional Australia. |
| Aims/Objectives | This research has three aims: (1) Determine the effectiveness of the TIC TOC intervention compared to usual care, (2) assess its cost-effectiveness, and (3) explore factors affecting its implementation.Research question: Does the TIC TOC intervention reduce the incidence of medication-related harm, including hospital readmissions and ED presentations? Primary objective: * To determine the effect of the TIC TOC intervention on medication-related hospital admission or ED presentation within 30 days of discharge.

Secondary objectives:* To determine the effect of the TIC TOC intervention on unplanned all-cause readmission and ED presentations and unplanned medication-related readmission and ED presentations within 30, 90 and 180 days compared with usual care.
* To determine whether the TIC TOC intervention increases the proportion of high-risk patients receiving a timely post-discharge medication review (within ten days from discharge)
* To assess the number, nature, and severity of medication-related problems identified in initial post-discharge medication review reports and in HMR follow-up(s) where applicable.
* To determine the cost-effectiveness of the TIC TOC intervention.
 |
| Study design | It is a prospective, randomised controlled clinical trial involving patients at high-risk of medication-related harm who are discharged from regional and rural hospitals to a domiciliary residence. Within the trial cost-effectiveness analysis of the TIC TOC intervention on 30-day medicine-related hospital readmissions and ED presentations will be undertaken from the health system perspective. For this proposal we will also conduct interviews before and after implementation using qualitative one-on-one semi-structured interviews with patients and clinicians to determine their beliefs, attitudes and perceived acceptability, facilitators and barriers to the implementation of the intervention. Interviews will be conducted by investigators who possess training in qualitative research methods using telephone or videoconferencing. |
| Planned sample size | 922 participants in total. |
| Inclusion/Exclusion criteria | Eligible patients must be aged ≥18 years, admitted under a medical specialty, including general medicine, discharged to a domiciliary setting, have a GP, have a Medicare card and be at risk of readmission (defined as high-risk according to the PHarmacie-R risk algorithm). Exclusion criteria include unmanaged substance use disorder or mental health condition, active palliative care, homelessness, admission for planned dialysis, unsafe home environment (domestic violence or aggression), planning to change residence in six months or previously recruited. |
| Study procedures | 1. Enrolment into the study: Research Assistant (RA) will identify potentially eligible patients using routinely collected data. Those fitting the inclusion criteria will be invited to participate in the study.2. Informed consent: Patients who meet the inclusion criteria and agree to enrol in the study will be asked to read a participant information sheet and sign a consent form. 3. Randomisation: Participants will be randomised in a 1:1 ratio in permuted blocks of 2 and 4 to: (1) intervention; or (2) usual care. Randomisation will be conducted using a centralised service to ensure allocation concealment. 4. Intervention: The intervention is based on the Consolidated Framework for Implementation Research as it has been used extensively to implement health services. The intervention will include virtual Transitions of Care Stewardship pharmacists ensure patients receive discharge counselling, discharge medical reconciliation, and communicate directly with primary care providers (GPs, practice nurses, community pharmacies and accredited pharmacists). They will provide accurate and timely medication handover to facilitate a timely post-discharge medication review. Pharmacists caring for Aboriginal and Torres Strait Islander peoples will complete Cultural Responsiveness Training by the Indigenous Allied Health Australia. 5. Safety Monitoring: Accredited pharmacists are trained to prioritise recommendations for resolution or prevention of any identified medication-related problems. Any critical issues will be verbally communicated to the referring medical practitioner. If necessary, 000 will be called for the patient.6. Data collection methods and Blinding: Patient demographics, comorbidities, Charlson Comorbidity Index, frailty index, medications, length of stay and re-presentations will be obtained from hospital information systems and GPs. Patients will be telephoned at 30, 90 and 180 days after discharge. Death data will be obtained from death registers. Due to the nature of the intervention, it is not possible to blind the hospitals or clinicians. However, the research staff collecting follow-up data and the data analyst will be blinded. |
| Analysis considerations | All analyses will be performed on an intent-to-treat basis. Comparisons between the intervention and usual care groups will be made using t-tests, Mann-Whitney U tests or chi-squared tests, depending on the variable of interest. The primary outcome will be assessed using a logistic regression analysis with stratification by site. Subsequently, potential confounders such as age, comorbidities, number of medicines and socioeconomic status will be considered. A competing risk analysis will be performed (death as the competing risk) should there be a considerable number of deaths within 30 days of hospital discharge. Appropriate regressions will be used to compare the two groups' unplanned bed days and medicine counts. Sensitivity analyses using a per-protocol approach will also be performed. A two-sided p-value ≤ 0.05 will be considered statistically significant.To determine the economic value of TIC TOC intervention, incremental cost-effectiveness ratios (ICERs) will be calculated as (i) the incremental cost per unplanned hospitalisation/ED visit for all unplanned cases, (ii) incremental cost per unplanned hospitalisation/ED visit for medication-related harm cases, and (iii) incremental cost per quality adjusted life years (QALYs). Primary outcomes for each treatment arm are calculated, all costs to implement the intervention and usual care throughout the trial are accounted. Costs might include staff time, training, and any additional resources required to deliver and engage stakeholders. For each patient, we will collect information related to their health service use within each care cycle. The cost-effectiveness analyses will be modelled using techniques appropriate for RCT and the non-normal nature of both the cost and outcome variables (e.g., a generalised linear model with robust standard errors). Following the base case analysis, univariate and probabilistic sensitivity analyses will be conducted around key parameters likely to influence the cost and effectiveness estimates, including variability in the sampling, trial sites, and patient populations by risk factors.Interviews will be conducted until saturation of themes is identified. Interviews will be transcribed and analysed using inductive thematic analysis. Interview questions and analysis will be iterative throughout the study, allowing emerging themes to be examined in later interviews. Concordant processes of memo-ing on codes will enable the clustering of related codes into categories. Two independent researchers will use constant comparative analysis to refine codes and categories.  |
| Study duration | 7 years |

**2. BACKGROUND AND RATIONALE**

After hospital discharge, over 90% of Australians have at least one medication-related problem.1 Transitions of care are a period when the risk of medication errors and adverse events is high. Improving medication safety at these transitions is one of three flagship areas of the World Health Organisation Global Patient Safety Challenge: Medication Without Harm.2,3 In Australia, an estimated 250,000 hospital admissions annually are medication-related, costing $1.4 billion per year.4,5 In particular, rural and remote Australians are up to 2.4 times more likely to have a preventable hospitalisation than non-rural Australians.7 Furthermore, Aboriginal and Torres Strait Islander people, who often live in rural and regional areas, are three times as likely to have a preventable hospitalisation than non-indigenous Australians.7,8 Medication-related hospital readmissions in rural and regional Australian hospitals have been shown to be due to inappropriate/suboptimal pharmacological therapy at discharge in 62% of cases and inadequate communication/monitoring in 41% of cases.17 Due to pharmacists’ expertise in medication management, two systematic reviews have shown that pharmacy-led transitions of care services can successfully reduce hospital readmissions.18,19 These systematic reviews showed that the combination of (i) targeting specific patient populations and (ii) utilisation of an effective transition of care stewardship (TOCS) intervention reduced 30-day readmissions18,19, with the meta-analysis showing a 32% reduction in odds for readmission.19 These TOCS interventions included discharge counselling, discharge medication reconciliation and medication reviews. In Australia, the Commonwealth funds pharmacist-led Home Medicine Reviews (HMRs), which have been shown to reduce medication errors and unplanned hospital readmissions if provided promptly.9-11 When high-risk patients receive a timely post-discharge HMR, the rates of unplanned readmission reduce (45% vs 28%, P<0.05).10 Despite this, strategies (i) and (ii) described above are not routinely implemented and the provision of HMRs to high-risk patients after discharge is unacceptably low at 1-2%.12,13

A recent study by our team (2022) explored the reasons for low uptake of post-discharge HMRs.14 We found many implementation issues14 that are reflected in the Consolidated Framework for Implementation Research (CFIR).20 These include the (i) outer setting (GPs not remunerated for participating in hospital-initiated medication reviews, HMR numbers capped for pharmacists, pharmacists not funded for case conferences), (ii) inner setting (limited staffing for transitions of care), (iii) processes (lack of streamlined pathways, no risk tools used) and (iv) individuals involved (poor prescriber awareness).14 To address these concerns, our team developed the SHPA Hospital-initiated Medication Review protocols to support hospital clinicians to facilitate timely post-discharge medication reviews.21 The SHPA pathway aims to maintain patients’ existing support structures by engaging with their usual GP. However, if the GP is unavailable or an urgent HMR referral cannot be organised via the GP, a referral by a hospital-based medical specialist will be facilitated (with GP notified of the review and provided with a copy of the pharmacist’s report).21 The SHPA protocols address screening/risk stratification, information flow, home visits, follow-ups and the roles and responsibilities of each clinician used as a basis for this study.21

Consumer Health Forum (CHF) research shows that most consumers (72%) also believe pharmacists should play a more significant role in providing primary healthcare services while keeping the GP informed.22 However, many rural and remote hospitals do not have onsite pharmacists to optimise patient care and prevent medication errors.23 Virtual clinical pharmacy services have been demonstrated as a feasible, acceptable and scalable solution to providing clinical pharmacy services in rural and remote hospitals in Western NSW.23 Our team successfully implemented virtual clinical pharmacy services in eight hospitals in NSW to overcome geographical and workforce barriers.23,24 We showed that between April 2020 and June 2021, the virtual service provided 7,021 occasions of pharmacy care for 1,306 patients, including patient counselling and medication reconciliation.23 Focus groups showed doctors, nurses, and allied health professionals endorsed the virtual service and valued having access to specialised medication advice.23 Data collected from this service also identified improved patient safety by identifying medication errors.23 However, the current virtual clinical pharmacy service is not routinely involved in the patient's discharge process back to the community after they have left the hospital.24 We propose that adding a virtual TOCS pharmacy service to routine care can assist rural and regional Australians to transition back safely to the community. Using implementation science framework (CFIR)20 and evidence from systematic reviews,18,19 the following processes will be implemented to ensure timely post-discharge HMRs:

(i) Identifying patients at high-risk of medication-related harm: In a regional and rural setting, the reasons for unplanned medication-related readmissions are complex and require a model that encompasses multiple comorbidities instead of a single disease state.17 Identifying patients at high-risk of medication-related harm is essential to implementing an integrated care intervention on a population basis.25,26 Yet research indicates clinicians are not able to accurately identify such patients.25 Our team developed and validated the PHarmacie-R risk tool (a Web-based app) to assist clinicians in identifying hospital inpatients at high-risk of readmission (C-statistic 0.72, 95% CI 0.68-0.75) in the Australian setting.16 PHarmacie-R is the first readmission risk prediction tool focussing on polypharmacy and high-risk medicines. The tool includes social determinants of health such as age, sex, living arrangements, rural/remote residence, indigenous or required an interpreter, comorbidities, prior ED presentation and the presence of high-risk medicines (e.g., anticoagulants, insulin, opioids, benzodiazepines, antipsychotics) or polypharmacy (≥5 regular medicines). We have shown that the PHarmacie-R risk tool identifies 15% of patients in an Australian hospital as being at high-risk for medication-related harm.27 In addition, our pilot data (n=189) shows that using a TOCS pharmacist with the PHarmacie-R risk tool increased post-discharge medication review referral rates for high-risk patients to 48%, compared to 1% without them.12

(ii) Transitions of Care Stewardship pharmacist: Virtual TOCS pharmacists can ensure patients receive discharge counselling and discharge medical reconciliation, and communicate directly with primary care providers (GPs, practice nurses, community pharmacies and accredited pharmacists) to ensure accurate and timely medication handover and facilitate timely post-discharge medication reviews.11,28-30 They will streamline the HMR process and provide the link for both the outer (primary care) and inner setting (hospital) as described in the CFIR.20 They will also educate clinicians on the importance of a timely post-discharge HMR.

**Our team’s contribution:** We have previously shown the feasibility and effectiveness of hospital-initiated medication review pathways to ensure timely post-discharge HMRs when GPs are unable to do them in a timely manner. Our feasibility study compared the timeliness of post-discharge HMR across three metropolitan hospitals in South Australia and found that a hospital-initiated medication review significantly shortened the time for patients to receive a medication review compared to GP initiated HMRs (6.5 days vs 11.0 days, P=0.02).9 Another RCT of 80 patients by our team showed that the proportion of at-risk patients who received a medication review within 28 days was significantly higher when hospitals initiated HMRs instead of GPs (90% vs 17.5%, P<0.01).31 The hospital-initiated pathway is essential if we aim to reduce 30-day readmission rates.

Our team has worked with the SHPA to develop protocols incorporating revised HMR program rules, to assist with implementing hospital-initiated post-discharge medication reviews to improve medication safety during transitions of care.21 Furthermore, our team developed the PHarmacie-R risk tool (a Web-based app).16,21 To reach Australians in regional and rural areas, members of our team have also successfully implemented and evaluated virtual clinical pharmacy services in eight hospitals in NSW to reduce medication errors and improve medication safety.23

Our team has an extensive track record of generating new evidence in medication safety, virtual clinical services, transitions of care, and providing timely post-discharge medication reviews. We are uniquely positioned to implement the TIC TOC study and test the effectiveness of a new virtual transition of care service to reduce unplanned hospital admissions in high-risk patients discharged from regional and rural Australian hospitals.

**3. STUDY AIMS/OBJECTIVES**

**Research question:** Does the TIC TOC intervention reduce the incidence of medication-related harm, including hospital readmissions and ED presentations?

**Primary objective**: To determine the effect of the TIC TOC intervention on medication-related hospital admission or ED presentation within 30 days of discharge.

**Secondary objectives**:

* To determine the effect of the TIC TOC intervention on unplanned all-cause readmission and ED presentations and unplanned medication-related readmission and ED presentations within 30, 90 and 180 days compared with best usual care.
* To determine whether the TIC TOC intervention increases the proportion of high-risk patients receiving a timely post-discharge medication review (within ten days from discharge)
* To assess the number, nature, and severity of medication-related problems identified in initial post-discharge medication review reports and in HMR follow-up(s) where applicable.
* To determine the cost-effectiveness of the TIC TOC intervention.

This research has three aims: (1) Determine the effectiveness of the TIC TOC intervention, (2) assess its cost-effectiveness, and (3) explore factors affecting its implementation.

**4. PARTICIPATING SITES**

In total, 19 regional and rural hospitals will be included in this study from Western NSW Local Health Districts.

**Table 2. Participating sites**

|  |  |
| --- | --- |
| **Hospital Name** | **State** |
| Baradine | NSW |
| Coolah | NSW |
| Coonamble | NSW |
| Dunedoo | NSW |
| Forbes | NSW |
| Gilgandra | NSW |
| Gulgong | NSW |
| Narromine | NSW |
| Wellington | NSW |
| Nyngan | NSW |
| Walgett | NSW |
| Warren | NSW |
| Blayney | NSW |
| Canowindra | NSW |
| Cowra | NSW |
| Grenfell | NSW |
| Mudgee | NSW |
| Oberon | NSW |
| Parkes | NSW |

**5. STUDY DESIGN**

**Aim 1: To determine the effectiveness of the TIC TOC intervention in regional and rural hospitals on hospital readmissions and ED presentations**

Study Design and Setting: The TIC TOC study is a prospective, randomised controlled clinical trial involving patients at high-risk of medication-related harm who are discharged from regional and rural hospitals to a domiciliary residence. This study will be conducted in rural and regional hospitals in Western NSW Local Health District. The patient recruitment will occur over 18 months with follow-up of all patients up to six months post-discharge. It will be registered on the Australian New Zealand Clinical Trials Registry and approved by relevant hospital ethics committees.

In total, 19 regional and rural hospitals will be included in this study from Western NSW Local Health Districts. Western NSW Local Health District is home to an estimated 309,700 people and is geographically dispersed over 433,379 square metres.32 It has 15% more preventable hospitalisations than the rest of NSW and contains significant vulnerable populations including 13% Aboriginal residents, 31% older residents (aged 55 years and over), socially disadvantaged residents (80% of the area occupies the five lowest 1-5 deciles for the index of relative socioeconomic disadvantage), and remote communities (44% are classified as remote or very remote).32 Hospitals included in this project are based in Baradine, Coolah, Coonamble, Dunedoo, Forbes, Gilgandra, Gulgong, Narromine, Wellington, Nyngan, Walgett, Warren, Blayney, Canowindra, Cowra, Grenfell, Mudgee, Oberon and Parkes, which have over 10,000 medical separations a year.

Consumer Engagement: The project team will harness consumer engagement mechanisms already existing in Western NSW Local Health District, allowing consumer collaboration for any required material, such as consent forms or patient surveys. In addition to the district-wide engagement process, the region has numerous program-specific committees with formalised consumer representation mechanisms, which can be canvased for consultation. For instance, integrated care programs for chronic disease and mental health services. We will also be establishing the Aboriginal Reference Group for our study to ensure that our research is community-driven, culturally sensitive, and aligned with the specific needs of the Aboriginal community. We have also prepared a comprehensive invitation letter that outlines the specific details and objectives of the study.

To ensure that the needs of Aboriginal and Torres Strait Islander patients are appropriately addressed, we have implemented several measures. Firstly, we have developed an Aboriginal Health Impact statement in collaboration with the Western NSW Local Health District. Furthermore, we will submit ethics through Aboriginal Health and Medical Research Council (AH&MRC). By seeking ethics approval through AH&MRC, we ensure that our research aligns with the highest ethical standards and addresses any potential risks or concerns for the Aboriginal community. In addition, we are in the process of setting up an Aboriginal reference group. This group will comprise members from the local Aboriginal community who will actively participate in shaping and informing our research. Their valuable perspectives, cultural insights, and lived experiences will guide us in conducting research that is relevant, respectful, and beneficial to Aboriginal and Torres Strait Islander patients. Our team consists of experienced researchers who have conducted trials in Aboriginal and Torres Strait Islander patients and includes CIO, who is an Aboriginal (Wiradjuri) pharmacist researcher. Furthermore, AH&MRC is our project partner to provide additional advice and support. A support letter from AH&MRC serves as a testament to the rigor and integrity of our research design, methodology, and commitment to community engagement.

Patient inclusion and exclusion criteria: Eligible patients must be aged ≥18 years, admitted under a medical specialty, discharged to a domiciliary setting, have a GP, have a Medicare card and be at risk of readmission (defined as high-risk according to the PHarmacie-R risk algorithm).

Exclusion criteria include unmanaged substance use disorder or mental health condition, active palliative care, homelessness, admission for planned dialysis, unsafe home environment (domestic violence or aggression), planning to change residence in six months or previously recruited.

Screening, recruitment and consent: Research assistants who are qualified researchers employed by the research team will identify potentially eligible patients using routinely collected data. Those meeting the inclusion criteria (see below) will be invited to participate in the study and sent an information statement and consent form. To determine if a readmission was medication-related, which is the primary outcome of the study, we will conduct a thorough review of each case with a panel of experts and assign appropriate codes. This meticulous process will be applied to all readmissions to ensure accurate identification of medication-related factors. Consent forms will include provision of access My Health Record and state-based government owned linked data. Eligible participants will be included after written informed consent is obtained. The participant will receive a study enrolment number, and this will be recorded on all study documents pertaining to that participant. (Figure 1).

Randomisation: Participants will be randomised in a 1:1 ratio in permuted blocks of 2 and 4 to: (1) intervention; or (2) usual care. Randomisation will be conducted using a centralised service to ensure allocation concealment.

Description of Control Arm: Usual care will include informing the patient's clinical inpatient team that they are at high-risk of medication misadventure, and they may benefit from a HMR. Usual pathways to communicate the need for a HMR to the patient's regular GP will be used.

Description of Intervention Arm: The intervention is based on the Consolidated Framework of Implementation Research as it has been used extensively to implement health services (Figure 2).20 The intervention will include virtual TOCS pharmacists to ensure patients receive discharge counselling, discharge medical reconciliation, and communicate directly with primary care providers (GPs, practice nurses, community pharmacies and accredited pharmacists). They will provide accurate and timely medication handover to facilitate a timely post-discharge medication review. Patients’ autonomy is central to the intervention, as they can choose whether they prefer a face-to-face HMR or a virtual HMR. Patients will also receive lay summaries of the HMR reports to empower them to take responsibility of their medication management. Furthermore, GPs, accredited and community pharmacists’ collaboration will be encouraged through case conferences to discuss complex patients (remunerated for their time). The intervention will also be adapted to local needs.20 Pharmacists caring for Aboriginal and Torres Strait Islander peoples will complete Cultural Responsiveness Training by the Indigenous Allied Health Australia.33 Furthermore, aim 3 will explore implementation aspects of the study.

|  |  |
| --- | --- |
| Diagram  Description automatically generated**Figure 1.** Flowchart of TIC TOC clinical trial |  |



HIMR: Hospital-initiated medicines review, GPs: General Practitioners, TOCS: Transition of Care Stewardship, HMR: Home Review Medicine, SHPA: The Society of Hospital Pharmacists of Australia.

**Figure 2:** Intervention components based on Consolidated Framework for Implementation Research.

Safety Monitoring: Accredited pharmacists are trained to prioritise recommendations for resolution or prevention of any identified medication-related problems. Any critical issues will be verbally communicated to the referring medical practitioner.34 If necessary, 000 will be called for the patient.

Outcome measures: Our primary outcome is the composite of a first unplanned medication-related hospitalisation or ED presentation within 30 days of hospital discharge. Other outcomes are described in Table 3.

**Table 3.** Measures and data collected at set timepoints

|  |  |  |
| --- | --- | --- |
| **Outcome Measure** | **Data source** | **Post-discharge (days)** |
| **0** | **30** | **90** | **180** |
| Medication-related readmission/ED presentation | Linked data/expert panel |  | ✓ | ✓ | ✓ |
| All-cause readmission or ED presentation | Linked data |  | ✓ | ✓ | ✓ |
| Total length of unplanned hospitalisation | Patient record |  | ✓ | ✓ | ✓ |
| Patient's quality of life  | EQ5D-5L35 | ✓ | ✓ | ✓ | ✓ |
| Patient experience of TOCS service (intervention) | Patient survey |  | ✓ |  |  |
| **Process measures** |  |  |  |  |
| Patients recruited and PHarmacie-R score | Patient record | ✓ |  |  |  |
| Medication reconciliation provided on discharge | Patient record | ✓ |  |  |  |
| Discharge summary provided on discharge | Patient record | ✓ |  |  |  |
| Discharge medication list provided to patient  | Patient record | ✓ |  |  |  |
| Time to post-discharge medication review | Accredited pharmacist |  | ✓ |  |  |
| Received follow up for HMR | Accredited pharmacist |  | ✓ | ✓ | ✓ |
| Number, type and severity of medication-related problems resolved by TOCS pharmacist37 | Indicators36 and expert panel | ✓ | ✓ |  |  |
| Number, type and severity of medication-related problems resolved during HMR37 | Indicators36 and expert panel |  | ✓ |  |  |
| Consumers’ self-efficacy for medication use | SEAMS Survey37 |  | ✓ |  |  |
| Number of medicines | Patient/My health record community Px | ✓ | ✓ | ✓ | ✓ |
| Appropriate medicines indicators | Patient/My health record community Px | ✓ | ✓ | ✓ | ✓ |

Data collection methods: Patient demographics, comorbidities, Charlson Comorbidity Index, frailty index, medications, length of stay and re-presentations will be obtained from hospital information systems and GPs. Patients will be telephoned at 30, 90 and 180 days after discharge. Death data will be obtained from death registers.

Blinding: Due to the nature of the intervention, it is not possible to blind the hospitals or clinicians. However, the research staff collecting follow-up data and the data analyst will be blinded.

Sample size: Based on an effect size of 10% absolute reduction (40% to 30%)10,12 in 30-day readmission or ED presentation, an alpha of 0.05 and power of 0.8, a 356 patients per group (712 total) is required. Accounting for an attrition rate of 15%,12 the sample size will be increased to 838 patients. In addition, to allow for the clustering design, using a variance inflation factor of 1.1 (i.e., intra class correlation 0.002 between sites), the total sample size required will be 922.

Statistical analysis: All analyses will be performed on an intent-to-treat basis. Standard summary statistics will be reported for all variables. Comparisons between the intervention and usual care groups will be made using t-tests, Mann-Whitney tests or chi-squared tests, depending on the variable of interest. The primary outcome (composite of a first unplanned medication-related hospitalisation or ED presentation within 30 days of hospital discharge) will be assessed using a logistic regression analysis with stratification by site. Subsequently, potential confounders such as age, comorbidities, number of medicines and socioeconomic status will be considered. A competing risk analysis will be performed (death as the competing risk) should there be a considerable number of deaths within 30 days of hospital discharge Sub-group analyses will also be carried out between sites and with Aboriginal and Torres Strait Islander patients. Secondary outcomes will be analysed similarly to the primary outcome. Appropriate regressions will be used to compare the two groups' unplanned bed days and medicine counts. Sensitivity analyses using a per-protocol approach will also be performed. A two-sided p-value ≤ 0.05 will be considered statistically significant.

**Aim 2: To determine the cost-effectiveness of the TIC TOC intervention compared to the usual care scenario**

A within-trial cost-effectiveness analysis of the TIC TOC intervention on 30-day hospital readmissions and ED presentations in regional and rural hospitals will be undertaken from the health system perspective. The comparator will be the current model of care, and the primary outcomes of the economic analyses include unplanned readmissions and ED visits and medication-related problems identified during the post-discharge 'cycle of care'). Incremental cost-effectiveness ratios (ICERs) will be calculated as the incremental cost per unplanned hospitalisation/ED visit (for all unplanned cases and medication-related harm cases).

The analysis will consist of three main parts. First, primary outcomes for each treatment arm are calculated (TIC TOC intervention versus best usual care). Second, all costs to implement the intervention and usual care throughout the trial are accounted. Costs might include staff time, training, and any additional resources required to deliver and engage stakeholders. For each patient, we will collect information related to their health service use within each care cycle. These data be either captured by the hospitals' electronic record systems or follow-up enquiries (see description below). Costs will be valued based on government charges using publicly available data and reported in Australian dollars. Third, the cost-effectiveness analysis will be modelled using techniques appropriate for RCT and the non-normal nature of both the cost and outcome variables (e.g., a generalised linear model with robust standard errors).

Following the base case analysis, univariate and probabilistic sensitivity analyses will be conducted around key parameters likely to influence the cost and effectiveness estimates, including variability in the sampling, trial sites, and patient populations by risk factors.35

We will conduct a supplementary economic analysis using an alternative outcome - health related quality of life measured by the EQ5D-5L, to compare the cost effectiveness of TIC TOC intervention to best usual care from quality-of-life perspective. We will convert the EQ5D-5L scores into utility, which will be used as the input for the cost-utility analysis. This analysis follows the same procedure and uses similar econometrics techniques as the (primary) cost-effectiveness analysis described above. Its outcome will offer additional evidence regarding the cost-effectiveness nature of the intervention.

**Aim 3: To explore factors affecting the implementation of the TIC TOC intervention by patients and clinicians.**

For this proposal we will also conduct interviews before and after the implementation using qualitative one-on-one semi-structured interviews with patients and clinicians (e.g doctors, nurses and pharmacists) to determine their beliefs, attitudes and perceived acceptability, facilitators and barriers to the implementation of the intervention. Interviews will be conducted by investigators who possess training in qualitative research methods using telephone or videoconferencing.

Interviews will be conducted until saturation of themes is identified. Based on previous studies, this will occur after approximately 60 interviews (30 patients and 30 clinicians) but may occur sooner.38 The interview guide will be based on the consolidated framework for implementation research.20 Interviews will be transcribed and analysed using inductive thematic analysis. Interview questions and analysis will be iterative throughout the study, allowing emerging themes to be examined in later interviews. Data analyses will follow the methodology proposed by Bernard and Ryan.39 Concordant processes of memo-ing on codes will enable the clustering of related codes into categories. Two independent researchers will use constant comparative analysis to refine codes and categories.39 Any disagreements will be discussed with a third researcher to reach consensus.

**6. MILESTONES AND PERFORMANCE INDICATORS**

**Milestones and Performance Indicators**

**Table 4.** Gantt Chart, project milestones and performance indicators.

|  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- |
| **Task** | **2023** | **2024** | **2025** | **2026** | **2027** |
| Q3 | Q4 | Q1 | Q2 | Q3 | Q4 | Q1 | Q2 | Q3 | Q4 | Q1 | Q2 | Q3 | Q4 | Q1 | Q2 |
| Steering group |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
| Local team |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
| Project advisory group |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
| Staff recruitment |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
| Database setup  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
| Obtain ethics  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
| **Aim 1** |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
| Train pharmacists |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
| Recruit patients |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
| Collect data |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
| Study close-out |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
| Data analysis  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
| **Aim 2:** |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
| Economic evaluation |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
| **Aim 3:**  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
| Interviews |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
| Thematic analysis |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
| Report writing |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |

HREC, Human Research Ethics Committee.

**Table 5.** Detailed milestones and performance indicators

|  |  |  |
| --- | --- | --- |
| **Milestones** | **Performance indicators** | **Timing (Months)** |
| Local implementation team | -Attendance and minutes | Weekly as needed |
| Steering group meeting | -Attendance and minutes | Monthly |
| Project advisory group meeting | -Attendance and minutes | 6-monthly |
| Ethics approval | -Ethics for all aims and sites obtained | 12 |
| Report writing | -Reports written | 48 |
| ***Aim 1*** |   |  |
| Recruitment of staff | -Research staff recruited and trained | 3 |
| Training of pharmacist | -Pharmacists trained | 12 |
| Recruit participants and implement intervention | -Participants recruited/randomised | 12 then monthly |
| -Intervention implemented |
| Data analysis | -All data analysis completed | 40 |
| ***Aim 2*** |   |  |
| Economic evaluation | -Economic evaluation completed | 45 |
| ***Aim 3*** |   |  |
| Recruitment of participants and conduct qualitative interviews | -Participants recruited | 30 then monthly |
| -Interviews and transcription |
| Thematic analysis | -All data analysis | 40 |

With these established collaborations, outstanding content expertise, strong track history of grant funding and outputs relative to opportunity, and successful translation of evidence into practice, the CI team is uniquely qualified to drive the TIC TOC study to a successful outcome.

**7. RISK MANAGEMENT PLAN**

|  |  |  |
| --- | --- | --- |
| **Risk theme** | **Risk** | **How risk is managed/mitigated** |
| People (Recruitment) | Recruitment of Project Research Personnel is delayed, which may delay project. | The project will be managed by CI Penm and the rest of the team until the positions are recruited. The Research assistants also have staggered starting times to coincide with major phases of the study. It is unlikely that there would be delays in recruitment for all, and employment at full-time allows us to tweak employee hours if required.Likelihood: Possible; Consequence: Minor; Acceptability: Acceptable. |
| Delivery (Budget) | Project requires more resources or breaches timepoints, which may cause the budget to be exceeded.  | Project plan will be approved and strictly monitored by the project team to ensure adherence to budget. Some leeway in time to recruit patients at each of the sites has been added. We have based recruitment over an 18-month period and if targets per week are met this will take less than the allocated time, however if consumer recruitment is more difficult the time buffer should allow us to still stay on our time targets.Likelihood: Unlikely; Consequence: Moderate; Acceptability: Acceptable. |
| Regulatory (Ethics)  | Ethics approval delay, which may delay recruitment and lead to further costs if timeline is extended.  | There are many research experts within the project team that have experience with applying for ethical approval and having representatives from each of the regional hubs as CIs on this grant will facilitate the Site-Specific Approval process. Ample time has been allocated to put together applications. Requests for more information by HRECs will be addressed immediately to ensure timely review. Delays of 1 month or more than planned in the timeline will be reported by ad-hoc reporting.Likelihood: Possible; Consequence: Moderate; Acceptability: Acceptable.  |
| Delivery (Resources) | The Educational tools to assist key providers could be delayed. | The educational packages for Virtual TOCS pharmacists, HMR pharmacists and GPs will be based of existing materials used in previous trials led by several CIs listed. The adaption of these tools has been adequately budgeted for in the first year of the project. In addition, team-based expertise will allow for timely development of resources.Likelihood: Unlikely; Consequence: Minor; Acceptability: Acceptable.  |
| People (People capability) | Difficulty in Identifying and training several accredited pharmacists, which may delay project planning and implementation. | Several strategies to improve recruitment are woven into this project. Accredited pharmacists can be identified via the PSA/SHPA public websites and recruitment of those conveniently located near hospital sites will be targeted. Further, accredited pharmacists from different cultural backgrounds will be targeted. 3. Accredited pharmacists will be reimbursed for their services via the project grant money, rather than via the Pharmacy Program Administrator subsidies. This will allow accredited pharmacists to provide this service without affecting the existing cap on numbers of HMRs that can be reimbursed for each pharmacist per month. 4. This project allows patient flexibility to have a HMR service via telehealth. Likelihood: Likely; Consequence: Moderate; Acceptability: Acceptable.  |
| Delivery (recruitment) | Difficulty in recruitment of consumers that agree to be part of the trial. | We have assessed the current numbers of consumers discharged at the hospitals each week and made conservative estimates of consenting rates of 50%. Conservative sample size estimates are based on 80% power to predict a 10% reduction in 30-day readmission. Generous timelines have been installed to mitigate the risk of delays in recruitment. Additional hospital sites could be utilised if needed. Adjustments to sample size would be a last resort. Likelihood: Likely; Consequence: Moderate; Acceptability: Acceptable. |
| Delivery (recruitment) | Difficulty in follow-up of patients. | A full-time research assistant will be employed to follow up this vital patient data. Home and mobile numbers as well as email addresses of consumers/carers will be obtained at time of consent.Likelihood: Unlikely; Consequence: Moderate; Acceptability: Acceptable. |

**8. ETHICAL CONSIDERATIONS**

Study procedure benefits: The study may benefit participants randomised to the intervention arm of the trial by improving their medication safety with respect to reduction in the incidence of medication-related harm, including hospital readmissions and Emergency Department presentations and may improve future treatment for people.

On a broader scale, the project will fill a research gap on effective strategies to reduce medication-related harm including hospital readmissions.

Study procedure risks: One of the expected outcomes of this study is to determine the effectiveness of an intervention designed to improve medication safety and thereby reduce the risks to participants. The intervention optimises and promotes the Transition of Care Stewardship and Home Medicines Reviews (HMR) service/s which is a currently available but not necessarily optimised or utilised effectively in this setting.

Similar to standard practice, participants randomised to the intervention group may have changes made to their medications in consultation with their healthcare providers. The HMR pharmacist will likely make recommendations to reduce the dose and/or cessation of medicines, alongside other changes in medications designed to improve medication safety.

Recommendations are implemented (or not) in consultation with whole team including the medical specialist, GP, pharmacists, and participants. The decisions to prescribe or deprescribe is ultimately at the discretion of the participant’s GP and is implemented in consultation with the participant.

The qualitative interviews carry minimal risk as they are an evaluation of patient’s and clinicians’ thoughts and experience on the pharmacist-led Transition of Care Stewardship service. In the event, that the participant experiences any distress during the interview, they will be advised to contact the following support services for assistance.

Other Ethical Considerations:

* Voluntary participation: Participant involvement is voluntary and informed written consent is required.
* Ethical care: We contest the proposed intervention is ethical as it offers care above that of ‘usual care’.
* Ethical care: We contest the random allocation to ‘usual care’ is ethical as Transition of Care Service is not routinely provided.
* Harm minimization: We contest we have endeavoured to minimise harm by including the attending clinicians.
* Privacy and confidentiality: We will protect participant privacy and confidentiality by maintaining and storing study records in a secure database (Redcap TM, cloud-based storage) and paper-based records will be kept in locked research filing cabinets.
* Data integrity: We will adopt best practice for managing data including audit of data entry at regular intervals. All investigators will be required to have current certification of ‘Good Clinical Practice, GCP’ training prior to commencement.
* Scientific robustness: The research design is rigorous which is also an ethical consideration as it represents value for money in the context of limited research dollars.

 **9. DATA LINKAGE**

Australian Institute of Health and Welfare (AIHW) for the nation-wide databases and NSW Centre for Health Record Linkage (CHeReL) for the state databases will be accessed. Separate Ethics applications will be submitted to the nation-wide and state-based data custodians. These data will be collected to validate medication history printouts and participant self-report of medication-related and all cause readmission or ED presentation.

**10. DATA STORAGE AND RECORD RETENTION**

Re-identifiable data will be stored in a password-protected cloud-based software, OneDrive. No data will be stored on personal computers. Data will be stored for 15 years according to the University of Sydney’s Research Code of Conduct 2019. After this period has elapsed, the research data will be destroyed permanently. Random checks of 10% of data will be conducted for quality assurance.

# 11. SAFETY REPORTING

Not applicable, as this study is a RCT regarding an already approved service and not a drug or device.

**12. DATA SAFETY AND MONITORING BOARD**

This study does not involve drugs or devices; therefore, establishment of a Data Safety and Monitoring Board is not applicable.

# 13. Early Termination (IF APPLICABLE)

It would be very unlikely that there would be an early termination of the study. No foreseeable adverse circumstance would make this applicable. In the event this study needs to be ceased prematurely for any reason, participants and HREC will be informed by study researchers, and a final study report will be compiled and submitted to HREC.

# 14. BLINDING AND UNBLINDING

Due to the nature of the intervention, it is not possible to blind participants or health care professionals to treatment group. However, we will assessor-blind data analysis of outcomes occurs.

**15. CONFLICT OF INTEREST**

There are no actual or perceive conflicts of interest of any of the investigators.

**16. FUNDING**

Commonwealth Government of Australia - 2022 MRFF Clinician Researchers - Nurses Midwives and Allied Health - MRFMMIP000023

**17. RESEARCH OUTCOMES**

A series of manuscripts will result from this trial and will be submitted to a variety of targeted peer reviewed journals. Dissemination of results may also be presented at scientific conferences, and meetings with key stakeholders. At this stage, no plans for sharing of future data, follow-up research or secondary use of data are anticipated.

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**APPENDIX**

1. **Attachment 1** Participant Information Statement
2. A**ttachment 2** Participant Consent Form
3. **Attachment 3** Participant Information Statement Qualitative Interviews (Participants)
4. **Attachment 4** Participant Consent Form Qualitative Interviews (Participants)
5. **Attachment 5** Participant Information Statement Qualitative Interviews (Clinicians)
6. **Attachment 6** Participant Consent Form Qualitative Interviews (Clinicians)
7. **Attachment 7** Data Collection Form – Enrolment Log
8. **Attachment 8** Data Collection Form – Screening Log
9. **Attachment 9** Data Collection Form – Patient Demographic and Baseline Data
10. **Attachment 10** Data Collection Form – Post Discharge Data Collection 30 days
11. **Attachment 11** Data Collection Form – Post Discharge Data Collection 90 and 180 days
12. **Attachment 12** Interview Guides Qualitative Interviews Participants
13. **Attachment 13** Interview Guides Qualitative Interviews Clinicians
14. **Attachment 14** Aboriginal Reference Group Invitation
15. **Attachment 15** Aboriginal Health Impact Statement
16. **Attachment 16** AH&MRC Letter of Support
17. **Attachment 17** Safety Protocol for participants