Preventing Adverse Drug Reactions After Hospital Discharge (PADR-AD): protocol for a randomised-controlled trial in older people

ABSTRACT

Background

Adverse drug reactions (ADRs) and adverse drug events (ADEs) in older people contribute to a significant proportion of hospital admissions and are common following discharge. Effective interventions are therefore required to combat the growing burden of preventable ADRs. The Prediction of Hospitalisation due to Adverse Drug Reactions in Elderly Community Dwelling Patients (PADR-EC) score is a validated risk score developed to assess the risk of ADRs in people aged 65 years and older and has the potential to be utilised as part of an intervention to reduce ADRs.

Objectives

This trial was designed to investigate the effectiveness of an intervention to reduce ADR incidence in older people and to obtain further information about ADRs and ADEs in the 12-24 months following hospital discharge.

Methods

The study is an open-label randomised-controlled trial to be conducted at the Royal Hobart Hospital, a 500-bed public hospital in Tasmania, Australia. Community-dwelling patients aged 65 years and older with an unplanned overnight admission to a general medical ward will be recruited. Following admission, the PADR-EC ADR score will be calculated by a research pharmacist, with the risk communicated to clinicians and discussed with participants. Following discharge, nominated general practitioners and community pharmacists will receive the risk score and related medication management advice to guide their ongoing care of the patient. Follow-up with participants will occur at 3 and 12 and 18 and 24 months to identify ADRs and ADEs. The primary outcome is moderate-severe ADRs at 12 months post-discharge, and will be analysed using the cumulative incidence proportion, survival analysis and Poisson regression.

Abbreviations
PADR-EC Prediction of Hospitalisation due to Adverse Drug Reactions in Elderly Community-Dwelling Patients
PADR-AD Preventing Adverse Drug Reactions After Discharge

Summary

It is hypothesised that the trial will reduce ADRs and ADEs in the intervention population. The study will also provide valuable data on post-discharge ADRs and ADEs up to 24 months post-discharge.

Abbreviations
PADR-EC Prediction of Hospitalisation due to Adverse Drug Reactions in Elderly Community-Dwelling Patients
PADR-AD Preventing Adverse Drug Reactions After Discharge

Key Words

Adverse drug reactions, adverse drug events, older people, hospital discharge, transitional care

INTRODUCTION

The World Health Organisation's third Global Patient Safety Challenge was introduced in 2017 with a goal to reduce severe avoidable harm related to medications by 50% within 5 years.[1] Adverse drug reactions (ADRs) are an important driver of the overall burden of medication-related harm, accounting for over 70% of adverse drug events (ADEs).[2] ADRs are defined *as "a response to a medicinal product which is noxious and unintended and which occurs at doses normally used in man for the prophylaxis, diagnosis or therapy of disease or for the restoration, correction or modification of physiological function"*.[3] The definition of ADEs is a broader term to describe an injury due to a medication.[4]

In older people (aged 65 years and older), ADRs are associated with one in ten hospital admissions, complicate 11.5% of hospital admissions and occur in one third of patients twelve months following hospital discharge.[5-7] A recent systematic review found 20% of adult and elderly patients continue to be impacted by ADEs after hospital discharge.[8] Fifteen percent of unplanned hospital admissions in older people were found to be ADR-related at a major public hospital in Tasmania, Australia.[9] Of those people, 1 in 8 returned in the following year with a repeat ADR.[10] The Australian Medical Research Future Fund recently called for research in this area.[11]

Transitions of care, such as hospital to home or hospital to aged care facility, are recognised as high-risk periods for medication-related harm.[12] Communication during transition of care between hospital and primary care is often compromised by delays and content omissions.[13]

There have been inconsistent benefits from interventions to reduce the incidence of medication-related harm after hospital discharge.[14-17] Results from some previous interventions have demonstrated benefit, with a trial by Bonnett-Zamponi et al. utilising drug review and education coupled with enhanced communication leading to fewer readmissions due to ADRs, although

underpowered.[14] Gillespie et al. showed that a comprehensive pharmacist-led intervention had positive effects on drug-related readmissions after hospital discharge.[15] A trial using general practice pharmacists showed a reduction in the incidence of hospital readmissions and emergency department presentations.[18] Not all interventions have shown benefit, with one intervention using pharmacist home visits increasing hospital admissions, with an increase in complexity of care a possible reason.[16] Physician-led counselling on discharge did not impact hospital readmissions, however there were significantly more ADR-related readmissions and ADR-related emergency presentations, perhaps due to increased awareness of ADRs.[17]

Effective interventions to reduce the impact of ADRs post-discharge by addressing those most likely to benefit while not increasing complexity of care are needed, noting the significant costs associated with healthcare delivery.[19] Studies targeting high-risk medication or disease states have been successful in delaying time to next hospitalisation for warfarin and heart failure patients and reducing warfarin-related complications.[20-22] Future research in reducing medication harm during transitions of care should include a focus on preventive interventions[23] and target high-risk populations to maximise the impact of limited health resources.[24]

The Prediction of Hospitalisation due to Adverse Drug Reactions in Elderly Community Dwelling Patients, (PADR-EC score) was developed and externally validated in elderly patients admitted to general medical wards in two public hospitals in Tasmania, Australia.[9] In the derivation cohort, 15% of admissions were associated with an ADR; independent predictors of an ADR were the number of antihypertensives, dementia, renal failure, recent medication changes and use of potentially inappropriate anticholinergic medications. These variables were used to develop the PADR-EC score, which was validated in a second cohort at a different hospital. A PADR-EC score of 6 indicates higher risk of ADR-related hospitalisation, with 72% sensitivity and 58% specificity. The risk of patients having an ADR-related hospitalisation was more than three times higher in those who scored $\geq$6

compared to those who scored <6. The authors proposed that the score could be used to guide interventions to prevent ADRs and ADR-related hospitalisation.

It is hypothesised that identification and communication of the ADR risk by a pharmacist while patients are hospitalised, using the PADR-EC score as a framework with associated clinical advice to the medical team, general practitioner (GP) and patient, will reduce the incidence of ADRs occurring during admission and in the 12 months post-discharge. It is further hypothesised that that those with a higher PADR-EC score will gain the most benefit from the intervention. The aim of this study is to investigate the effectiveness of an intervention to prevent ADRs following hospital discharge and provide further valuable data on the incidence and characteristics of ADRs and ADEs following hospital discharge.

METHODS AND ANALYSIS

Study design

The PADR-AD (Preventing Adverse Drug Reactions After Hospital Discharge) trial is an open-label single-centred randomised controlled trial at the Royal Hobart Hospital (RHH) in Tasmania (Australia) with up to a 24-month follow-up period. The intervention is designed to complement usual care, providing an ADR risk assessment and interpretation to reduce ADRs in the 12 months following hospital discharge. Participants will also be followed for ADEs in the community to obtain valuable data on injuries arising from compliance issues or medication errors to 24 months post-discharge.

The trial is designed to evaluate the effectiveness of a pharmacist intervention, using the PADR-EC score as a framework, to reduce the incidence of ADRs in the 12 months following hospital discharge compared to usual care. The intervention involves communication of the PADR-EC risk to the clinical team and participant during the admission and to guide the provision of targeted advice from a clinical pharmacist to GPs and community pharmacists in the immediate post-discharge period to reduce ADRs. The PADR-EC score provides a global estimate of the risk of ADR-related hospitalisation

and a frame for the intervention; however, it is not intended to provide the sole basis for the advice provided by the pharmacist.

Setting

The trial will be conducted at the RHH, a 500-bed teaching hospital in Tasmania. The RHH is the only public hospital in Southern Tasmania, servicing approximately 250,000 people. It is likely that participants enrolled in the trial at this hospital will return to the same hospital if a readmission occurs.

Inclusion criteria

Patients aged 65 years and older with an unplanned overnight admission to a general medical ward who will be discharging to the care of their GP will be included in the trial.

Exclusion criteria

Patients will be excluded if they are unavailable for follow-up, already enrolled in another post-discharge intervention or discharging to an aged care facility or a palliative care unit. Patients unwilling or unable to consent to the study and without a consenting authority present at the hospital, and those unable to be interviewed due to health reasons or whose medical notes are not available in hospital will also be excluded.

Procedure and processes

A clinical pharmacist researcher will screen the bed-list for medical admissions from Monday-Friday each week, removing those under the age cut off, already enrolled in the trial, already approached, or usually residing in an aged care facility. Potentially eligible patients will be invited to participate, with a discussion about the research. They will be left with an information sheet and consent form and approached again in 24h or at a time of their request after reflecting on their desire to be involved.

Once enrolled, the process outlined in Figure 1 will be followed. Enrolment will be considered the index admission to hospital during the recruitment period. Clinical pharmacist researchers will be involved in the data collection and intervention at the hospital. Participant information will be collected by interview with a pharmacist researcher and combined with medical records at the hospital to calculate the PADR-EC score to create a management plan. A paper-based system will be used initially, with information added to a database. Participant recruitment will take place throughout 2020 and 2021, with follow-up finalising in 2023. Data collection will be monitored and periodically audited by a second pharmacist researcher.

The data will include demographics, past medical history, current diagnosis, medication list, relevant pathology results, documented allergies and any other pertinent information. Follow-up data will include patient reported events, GP reports, community pharmacy records and hospital records.

Randomisation

The participants will be randomised on a 1:1 basis to controls and interventions using an online randomisation system provided by the Griffith Randomisation Service.[25] After randomisation, patients identified as not meeting the full eligibility criteria through not discharging to the care of their GP will be excluded.

Blinding

The trial is an open-label study with the participants and researchers not blinded to the assigned groups. This is necessary due to the nature of the intervention (pharmacist service). ADR assessment after hospital discharge will be confirmed by a blinded panel.

Intervention

In addition to usual care, a medication management plan for each participant will be developed by a clinical pharmacist researcher utilising the PADR-EC score along with identification of other high-risk medication unique to the participants. Patients will be counselled on their calculated risk, with educational advice given specific to their medication and situation. The participant's PADR-EC ADR

score will be added to the hospital notes (Appendix A) to inform the clinical team regarding the identified risk factors and any immediate recommendations. A medication management plan will be provided to the participant's GP on discharge to interpret the score to help guide further changes, monitoring or services that the GP may wish to employ. High-risk situations related to medication not highlighted in the PADR-EC score, or unique to a participant will also be highlighted based on the clinical pharmacist's judgement. The discharge PADR-EC score and medication management plan will be promptly faxed to the GP when the hospital discharge summary and plan is ready. A copy of the PADR-EC score and plan will also be faxed to the participant's nominated pharmacy to ensure that they are aware of the recommendations made to reduce the risk of medication-related events, and potentially address these in their ongoing care of the patient.

Control group

Control participants will be managed through usual clinician care. Control participants' GPs will be notified that their participant is in the trial soon after discharge. Control participants' clinical information will be collected, and they will have their PADR-EC score calculated for comparison.

Primary outcome

The primary outcome is the incidence of moderate to severe ADRs (defined as those requiring hospital treatment, change in therapy or specific treatment) at 12 months post-discharge. This outcome includes ADRs experienced during the admission (after the intervention), and post-discharge.

Secondary outcomes

Secondary outcomes include the incidence of ADR-related hospitalisation after hospital discharge to 12 months, the incidence of in-hospital ADRs during the index admission, the incidence of ADEs occurring in the community to 24 months following discharge, and the number of emergency department presentations and hospital admissions during the follow-up period.

Outcome identification

ADRs will be identified through hospital records related to readmissions to hospital. Participant-reported ADRs and ADEs will also be collected and confirmed with GP and pharmacy records. Participants will be guided through a phone interview to identify ADRs and ADEs utilising a combination of open-ended and detailed questions as suggested by a Cochrane review of approaches to adverse effect reporting.[26]

An ADR will be suspected if the participant's symptoms, signs and/or laboratory abnormalities are consistent with the known adverse effect profile of a drug, after other causes are excluded. All participants initially categorised by the clinical pharmacist researcher as having an ADR after hospital discharge will be independently and blindly assessed by two investigators. The two investigators will be selected from a panel including a geriatrician, GPs and pharmacists involved in the trial. The causality, severity and preventability will be determined using the Naranjo ADR Probability Scale,[27] the Hartwig ADR Severity Scale,[28] and the modified Schumock and Thornton Preventability Scale.[29] Only definite or probable ADRs from the Naranjo Probability scale[27] will be considered ADRs.

ADEs will be suspected if patient-reported symptoms do not meet the definition of an ADR but are consistent with the definition of an ADE, including poor compliance or deliberate over-dosing. These events will be verified with the patient's GP and community pharmacy, and the severity and preventability will be assessed as for ADRs.

Follow-up procedures

Control and intervention participants will receive a guided telephone call at 3, 12, and up to 24 months after discharge. Participant-reported ADRs and ADEs will be documented. After 12 months, the participant's GP will be contacted by fax or phone to confirm patient reported ADRs. Hospital records will also be reviewed for ADR-related emergency department presentations and hospital admissions. ADEs will be documented in the time after index hospitalisation up to 24 months.

A three-question survey will be sent to the GPs one week after the intervention to gauge perceptions on the utility of the service, and 12-month follow-up will identify if changes to medication regimens has occurred after the intervention.

ADRs contributing to the index admission and occurring during the hospital stay will be reviewed utilising the hospital coding system.

Figure 1. PADR-AD Trial Flow Chart

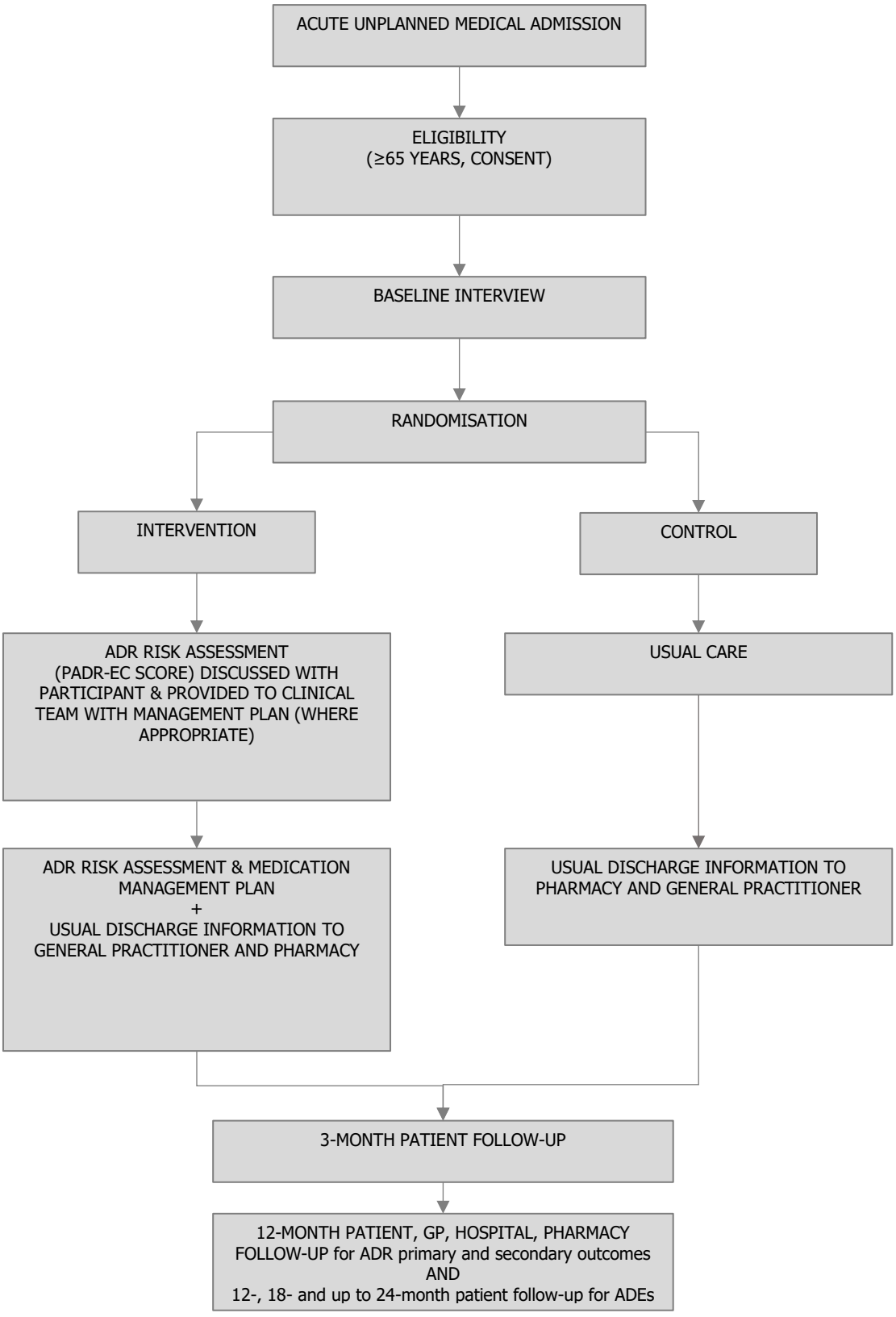

Figure 1. PADR-AD Trial Flow Chart

Governance

The trial governance includes a smaller operational team, a wider research team and a stakeholder group, supported by a protocol (ANZCTR registration number ACTRN12619000729123), a data management plan and standard operating procedures. Any unintended harms of the intervention will be addressed by the investigators, with those representing the hospital and general practice deciding on the best course of action. Privacy will be maintained using locked cabinets in a secure room, with database access limited to people linked to the trial on university servers.

Sample size

A sample size of 435 participants per group is required to detect a 5% difference in the primary outcome (power of 80% and alpha set at 0.05). There are a wide range of medication-related harm incidence rates noted in the literature, ranging from 1% to 50% in the 12 months post-discharge.[12] The rate depends on a range of factors, including the risk of medication-related harm, the primary outcome used and the method of follow-up. The sample size calculation is based on a 10% incidence rate of the primary outcome in the control group. The 5% difference represents a 5% absolute reduction in the rate of the primary outcome (in this case also a 50% relative risk reduction). One thousand participants will be targeted to allow for drop-out and loss to follow-up.

Statistical analysis

Participant characteristics will be compared between intervention and control groups at baseline. These will include demographic variables, reason for admission, key laboratory parameters, number of co-morbidities using the Charlson Co-Morbidity Index, number of medicines, drug classes through WHO ATC level 1[30] and the ICPC Chapter Headings for disease groups[31] and PADR-EC score. Statistical analyses will be performed using SPSS 28 IBM, Armonk, NY.

The primary outcome (incidence of moderate to severe ADRs to 12 months) will be compared on a presence of any ADR per participant basis using the Chi-Square test, ADR count per participant will be compared using the Mann-Whitney test, and time to first ADR event will be analysed using

survival analysis. Logistic and Poisson regression will be used to adjust for confounding variables when comparing the incidence of any ADR and the incidence rate. ADR type, severity and preventability will be descriptively summarised.

The secondary outcomes of ADR-related hospitalisation and ADEs in the community during the follow-up period up to 24 months will be analysed using the same strategy as the primary outcome. The impact of the intervention stratified based on a PADR-EC score cut-off of 6 and above will also be assessed. The number of emergency department presentations and hospital admissions will be compared using the Mann-Whitney test.

Ethics and dissemination

The Tasmanian Health and Medical Research Ethics Committee has approved this trial (H0018196). Trial registration number ACTRN12619000729123. The results will be reported to the funding body, HCF, and publications sought.

DISCUSSION

The randomised controlled trial uses a novel ADR-prediction score communicated to patients, hospital staff, GPs and pharmacies at different stages of the patient's hospital journey. The tool is simple to use and interpret and could easily be added to existing services to reduce the risk of future ADR-related hospitalisation.

The identification of high-risk patients will allow decisions to be made about targeting interventions shown to be beneficial in other studies.[21,22,32] Doing so effectively, even in high-risk patients, can be difficult. Tools such as the Beers Criteria, the Medication Regimen Complexity Index and clinical judgement have shown questionable ability to identify patients at risk of medication-related harm.[33-35] It is known from the investigators' previous research that patients readmitted to hospital with ADRs had a higher PADR-EC score than those who did not.[10] This tool will be used in conjunction with the judgement of a clinical pharmacist to help practitioners identify high-risk patients where

242 additional actions and services may be appropriate to utilise. Pharmacist-led interventions have
243 been successful in the past, using a comprehensive approach with patient education and follow-up
244 phone calls, along with a drug review and additional information provided to the primary care
245 physician.[15] It is hypothesised that the PADR-AD intervention may be more successful in patients
246 with a higher ADR risk score, and hence higher risk of complications associated with their
247 medication. This is a crucial first stage in development of a pharmacist-led service to reduce ADRs in
248 older people that can be targeted using ADR-risk assessment.

249 The term 'ADR' provides consistency with terminology used in the hospital setting and as a cause of
250 admission and is hence used as the primary outcome. ADEs will be included in the community
251 setting to understand further the impact of medication adherence in the longer time of 24 months.
252 This secondary outcome will report ADEs to also capture the errors and adherence issues
253 participants experience in the community.

254 A multi-modal approach to ADR reporting will be used, with a variety of methods including hospital
255 coded, patient reported, GP confirmed and a review of hospital records for repeat visits to ensure
256 events are identified.[4] Algorithms for probability, severity, and preventability will be used to ensure
257 consistency of reporting of the outcomes.[27-29] Pharmacist-identified ADRs will be confirmed by a
258 blinded panel incorporating medical practitioners. The addition of ADEs in the community adds a
259 broader perspective to patient factors that may be contributing to these events. A single-centred
260 site has been used due to the pragmatic approach to this trial which is a crucial first step in designing
261 an effective and targeted intervention. Further research of this service would use multicentred sites
262 with multiple pharmacists interpreting the score to improve the generalisability of the service and
263 reduce the risk of contamination. Blinding of the trial is not possible due to the use of a specific tool
264 and the nature of the service. It is service-based and with a specific tool and management. However,
265 blinding will be used with the panel assessing the reported ADEs and ADRs after discharge.

The PADR-EC tool was developed for community dwelling patients hospitalised with ADRs. It has not yet been employed in the hospital and discharge setting or for moderate ADRs that do not result in hospitalisation. Only patients discharged to the community setting will be recruited to reflect the manner in which the PADR-EC score was developed along with the pragmatic ability to provide the score to the person responsible for ongoing care of the patient.

The uptake of the recommendations by the GP will not be determined. This approach was chosen to reduce GP workload, although it will limit the understanding of the GP's interpretation and actions based on the risk score and pharmacist recommendations including for high-risk patients. However, GPs' perception on the utility of the tool and plan will be available.

SUMMARY

The intention of this study is to investigate the effectiveness of an intervention to reduce the incidence of ADRs and ADEs in older vulnerable people. The results may potentially lead to the implementation of improved medication management services at the point of hospital discharge to reduce ADRs and ADEs. The trial will also provide valuable data on ADRs and ADEs occurring after hospital discharge.

Trial registration

The trial is registered on the Australian and New Zealand Clinical Trials Registry (ANZCTR). Registration number ACTRN12619000729123.

Funding

This trial is funded by an HCF Health and Medical Research Foundation Grant- Health Service and Research Program (HCF). The funding body did not have a role in the study design and data collection, and will not have a role in the analysis, interpretation of data, writing of the report or decision to submit the report for publication.

Declarations of interest

None.

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395

Appendix A

UNIVERSITY of TASMANIA

College of Health and Medicine

This patient is enrolled in the **PADR-AD Trial**
(Preventing Adverse Drug Reactions After Discharge Trial).
Their risk for a future adverse drug reaction (ADR) has been calculated using the ADR risk assessment score named the PADR-EC score.
Patients with a PADR-EC score 6 or higher are almost three times more likely to experience an ADR-related hospital admission than patients with a score less than 6. *However, please note that patients with a lower score may still be at risk of ADRs due to their unique circumstances.*

PADR-EC score =

☐ **Higher Risk**
☐ **Lower Risk**

Their risk factors for ADRs are ticked below:

- ☐ **Drug changes within 3 months (2 points)**
- ☐ **Dementia (2 points)**
- ☐ **Renal failure (eGFR less than 60 ml/min) (2 points)**
- ☐ **Multiple antihypertensives (3 or 5 points)**
- ☐ **Use of anticholinergic drugs (2 points)**

This risk assessment and accompanying recommendations (if any), are intended to assist clinicians in the provision of medication management strategies for the prevention of ADRs; it is accepted that there may be sound reasons for not implementing changes.
A management plan will be sent to the patient's general practitioner in addition to the discharge plan. You may wish to delay some changes until after discharge or discuss them with the contacts below.
Contact Justin Cousins or Nibu Parameswaran Nair Justin.Cousins@utas.edu.au Ethics approval H0018196 Prediction of Hospitalization due to Adverse Drug Reactions in Elderly Community-Dwelling Patients (The PADR-EC Score) https://journals.plos.org/plosone/article?id=10.1371/journal.pone.0165757