



Assessment of medicines underutilisation in Aboriginal and Torres Strait Islander patients with chronic disease receiving integrated pharmacist support within Aboriginal Community -Controlled Health Services (IPAC project)

**REPORT TO THE PHARMACEUTICAL SOCIETY OF AUSTRALIA
FOR THE IPAC PROJECT**

Final Report, February 2020.

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Confidential

Integrating Pharmacists within Aboriginal Community Controlled Health Services (ACCHSs) to improve Chronic Disease Management (IPAC) Project.

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Acknowledgements:

The authors (A/Prof Sophia Couzos, Dr Deb Smith, Dr Petra Buttner, and Dr Erik Biro) wish to acknowledge the Australian Government as the funding body supporting the implementation of the IPAC Project, under the Sixth Community Pharmacy Agreement (6CPA), with funding allocated for a Pharmacy Trial Program (PTP). The PTP will trial new and expanded community pharmacy programs which seek to improve clinical outcomes for consumers and/or extend the role of pharmacists in the delivery of primary healthcare services through community pharmacy. All PTP trials will be evaluated by an independent health technology assessment (HTA) body.

The authors also acknowledge the Project Partners and Project Team members: Ms Hannah Loller, Ms Megan Tremlett, Mr Mike Stephens, Ms Alice Nugent, Ms Fran Vaughan, the Affiliates of the National Aboriginal Community Controlled Organisation, the participating ACCHSs, IPAC pharmacists, and the IPAC Steering Committee members.

ABSTRACT

Objective

To assess the effect of integrated non-dispensing pharmacist interventions on medication underutilisation in Aboriginal and Torres Strait Islander adults with chronic disease attending Aboriginal Community Controlled Health Services (ACCHSs) enrolled in the *Integrating Pharmacists within Aboriginal Community Controlled Health Services (ACCHSs) to improve Chronic Disease Management (IPAC)* study, compared with usual care pre-intervention.

Design and participants

Consented participants enrolled in a non-randomised, prospective, pre and post quasi-experimental community-based, participatory, and pragmatic study that integrated a registered pharmacist within ACCHS in Qld, NT and Vic. Participants were recipients of the IPAC intervention which comprised a prescription quality review by pharmacists as part of 10 core integrated-pharmacist roles within ACCHSs. The review included the assessment of the underuse of medications (AoU). Deidentified participant data was electronically extracted from health records.

Outcome measures

Proportion of participants with at least one potential prescribing omission (PPO), and number and type of PPO from high-value pharmacotherapies predominantly for cardiovascular disease (CVD). Omission criteria were based on ten explicit evidence-based recommendations from clinical practice guidelines targeting chronic diseases responsible for Aboriginal and Torres Strait Islander health disparities. IPAC criteria for PPOs: underuse of blood pressure and lipid-lowering therapy in patients at high primary CVD risk; anti-platelet therapy for those with existing CVD; angiotensin-converting enzyme or angiotensin-2 receptor blocker (ACEI, ARB) in those with Type 2 diabetes mellitus (T2DM) and/or chronic kidney disease (CKD) with or without existing CVD; ACEI or ARB therapy in those with heart failure (low ejection fraction <0.4); metformin or other oral hypoglycaemic for T2DM; 23-valent polysaccharide pneumococcal vaccination (23vPPV); antibiotic chemoprophylaxis for acute rheumatic fever (ARF) or rheumatic heart disease (RHD); and 'other' implicitly identified omissions.

Results

Participants (n=1,456) from 18 ACCHSs involving 26 integrated pharmacists, with 390 participants selected (non-probabilistic) by IPAC pharmacists for prescribing quality (AoU) review at baseline and at the end of the study. Loss to follow-up (n=37 without repeat AoU) left 353 participants for paired data analysis (median interval of 266 days). Participants had CVD, T2DM, CKD, or other chronic disease (87.5% had co-morbidity); 93.2% were Aboriginal and/or Torres Strait Islander with a mean age of 57.2 years (SD±15.4) and a mean of 7.2 (SD±8.0) medications each. At baseline, 51.2% (181/353) of participants had at least one PPO from explicit and implicit criteria, totalling 256 PPOs or 0.73 (SD± 1.3) PPOs per participant. The most common PPO of the 10 criteria was for 23vPPV and blood pressure (BP) and/or lipid lowering therapy for those at high primary CVD risk. No chemoprophylactic PPOs for participants with ARF/RHD were identified. Other PPOs included symptomatic therapy for a range of chronic conditions. At follow-up (mean 267 days post-baseline), there was a significant (58%, p<0.001) reduction in the number of participants with potential prescription-based medication underutilisation, and a significant relative reduction in the mean number of PPOs per participant (60.3%, p<0.001). The PPOs that were averted were for pneumococcal vaccination, BP and/or lipid lowering medication in those clinically at high primary CVD risk, ACEI or ARB for participants with T2DM and albuminuria, and metformin for those with T2DM.

Conclusion

PPOs were common in this cohort. Improvements in prescribing quality arising from non-dispensing pharmacists integrated within ACCHSs significantly averted PPOs to high-value pharmacotherapies. The magnitude of potentially undertreated Aboriginal and Torres Strait Islander patients with chronic disease and the magnitude of benefit observed following integrated pharmacists within ACCHSs, would at a population level, contribute to improved health outcomes for this target group. Generalisability of the outcomes observed from the integrated pharmacist intervention to the broader ACCHS adult patient population with chronic disease who are at risk of developing medication related problems, is supported.

INTRODUCTION

In Australia, Aboriginal peoples and Torres Strait Islanders are five times more likely to die from chronic disease before the age of 75 years (premature mortality) than other Australians (2011-15).¹ This profound health disparity has generated many policies and programs to encourage better chronic disease prevention and management within primary healthcare services. Yet, despite their higher burden of disease, medication underutilisation by Aboriginal peoples and Torres Strait Islanders persists. For years, the Indigenous Australians per person expenditure for medicines through the Pharmaceutical Benefits Scheme (PBS) has been a fraction (33% in 2013-14) of the expenditure for non-Indigenous Australians.² The PBS subsidizes the cost of pharmaceuticals for every Australian and requires a capped client co-payment adjusted for concessional status. A safety-net ensures the cost of medicines also does not exceed a capped level for each patient. Medication underuse persists for many Aboriginal peoples and Torres Strait Islanders even though PBS co-payments have either been eliminated or reduced for eligible members of this population since 2008.³

Continuing barriers to optimal use of medicines for Aboriginal peoples and Torres Strait Islanders include health system factors such as poorer access to primary health care services,⁴ culturally unsafe pharmaceutical support,⁵ lack of health service integration,⁶ disease profiles inconsistent with medicines listed on the PBS,⁷ and suboptimal prescribing quality.⁸ Patient factors include insufficient health literacy for optimal self-management of disease,⁹ distrust of health services,¹⁰ family and community obligations,¹¹ and belief in traditional medicines,¹² whilst condition-related factors include disproportionately high multimorbidity.¹³ Socioeconomic factors may also affect the personal management of medicines such as adherence and storage.¹⁴

A whole of health system response is needed to tackle these factors. This is difficult when system improvements are mostly directed to reducing overuse than the underuse of medicines.¹⁵ Moreover, the quality of prescribing is not systematically examined for Aboriginal peoples and Torres Strait Islanders with chronic disease. National key performance indicators for health services to this population encourage regular clinical audit to improve activity such as assessing the absolute risk of a cardiovascular event (over 5

years),¹⁶ but are lacking indicators of prescribing quality. The National Prescribing Service supports general practices to undertake small prescribing audits,¹⁷ but it is unclear if this reduces underprescribing.

For the primary and secondary prevention of cardiovascular disease in the Aboriginal and Torres Strait Islander population, assessing cardiovascular risk is essential to prevent the underuse of treatment in those at high-risk.^{18 19} Research has shown that underprescribing with blood pressure and lipid-lowering medications is common in Aboriginal and Torres Strait Islander patients at high-risk for cardiovascular disease (CVD).^{20 21 22} High BP and lipid levels are major contributors to CVD risk and the overall disease burden in the Aboriginal and Torres Strait Islander population. Any effort to close the gap in health status will therefore depend on reducing these risks.²³ Pharmacological reductions in BP can significantly reduce the risk of major CVD events, coronary heart disease, stroke, heart failure and all-cause mortality including in patients with comorbidities.²⁴ These benefits are also evident for populations in resource-poor settings where combined pharmacotherapy for BP, lipid-lowering, plus aspirin use in those at high absolute risk for CVD was estimated to generate a 2-year gain in life expectancy (compared with no treatment) when modelled until death.²⁵ Addressing the underuse of BP and lipid-lowering therapy are examples of high-value interventions that will confer significant benefits on patients and represent value for money.²⁶

Not a great deal is known about how well other best practice pharmacotherapeutic recommendations are applied in practice to reduce the undertreatment of Aboriginal and Torres Strait Islander peoples. An audit of the medication records of Aboriginal Australians in remote Western Australia (WA) found that 12% (33/273) of patients had potential underprescribing. An example of one criterion was if patients with a history of hypertension lacked antihypertensive therapy.²⁷

In order to investigate the potential gains in health outcomes arising from integrated models of care within Aboriginal health settings, the *Integrating Pharmacists within Aboriginal Community Controlled Health Services (ACCHSs) to improve Chronic Disease Management* (IPAC) Project was developed. The project explored if integrating a registered

pharmacist as part of the primary health care (PHC) team within ACCHSs (the intervention) leads to improvements in the quality of the care received by Aboriginal and Torres Strait Islander peoples with chronic diseases. Commencing in 2018, this study measured medication appropriateness and underutilisation in a subset of adult patients with chronic diseases who enrolled in this project.

The IPAC project defined the underuse of medications as a *potential prescribing omission* (PPO). A PPO occurs when there is an omission of potentially beneficial medication that is clinically indicated for the treatment or prevention of a disease.²⁸ IPAC pharmacists undertook an assessment of the underutilisation (AoU) of beneficial medications at baseline by auditing each study participant's pharmacotherapy against a set of current evidence-based clinical practice guideline (CPG) recommendations for the Aboriginal and Torres Strait Islander population. Assessments were repeated at the end of the study to assess change in medication underutilisation following the intervention. In order to explore if underprescribing can be reduced, this study quantified the change in the proportion of participants with at least one PPO and the number and type of PPOs from high-value pharmacotherapies in Aboriginal and Torres Strait Islander participants who received integrated pharmacist services.

METHOD

The IPAC project was a community-based, participatory, pragmatic, non-randomised, prospective, pre and post quasi-experimental study (Trial Registration Number and Register: ACTRN12618002002268) that integrated a registered non-dispensing pharmacist within the ACCHS primary healthcare team for up to a 15-month period. ACCHS sites (n=18) were recruited for the project across three jurisdictions: Victoria, Queensland and the Northern Territory. Health service staff and pharmacists invited patients into the study as they were attending ACCHSs for usual care. Patients recruited into the study were aged 18 years and over with a diagnosis of: cardiovascular disease (CVD), Type 2 diabetes mellitus (T2DM), chronic kidney disease (CKD), or other chronic conditions and at high risk of developing medication-related problems (e.g. polypharmacy).

The IPAC project methodology has been described in detail elsewhere,²⁹ and health services characteristics were summarized in a separate report.³⁰ Briefly, IPAC pharmacists delivered non-dispensing clinical pharmaceutical services within ACCHSs through a coordinated, collaborative and integrated approach to improve the quality of care of patients. Their intervention targeted both consented patients and practices, with practice-specific activities directed to health professionals and systems within the service. Pharmacists were required to undertake 10 core roles that comprised: providing medication management reviews, assessing patient adherence and medication appropriateness, providing medicines information and education and training, collaborating with healthcare teams, delivering preventive care, liaising with stakeholders, providing transitional care, and undertaking a drug utilisation review.³¹

Prescription quality review

Prescribing quality was comprehensively assessed by integrated pharmacists in a subset of IPAC participants using the Medication Appropriateness Index (MAI)^{32 33} and the AoU. Pharmacists then used the MAI and medication underuse assessments to inform medication management plans and recommendations for prescribers, as needed. The MAI is a prescription quality review tool that assesses the potential for medicine-related risks that outweigh the benefits to the patient. These risks are associated with suboptimal prescribing which is defined as inappropriate use, overuse, and the underuse of medications. However, the MAI is unable to inform on the underutilisation of medications. For this reason, all MAI subset participants were also simultaneously assessed for medication underuse using criteria developed for the project.

Study participants

A non-probabilistic, pragmatic participant sampling method was used by pharmacists to select a sample of enrolled participants for MAI and AoU assessment according to their clinical need for a prescription review. The sample size was set for feasibility reasons, due to the length of time usually required for pharmacists to undertake the MAI assessment and the large number of participants expected to be enrolled into the study.³⁴ The number of MAI assessments was adjusted pro-rata to be consistent with the level of pharmacist appointment within the ACCHS.

The clinical need for the prescription quality review was reflective of usual care and based on criteria such as for Home Medicines Review where the patient must have 'a chronic medical condition or a complex medication regimen, and not [have] their therapeutic goals met'.³⁵ The study did not use random selection of participants for MAI audit in order to reflect usual care clinical processes and services consistent with a pragmatic trial.³⁶ In another report, it was shown that the selected participants did not differ from other IPAC participants in terms of demographic characteristics, by presence and type of chronic disease, utilization of health services, biomedical parameters, or self-assessed health status. Health service characteristics did not effectively change from baseline to the end of the study.³⁷

Pharmacists were instructed to complete the assessments shortly after participant enrolment and within the first three months of the study (baseline) and again prior to the end of the study (set as the 31st October 2019). Participant attendance was not required to undertake the review.

Pharmacists

The Pharmaceutical Society of Australia (PSA) recruited pharmacists to be integrated within ACCHSs, whilst the National Aboriginal Community Controlled Health Organization (NACCHO) supported ACCHSs. IPAC pharmacists fulfilled the following eligibility criteria: registration with the Australian Health Practitioners Regulation Agency (AHPRA); more than 2 years' post-registration experience; and post-graduate clinical qualifications or demonstrated clinical experience.

As a member of the health care team, all pharmacists had access to participants electronic medical records held at the ACCHS. Medications were accepted by pharmacists as 'prescribed' if they were included in the patient's current medication list within the records. Pharmacists were also able to check other sources of information to validate the current medication list such as information within the CIS, correspondence from specialist clinicians or discussion with other clinical staff. Pharmacists entered each medication into an

electronic logbook (developed for the project) as they reviewed the participants clinical history systematically against MAI and underuse criteria.

Assessment of medicines underutilisation (AoU)

Clinically relevant potential prescribing omissions (PPO) categories were derived by a team of four pharmacists and a public health physician from appropriate evidence-based clinical practice guidelines (CPG). A list of ten (10) evidence-based categories were agreed by consensus, to define clinically relevant potential prescribing omissions (PPO) for CVD, T2DM, CKD, pneumococcal vaccination, acute rheumatic fever (ARF) and/or rheumatic heart disease (RHD). These conditions were known to contribute significantly to the burden of disease and healthcare disparities in Aboriginal peoples and Torres Strait Islanders (especially in remote Australia).³⁸ Prescribing recommendations from CPGs were selected if they were unambiguous and represented high-value interventions known to be underused.³⁹ The recommendations defined the type of PPO within each underuse category, which if ameliorated would benefit Aboriginal peoples and Torres Strait Islanders with the listed conditions. The selection of recommendations was kept small to reflect key omissions and to minimise the reporting burden on pharmacists (Table 1). The use of evidence-based guidelines applicable to Aboriginal and Torres-Strait Islander peoples informed the face and content validity of the underutilisation criteria. Other explicit criteria-based methods to detect PPOs were considered unsuitable in the context of the IPAC study (Table 2).

The final set of prescribing recommendations were explicit (clearly defined clinical circumstances) and categorised potential prescribing omissions from A to J, with a final category K representing 'other' omissions assessed implicitly by the pharmacist. Categories A, B and C defined recommendations for patients at high absolute risk (>15%) of developing a cardiovascular event over the next 5 years for the primary prevention (calculated high-risk or existing clinical criteria for high-risk)⁴⁰ and secondary prevention (pre-existing CVD) of cardiovascular events.^{41 42} Category A and B recommendations were mutually exclusive- participants either had a clinically high primary risk for CVD or were at high primary risk based on risk assessment using the Framingham risk equation.⁴³ Participants already at clinically high risk for a CVD event did not require their absolute CVD risk to be calculated.

These participants had the following conditions: diabetes and aged greater than 60 years; diabetes with microalbuminuria ($>2.5\text{mg}/\text{mmol}$ for males and $>3.5\text{ mg}/\text{mmol}$ in females); moderate or severe CKD (persistent proteinuria or $\text{eGFR} <45\text{ ml}/\text{min}/1.73\text{m}^2$); a previous diagnosis of familial hypercholesterolaemia; systolic blood pressure (BP) $\geq 180\text{mmHg}$ or diastolic BP $\geq 11\text{mmHg}$; serum total cholesterol $>7.5\text{mmol}/\text{L}$; Aboriginal and Torres Strait Islander adults aged over 74 years.⁴⁴

Category D and E recommendations aimed to reduce the risk of CVD events (irrespective of the presence of CVD) in patients with T2DM with albuminuria and to protect against the progression of CKD in those with a clinically high CVD risk (with or without diabetes).^{45 46 47}

⁴⁸ These recommendations were to inform on recommended and preferential treatment with angiotensin converting enzyme inhibitor (ACEI) or angiotensin 2 receptor antagonist (ARB) treatment. This treatment is particularly important for the Aboriginal and Torres Strait Islander population (with or without diabetes) in view of their higher prevalence of CKD, evidence indicating that macroalbuminuria is predictive of CKD and CVD deaths, and a demonstrated 50% reduction in all-cause natural deaths with ACEI therapy and additional agents after a mean follow-up of 3.39 years.⁴⁹ Therapy with both ACEI and ARB in the same patient is contraindicated.⁵⁰

Category F defined recommendations for patients with heart failure and a reduced left ventricular ejection fraction (of 40% or less) to reduce hospitalisation and mortality.⁵¹

Categories G and H defined recommendations for those with T2DM to improve glycaemic control and prevent macro and microvascular complications.^{52 53} Category I recommended 23-valent polysaccharide pneumococcal vaccination (23vPPV) to prevent invasive pneumococcal disease in patients at high-risk.^{54 55} Category J recommended antibiotic chemoprophylaxis for patients with ARF or RHD for the secondary prevention of recurrent rheumatic fever.^{56 57}

Pharmacists assessed if participants with the above clinical criteria had been prescribed the recommended medications. Category K allowed pharmacists to implicitly identify any other PPO relevant to the participant (Table 1).

The first AoU after participant enrolment was defined as 'baseline'. Medication underutilisation was reported as the *proportion of patients with at least one PPO*. All participants with <90 days of follow-up were removed from the analysis (Figure 1) to allow for a minimum time for pharmacist's recommendations to be acted upon. The intervention phase of the study comprised the period from participant enrolment to the end of the study (31st October 2019).

Data collection

All collected data was deidentified. Participant clinical information was sourced from the electronic health records of participating services as well as data entered by pharmacists into an electronic logbook. Demographic, biomedical and health service utilization indices were extracted from Clinical Information Systems (CISs) in deidentified form using an electronic tool called GRHANITE that required remote installation and regular extraction from IPAC sites for the term of the project.⁵⁸ Participant consent was recorded in the CIS by pharmacists. GRHANITE only extracted data for consented patients and copied it to a JCU databank employing internationally recognised point-to-point encryption (P2PE) mechanisms to protect data in transit. The scope of the data extractions was agreed based on IPAC-specific data requirements and extract definitions for GRHANITE XML's (site interfaces) to ensure they were fit-for-purpose. All sites consented to the installation of GRHANITE and the deidentified data extractions required for the project. Each initial site extraction successfully completed 'site acceptance testing' that confirmed the extraction of fit-for purpose data. The integrity of the data extraction was regularly checked with weekly uploads. XML interface maintenance ensured that any software vendor upgrades to the CIS were aligned with data extract definitions. The deidentified CIS patient identification numbers recorded by pharmacists in the logbook linked with patient data in the GRHANITE extractions.

The pharmacist logbook was a secure password protected online database, accessible from any device connected to the internet, with dual recording and reporting functionality. The electronic interface was developed to be intuitive and user-friendly to minimise the burden of data entry and reporting. Pharmacists were trained to assign PPOs to each underuse

category and record the results of the assessment in the logbook. They assessed for contraindications and intolerance to the recommended medications and reported an omission *only* if the medication was indicated and potentially of benefit. Pharmacists were also trained to look for clear documentation of a clinical decision *not* to use the recommended medications (in which case they would not document a PPO).

In order to assess for category A omissions for patients without pre-existing CVD, pharmacists used the participant's electronic health records to check their absolute 5-year risk for a CVD event, which according to Australian guidelines is based on the 1991 Framingham risk equation.⁵⁹ Information (if available) on the participants age, sex, systolic blood pressure, smoking status, total cholesterol, high-density lipoprotein cholesterol, and the presence of diabetes was necessary to estimate the calculated CVD risk for Aboriginal and Torres Strait Islander participants aged 30 years to 74 years of age. Pharmacists had the discretion to base CVD risk on local guidelines used by their health service and CIS software.⁶⁰ Pharmacists were not instructed to routinely adjust absolute risk estimates upwards (because current risk equations underestimate CVD risk for the Aboriginal and Torres Strait Islander population) as this is subject to clinician discretion or local health service guidelines.⁶¹ Further information on pharmacist training is described elsewhere.⁶²

Pharmacists recorded clinical diagnoses in the logbook based on what was documented in electronic health records or supplemented by discussion with clinicians. Patients with 'existing CVD' were defined as participants with a logbook recorded clinical diagnosis of: coronary heart disease, CVD, or peripheral vascular disease (PVD).

After assessing underutilisation, pharmacists recorded an omission (and the category of omission) or a lack of an omission in the logbook. A participant could have several PPO's across multiple omission categories. The pharmacist who determined medication appropriateness also assessed medication underuse in the same participant. The majority of follow-up MAI and underuse assessments (79%) were completed by the same pharmacist who completed the baseline assessment. The remaining follow-up assessments were completed by a different pharmacist due to pharmacist turnover in some sites. There were very few discordant MAI results within and between pharmacists when a sample of

pharmacists were investigated for inter and intra-rater reliability.⁶³ The reliability of PPO assessments by pharmacists was not tested.

Data analysis

All participants with less than 90 days of follow-up were removed from the analysis due to their short length of stay in the study. Health Care Homes (HCH) participants who were also concomitantly enrolled in another program- the '*Community Pharmacy in Health Care Homes Trial*'⁶⁴ - were also removed from the analysis.

Participant characteristics data was extracted from the JCU SQL Server database using the Navicat 15 for SQL Server (PremiumSoft) database management tool; MAI and AoU data was extracted from the pharmacist logbook as Microsoft Excel files; and health services data was sourced from HSA survey. All data was subsequently analysed using a number of statistical tools including the SPSS Statistics Premium version 24 (IBM) statistical package, Stata/MP 13.0 (StataCorp LP), and Microsoft Office 2016 (Microsoft). Nominal variables are presented as absolute and relative frequencies whilst continuous variables are presented as mean and standard deviation (SD) or median and interquartile range (IQR) as indicated accordingly. The percentages of participants with improvements in outcomes were compared to determine the absolute and relative change pre and post intervention.

All participant-related analyses were adjusted for the clustering effects of the ACCHSs. P-values for comparisons of paired data (continuous variables) were derived from the cluster-adjusted confidence interval (ACCHS cluster) as this is equivalent to a paired t-test. P-values for comparisons of unpaired data (continuous variables) were determined using logistic regression analyses that were cluster-adjusted for ACCHSs. P-values for comparisons of paired data (nominal variables) were determined using conditional logistic regression analyses that were cluster-adjusted for ACCHSs. Statistical significance was assumed at the conventional 5% level.

Ethics approval

Ethics approval for the project was received from four ethics committees in the three jurisdictions including St Vincent's Hospital Melbourne (SVHM) Human Research Ethics Committee (HREC), Victoria (HREC/17/SVHM/280), James Cook University HREC (mutual

recognition of SVHM HREC, approval HREC/H7348), Menzies School of Health Research (HREC/2018-3072) and the Central Australian HREC (HREC/CA-18-3085).

RESULTS

The total IPAC project cohort comprised 1,456 participants who remained in the study until the end. From this, 390 participants had a baseline MAI and AoU with a loss to follow-up of 37, meaning the final subset comprised 353 (24.2%) participants with both a baseline and follow-up AoU from 18 ACCHSs (Figure 1). AoU assessments were completed by pharmacists at each of these ACCHSs. The median length of stay in the study for participants with an AoU was 330 (IQR: 288-365) days.

Almost all participants were Aboriginal and/or Torres Strait Islander (93.2%) with a mean age of 57 years and were prescribed a mean of 7.2 medications each. Most of the cohort had T2DM (62.3%) and multimorbidity and were concession card holders. Eight participants had a history of rheumatic heart disease (RHD) or acute rheumatic fever (ARF) (Table 3).

Most baseline assessments were completed within 100 days of participant enrolment and participants were followed-up for a median of 266 days post-baseline (Table 4). A total of 256 individual PPO's were identified at baseline for underuse categories A to K, with a mean number of 0.73 PPO's (SD ± 1.3) per participant, or a mean number of 1.41 PPOs (SD ± 1.3) for each participant with an identified omission (Table 4). By the end of the study, the total number of individual PPOs had reduced by 59.8% to 103 PPOs, and to a mean of 0.29 PPOs per participant ($p < 0.001$). Of participants, 51.3% (181/353) had at least one PPO at baseline. By the end of the study, the number of participants with at least one PPO in any of the underuse categories had significantly reduced by 58.0% to 76 participants ($p < 0.001$).

The most common type of PPO identified for AoU categories A-J at baseline and follow-up was for people for whom 23vPPV was indicated (category I, Table 5) affecting 16.7% of all participants and 23.0% of all PPOs at baseline. This was significantly reduced to only 4.2% of participants at follow-up- a relative reduction in this PPO of 74.6% ($p < 0.001$). The majority of participants who lacked evidence of necessary vaccination with 23vPPV at follow-up were aged 50 years or older.

The next most common type of PPO was for absent BP and/or lipid- lowering medications for participants who had a high risk for CVD. At baseline, this comprised 22.6% (58/256) of all PPOs from combined category A and B omissions (in those at high primary risk of a CV event). Of the PPO types, 27.1% (13/48) were for absent BP lowering therapy; 52.1% (25/48) were for absent lipid- lowering therapy, and 20.8% (10/48) were for the absence of both BP and lipid-lowering therapy.

The number of participants with a high calculated CVD risk (category A) who had at least one PPO for BP and/or lipid lowering therapy did not change at follow-up. However, significantly fewer participants who were clinically at high risk for a primary cardiovascular event had a PPO for necessary BP and/or lipid-lowering therapy at follow-up (category B, $p=0.002$). This was a 61.3% relative reduction with 19 fewer participants having a PPO of this type. Anti-platelet therapy was missing in 9 participants with established CVD (category C) at baseline, and 7 fewer participants had a PPO of this type at follow-up, but the difference was not significant after cluster adjustment ($p=0.052$, Table 5).

Pharmacists identified 30 participants (with T2DM and micro or macroalbuminuria) at baseline who potentially could benefit from an ACEI or an ARB to protect against CKD progression and cardiovascular events but were not receiving this therapy (category D). This reduced significantly to 13 participants at follow-up - a 56.7% relative reduction in the proportion of participants with a PPO of this type ($p=0.005$).

The number of participants with CKD and macroalbuminuria (without diabetes) with a PPO for ACEI or ARB (category E) was small at baseline and did not change at follow-up ($p=0.33$). Similarly, only 3 participants were identified to have a PPO with regard to ACEI or ARB in the presence of heart failure (category F) but the reduction at follow-up was also not significant ($p=0.57$).

There were 17 participants with T2DM who could potentially have benefited from metformin (category G) but were not receiving this therapy at baseline. At follow-up, 12 fewer participants had this PPO -a significant relative reduction of 70.6% and absolute change of -3.4% ($p=0.012$). The number of participants with T2DM who could have

benefitted from a second hypoglycaemic medication (category H) to better optimise glycaemic control was small and this number did not change at follow-up. No patient was reported to have a PPO with regard to antibiotic chemoprophylaxis for RHD/ARF (category J).

Pharmacists identified 65 (18.4%) participants with 'other' PPOs at baseline (category K) for clinical indications other than for the explicit high-risk underuse categories A-J (Table 6) and this number reduced significantly at follow-up ($p < 0.001$). These PPOs included symptomatic treatment such as pain relief, glyceryl trinitrate for angina, bronchodilators for asthma, laxatives, and antiemetics. Other pharmacotherapy for chronic diseases included antipsychotics, insulin, and medication for osteoporosis, hypertension and dyslipidaemia to improve the control of individual risk factors.

DISCUSSION

This project was set in primary health care services that were ACCHSs and is the first to explore the impact of integrated pharmacists on medication underuse for a range of pharmacotherapies in Aboriginal and Torres Strait Islander patients with chronic disease. Medication underuse was defined as a PPO from ten pre-defined explicit clinical categories for high-value pharmacotherapies and one implicit 'other' category. IPAC pharmacists identified a range of clinically relevant and significant PPOs in just over 50% of Aboriginal and Torres Strait Islander study participants at baseline who had a comprehensive review of prescribing quality. At baseline, PPOs for BP and/or lipid-lowering medications were identified in 48 participants who were deemed by pharmacists to be at high primary CVD risk (category A/B), representing 13.6% ($n=353$) of all participants assessed for medicines underutilisation. There were 30 participants with T2DM (with or without existing CVD) who had a PPO of an ACEI or ARB that was clinically indicated to protect against cardiovascular events and CKD progression (category D). ACEI or ARB potential prescribing omissions in those with macroalbuminuric non-diabetic CKD (with or without CVD) was also found in 6 participants at baseline (category E). A PPO for 23vPPV was evident for 59 (16.7%) participants (category I).

After receiving integrated pharmacist services, the proportion of participants with at least one PPO reduced significantly – an absolute reduction of 29.7% after a median of 266 days between assessments for medication underuse ($p < 0.001$). Only 3.4 participants needed to be assessed for medication underutilisation for one of them to potentially benefit from a correction of the omission.

At follow-up, PPOs were significantly reduced for participants at clinically high risk for CVD, those with T2DM and albuminuria (with or without CVD), those with T2DM who need metformin, and participants for whom a 23vPPV was indicated. The magnitude of benefit was such that only 21 participants needed to receive the integrated pharmacist intervention so that one less person with T2DM and albuminuria was potentially underprescribed for an ACEI or ARB. These benefits for Aboriginal and Torres Strait Islander participants were observed even within already high performing ACCHS settings based on their participation in other quality improvement activity.⁶⁵

IPAC underuse criteria explored an absolute-risk approach to the management of BP and cholesterol levels because this has been shown to be more cost-effective than managing single-risk factors⁶⁶ and can better avoid under and overtreatment of patients as the risk of future CVD events is more accurately predicted.⁶⁷ We found that compared with usual care, for every 19 participants at clinically high risk for CVD who received integrated pharmacist services, there was one less participant with a PPO for BP-lowering, lipid-lowering, or combined BP and lipid-lowering therapy. Reducing omissions of high-value pharmacotherapies like this may generate substantial clinical benefits at a population level according to average treatment effects reported in other studies. For example, in adults clinically assessed to be at high primary CVD risk, lipid-lowering therapy with statins reduced CVD events (pooled composite outcomes such as CV deaths, fatal and nonfatal myocardial infarction, stroke, heart failure) over 1-6 years of follow-up. The relative risk reduction in CVD events from treatment compared with placebo or no-statin was 30% and the number needed to treat (NNT) was 72.⁶⁸

A study involving patients with T2DM (with or without a previous CVD event) who were treated with ACEI for 4.5 years (compared with placebo), demonstrated 37% fewer deaths

from CVD, and a 17% reduction in overt nephropathy. The magnitude of benefit was such that 29 people needed to be treated in this way to prevent one CVD death.⁶⁹ For Aboriginal peoples with T2DM and albuminuria, the benefits from ACEI therapy could be even greater. A study including Aboriginal peoples with diabetes and micro or macroalbuminuria who were treated with ACEI plus other agents to reach blood pressure targets (including attempts to control glucose and lipid levels) required only 11.6 people to be treated over a mean 3.39 years to avoid one death.⁷⁰ If this finding is applied to IPAC participants, 1.5 deaths could be averted if the intervention was sustained over this time given that ACEI or ARB underprescribing was ameliorated for a net 17 people with T2DM (and albuminuria) following the intervention.

Similarly, UK Prospective Diabetes Study investigators found that metformin therapy reduced death from all causes by 36% (NNT 12-14) compared to conventional treatment for obese patients with T2DM (mean BMI of 31) over a median period of 10.7 years.⁷¹ Based on this potential for benefit if the effect of the IPAC intervention was sustained, and given the mean BMI of IPAC participants with T2DM was 31.8, one death may be averted as the PPO for metformin therapy was eliminated for 12 participants over the study follow-up period ($p=0.012$). Clearly, the effects of the intervention on distal health outcomes such as mortality depends substantially on medication adherence by the patient as well as health system follow-up.

No PPOs for ARF/RHD chemoprophylaxis were reported by IPAC pharmacists which is most promising, although the number of enrolled participants with these conditions was small. This may be because ACCHS prescribers are now better supported to start and also stop prophylactic therapy through jurisdictional RHD register and control programs, guidelines, performance indicators, and other supports but patient adherence to secondary chemoprophylaxis remains low.⁷²

Although half of participants had at least one PPO at baseline, the majority also had polypharmacy (usually defined as a person taking five or more medications) that is often considered an indicator of medication overuse.⁷³ Up to 76% of participants had two or more chronic diseases and, when they were implicitly assessed for medication appropriateness,

most did not have medicines overuse but had 'appropriate polypharmacy'.^{74 75} This suggests that correcting underprescribing will offset attempts to reduce expenditure on medications. For this reason, progress towards *equitable* healthcare resource use should be a health system goal for the Aboriginal and Torres Strait Islander population, avoiding mainstream economic measures such as reductions in medicines expenditure applied to this population. Rather, quality measures to assess reductions in the unnecessary use of medications are needed, where inappropriate medications are replaced with those that are necessary, and prescribing omissions are corrected. For example, the broader impact of integrating pharmacists within ACCHSs as well as other strategies to reduce medication underuse could be monitored using key performance indicators (KPI). In the NT, the use of ACEI or ARB in patients with T2DM and albuminuria (>3.4 mg/mmol) is routinely monitored in primary health care settings for quality assurance,⁷⁶ but not elsewhere. Other underuse *studies* have employed single-item CPG recommendations, such as lipid-lowering therapy in those with high primary CVD risk, which may also be a useful indicator for services to use.^{77 78}

If a large portion of the CVD disease burden in the Aboriginal and Torres Strait Islander population is to be avoided, then PPO's for those with a high absolute CV risk need to be reduced. This makes pharmacist medication reviews an important risk reduction strategy to identify PPOs in those who are most likely to benefit. The provision of medication management reviews (and prescribing quality reviews such as the MAI) was a core role for integrated pharmacists within ACCHSs. Medication reviews can improve prescribing quality,⁷⁹ reduce both underuse and overuse of medications,⁸⁰ support patients with medication adherence, chronic disease self-management, and their adoption of a healthy lifestyle.⁸¹ However, pharmacists need to be skilled in identifying medication underuse and to target high- value interventions based on prescribing recommendations for the Aboriginal and Torres Strait Islander population.⁸² A receptive clinical environment, trusting relationships with prescribers, and access to patients' medical records were key characteristics of the IPAC intervention that have also been identified in other integrated models of care involving pharmacists.⁸³ Other system-wide strategies to improve prescribing quality include electronic decision-support,⁸⁴ continuing professional development,⁸⁵ and access to prescribing guidelines.

Limitations

The use of other relevant explicit criteria-based tools to assess medication underuse^{86 87} were not suitable for the IPAC project (Table 2). Instead, CPG recommendations to measure medication underutilisation were used as reported in other studies,^{88 89} rather than using established tools. The IPAC explicit criteria for medicines underuse had face and content validity because they were derived from Australian patient-relevant CPGs and also shared criteria with both the START and the RAND/UCLA methods (Table 2). START criteria have been validated to identify underprescribing in a variety of clinical contexts⁹⁰ and are reliable,⁹¹ but are unsuitable for use with younger cohorts. The RAND/UCLA method of assessing medication appropriateness had face and content validity for use with an older cohort but duplicated MAI assessment, and its reliability in the Australian context was untested.⁹² The reliability of the IPAC AoU criteria when used by pharmacists was not assessed, which is a study limitation. However, the project did adopt measures to enhance reliability with appropriate and focussed training, regular workforce support, and the development of an electronic logbook that reminded pharmacists of the AoU criteria helping to guide assessment and reporting. Pharmacists were also blind to the results at baseline when performing follow-up assessments. The IPAC approach also supports the external validity of the study findings as the use of CPG recommendations when undertaking pharmacist medication management reviews is considered usual care.

Not all physiological systems were included in the IPAC AoU criteria although pharmacists could report 'other' PPOs. This may have underestimated the number of PPOs, especially with regard to musculoskeletal, gastrointestinal and respiratory conditions as these were not included in the AoU. Having fewer clinical criteria for the assessment of medication underuse may have enhanced reliability as pharmacist's attention was directed mainly to high-value PPOs. Nevertheless, many PPOs were identified by pharmacists using clinical judgement (implicit criteria for category K omissions). These PPOs were patient-specific and identified a much broader range of necessary but underused pharmacotherapies including other physiological systems not included in the explicit-criteria AoU. Implicit criteria-based approaches to identify PPOs are believed to be time-consuming and very much dependant on clinical expertise,⁹³ which is one reason why few methods exist to assess underuse (Table

2). The IPAC approach used both explicit and implicit ways of identifying PPOs for pragmatic reasons to be consistent with usual care.

Pharmacists were trained to account for contraindications to medications that may explain a PPO, but there may have been other patient and clinical factors influencing prescribing decisions than was possible for pharmacists to ascertain from medical records or from contact with the prescriber. Errors in medication lists could have influenced PPO ascertainment although this is a limitation inherent with all tools used to assess prescribing quality. Patient unwillingness to take medications or health professional assumptions about patient unwillingness,⁹⁴ or clinical discretion favouring other therapeutic priorities may explain some PPOs. For some 'other' PPO entries, pharmacists included the treatment of uncontrolled hypertension and dyslipidaemia, which suggests that some pharmacist prescribing recommendations for BP or lipid-lowering therapy was based on an elevated individual risk factor rather than on the patient's absolute risk of a CVD event. If an individual risk factor approach to PPO ascertainment influenced results, it is unclear if this would underestimate or overestimate the overall number of PPOs identified. Finally, a reluctance for some prescribers to take-up pharmacist prescribing recommendations may have explained some persistent PPOs,⁹⁵ a finding also identified in the qualitative evaluation of the IPAC project.⁹⁶ This would have the effect of underestimating the magnitude of the PPO reductions observed.

It is unlikely that the observed PPO reductions are an artefact of making participants medication records more accurate. Pharmacists made efforts to check the validity of participants prescribing information contained within CISs before submitting data to the logbook. The use of logbook data for analysis rather than using medications data extracted directly from health service CISs makes this artefact less likely, as it acted as a quality check. Moreover, the significant improvement in prescribing quality identified through MAI assessments for the same participants as reported elsewhere⁹⁷ could not have occurred merely by updating CIS medication records. Pharmacists also documented their recommendations for medication changes in the logbook. Medication records in the CIS are also unaffiliated with vaccination records, yet the number of participants with a PPO for

23vPPV significantly declined following the intervention. These factors provide further support that the observed prescribing quality changes were real.

Although this study lacked a control group, it is unlikely that the significant PPO reductions observed in intervention sites would have been observed over the same follow-up period without the intervention. Firstly, the magnitude of the observed reduction in the number of PPOs and participants with at least one PPO was significantly different to baseline (usual care). Factors that may have improved usual care, independent of the intervention, could have been external prescriber influences such as education from other sources, or artefacts (such as improved medical record keeping), or increased consumer demand for quality prescribing. It is unlikely that such independent influences could have occurred across multiple ACCHS settings over the same time period. Secondly, whilst other health service factors (such as the number of clinical staff per service, access to specialists and allied health, community pharmacy support, and the number of Health Care Home participants) may also explain improvements in PPO ascertainment over time, these factors did not significantly change during the project period.⁹⁸ Finally, the observed PPO reductions occurred within a short window of time which is difficult to explain if factors other than the intervention influenced this change.

Another potential confounder to the relationship between the intervention and prescribing quality was the HCH program. However, all participants concurrently enrolled in the *Community Pharmacy in Health Care Homes* (HCH) Trial program (undertaken in the NT around the same time as the IPAC project⁹⁹) were removed from the IPAC analysis (Figure 1). Of the few IPAC participants concurrently enrolled in the broader HCH program, they were not in receipt of additional community pharmacy support beyond usual care and comprised only 10.8% of subjects (n=38). Moreover, the IPAC pharmacist was integrated within those services operating concurrently as a HCH trial site, which implies that the HCH program could not have acted as a confounder independently of the pharmacist.

Up to 53% of participants had missing ACR results at baseline. According to CPGs, every Aboriginal and/or Torres Strait Islander patient older than 30 years of age should have an eGFR and ACR at least once every 2 years, and patients with T2DM should have at least

annual screening.¹⁰⁰ Patients in Stage 3A of CKD should have 6-12 monthly ACR and eGFR depending on the presence of microalbuminuria to monitor response to therapy and disease progression.¹⁰¹ The absence of ACR results in the medical records may have led pharmacists to underestimate PPOs in those with T2DM and CKD (category D) as they would be unaware if the patient had albuminuria. For participating IPAC services, the prevalence of missing ACR results approximates the national average for KPI data in 2017 as 50% of Aboriginal and Torres Strait Islander clients (aged 15 years and over) with T2DM had missing ACR results in the preceding 12 months.¹⁰² Of the IPAC participants with test results in the 12 months prior to study enrolment, an abnormal ACR was common (61%), which is also consistent with national nKPI data for patients with T2DM (also 61% in 2017).¹⁰³ As it is difficult to identify a PPO with ACEI or ARB if the patient with T2DM is missing an ACR result, this underlines why comprehensive screening is vital for optimal prescribing practice. It also suggests that integrated pharmacists may be able to play a role in better supporting patients to be screened.

In a separate analysis, the characteristics of the participants assessed for medication appropriateness (which includes those with an AoU) were shown to be similar to the broader IPAC cohort even though they represented about 24% of the whole cohort.¹⁰⁴ It is therefore likely that the whole IPAC cohort had similar rates of medication underuse. Generalisability of the outcomes observed from the integrated pharmacist intervention to the broader ACCHS adult patient population with chronic disease who are at risk of developing medication related problems, is supported. All study participants were accessing ACCHSs, a large number of these services participated, and the study design was pragmatic. It is also possible that the prevalence of PPOs, especially for those who are not accessing primary health care or lack access to culturally appropriate care, may be much higher than estimated in this study. Measures to increase Aboriginal and Torres Strait Islander peoples' access to comprehensive and culturally appropriate primary health care, is an important priority in efforts to support prescribing quality improvement.

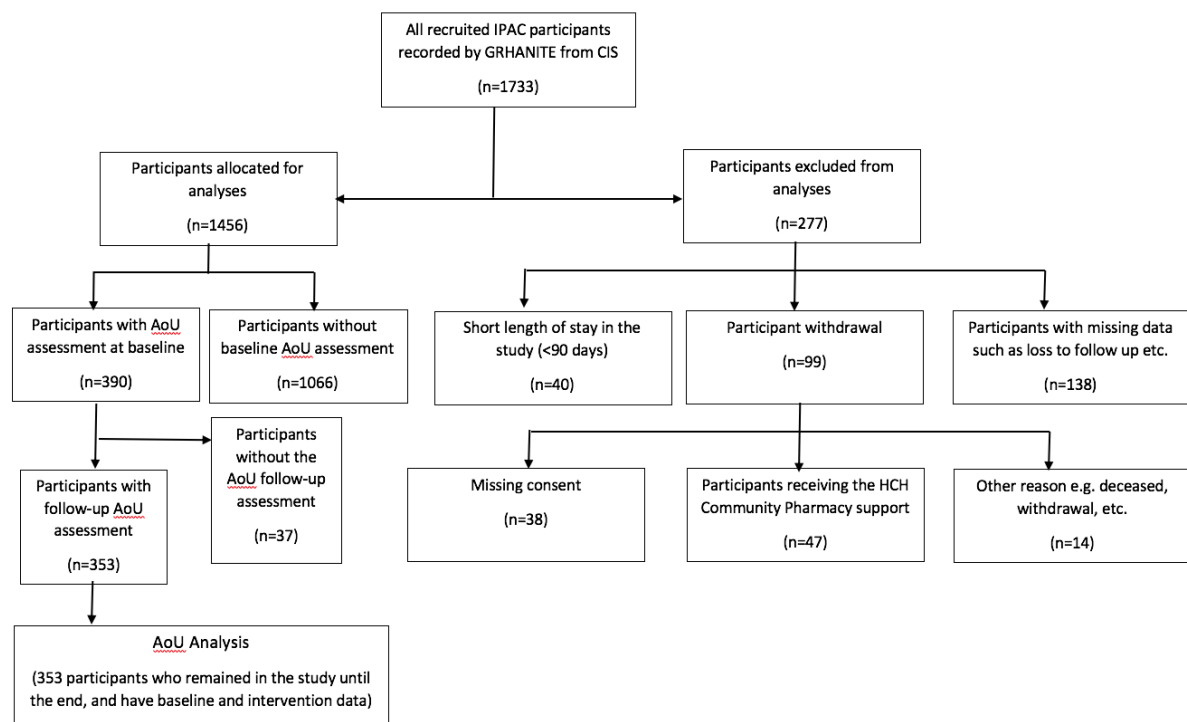
CONCLUSION

Over half of the Aboriginal and Strait Islander patients assessed by pharmacists in this study lacked one or more prescriptions for medicines recommended by CPGs and considered

essential to optimally manage their chronic disease. Following the integration of pharmacists within the primary health care team of ACCHSs, there was a significant (58%) reduction in the number of participants with prescription-based medication underutilisation. Potential prescribing omissions that were averted included: pneumococcal vaccination, BP and/or lipid lowering medication in those clinically at high risk for CVD, ACEI or ARB for participants with T2DM and albuminuria, and metformin for those with T2DM. The magnitude of undertreated patients in each chronic disease group would at a population level, contribute significantly to morbidity that could otherwise be averted through the prescribing quality improvements observed from integrated pharmacist intervention within ACCHSs.

Progress towards *equitable* healthcare resource use should be a health system goal for the Aboriginal and Torres Strait Islander population, meaning that medicines expenditure needs to increase if underuse is to be corrected. In a context where the Aboriginal and Torres Strait Islander population experiences significant medicines underutilisation, the support provided by pharmacists to the health care team when integrated within the ACCHS setting significantly reduced the number of participants with a PPO over a median period of nearly 9 months, compared with their usual care situation at baseline. Reducing PPO's with the support of a pharmacist within primary health care services is one part of a system-wide approach to reducing underuse of high-value health services and inequitable health outcomes¹⁰⁵ for Aboriginal and Torres Strait Islander patients with chronic disease.

Figure 1. Flow diagram for assessment of medication underutilisation (AoU) in the IPAC study



AoU= Assessment of Underutilisation (IPAC method)

CIS= Clinical information systems

GRHANITE= Data extraction tool

HCH= Health Care Homes

HCH Community Pharmacy support= Community Pharmacy in Health Care Homes Trial Program

Baseline = the first AoU after participant enrolment.

Intervention phase= comprised the period from participant enrolment to the end of the study.

End of the study= 31st October 2019.

Table 1. Categories for the assessment of underutilisation of medicines that was used to define a potential prescribing omission (PPO).

Category	Patient	Core Recommendation	Prescribing omission (tick)
A	Patient with high <u>calculated</u> risk (>15%) of CVD	If high risk (calculated>15%) the patient should be prescribed both BP and lipid lowering therapy ¹⁰⁶	<ul style="list-style-type: none"> • Absence of bp-lowering therapy • Absence of lipid-lowering therapy • Absence of both bp-lowering & lipid- lowering therapy • Other
B	A patient in a <u>clinically</u> high-risk (>15%) category for CVD	If high risk (clinically determined) the patient should be prescribed both BP and lipid lowering therapy ¹⁰⁷	<ul style="list-style-type: none"> • Absence of bp-lowering therapy • Absence of lipid-lowering therapy • Absence of both bp-lowering & lipid--lowering therapy • Other
C	A patient with an established diagnosis of cardiovascular disease	The patient should be commenced on low-dose aspirin treatment (75- 150mg) unless contraindicated. Consider alternative antiplatelet agents such as clopidogrel (75 mg) if aspirin hypersensitivity is present. ^{108 109}	<ul style="list-style-type: none"> • Low-dose aspirin (75-150mg) • Clopidogrel (75mg) • Other
D	A patient with Type 2 diabetes and micro- or macro - albuminuria	In people with type 2 diabetes and micro- or macro- albuminuria, an ACEI or ARB should be used to protect against progression of kidney disease ¹¹⁰	<ul style="list-style-type: none"> • ACEI • ARB • Other
E	A patient <u>without</u> diabetes who has CKD and macro-albuminuria	In adults <u>without</u> diabetes who have CKD and macroalbuminuria, advise treatment with an ACEI or ARB regardless of eGFR or BP level. ^{111 112 113}	<ul style="list-style-type: none"> • ACEI • ARB • Other
F	A patient with heart failure with a reduced left ventricular ejection fraction (HFrEF)	An ACE inhibitor or ARB is recommended in all patients with HFrEF unless contraindicated or not tolerated. ¹¹⁴	<ul style="list-style-type: none"> • ACEI • ARB • Other
G	A patient with T2DM who needs metformin	Metformin is the first- choice antihyperglycaemic drug in T2DM. ^{115 116}	<ul style="list-style-type: none"> • Metformin
H	A patient with T2DM who needs a second antihyperglycaemic drug	If glycaemic targets are not met with lifestyle measures and the maximum tolerated dose of metformin, the next step is to add a second antihyperglycaemic drug ¹¹⁷	<ul style="list-style-type: none"> • Sulfonylurea • DPP-4 inhibitor • GLP-1 agonist • Other
I	People for whom 23vPPV vaccine is indicated	Recommend 23vPPV in those aged 15-49 years <u>and</u> all patients >50 years ^{118 119}	<ul style="list-style-type: none"> • >=15-49 years (without chronic disease- as per NT Schedule) • >=15-49 years with chronic cardiac, lung, liver, or other chronic disease • >=15-49 years without chronic disease but is alcohol dependent • >=15-49 years without chronic disease but is a smoker • >=50 years
J	People with Acute Rheumatic Fever (ARF) or Rheumatic Heart Disease (RHD) who still require antibiotic prophylaxis <i>*long term= at least 10 years</i>	Recommend long-term prophylactic antibiotics (either benzathine penicillin every 21-28 days or the less preferred option of daily oral penicillin V) for the prevention of recurrent rheumatic fever attacks ^{120 121}	<ul style="list-style-type: none"> • Benzathine penicillin • Oral penicillin • Other
K	Other prescribing omission		<ul style="list-style-type: none"> • No • Yes

Table 2: Comparison of the IPAC method for medication underuse assessment to other explicit criteria-based methods

Method	Description	Target group	Comparison with IPAC method	Criteria that match IPAC method
IPAC method	Explicit evidence-based recommendations for CVD, T2DM, CKD, ARF/RHD and pneumococcal vaccination; and implicit other omissions.	Aboriginal peoples and Torres Strait Islanders >=18 years with chronic disease	N/A	N/A
Beers criteria ¹²² 123 124	Considered the gold standard for assessing potentially inappropriate prescribing. List of 88 medicines (USA) that pose a potentially higher risk for harm or unnecessary increase in drug-related costs.	>=65 years	IPAC participants were much younger than the population for which Beers criteria were designed; medicines do not reflect the age nor disease burden of the Aboriginal and Torres Strait Islander population; many criteria are irrelevant given Australia's PBS system offers a more controlled scope of prescribing than in the USA. Not developed to specifically assess underuse and may miss the underuse of medications.	Nil.
Assessment of underutilisation (AOU) index ¹²⁵	Developed in the USA. Identifies medications that have been omitted despite being indicated and potentially beneficial. The tool matches the patient's problem list with a list of drugs for each condition. The absence of a drug for a listed condition is considered an omission unless there are documented contraindications or patient preference	Age not specified.	Relies on a USA-based pharmacopeia that is inappropriate in the Aboriginal and Torres Strait Islander context.	N/A
START (Screening Tool to Alert doctors to the Right Treatment) criteria ¹²⁶	Contain 22 indicators of common prescribing omissions developed in the UK and Ireland.	>=65 years	Similar to Beers, recommendations are focused on pharmacotherapy for the elderly, and are not specific to the burden of disease affecting Aboriginal peoples and Torres Strait Islanders.	<ul style="list-style-type: none"> metformin use with T2DM; ACEI or ARB in T2DM with micro or macroalbuminuria; aspirin or clopidogrel in patients with established CVD
RAND/UCLA method ¹²⁷	Adapted to the Australian setting and comprise 41 criteria for medication appropriateness. Includes criteria for medication underuse.	>=65 years	Underuse criteria refer to patients with T2DM (who have both hypertension and albuminuria) and if they are taking an ACEI or ARB. The IPAC method did not require patients with T2DM to be hypertensive, and clinical practice guidelines (CPG) for Aboriginal and Torres Strait Islander patients with T2DM recommend ACEI or ARB therapy if microalbuminuria is also present. The 2008 RAND/UCLA criteria included statin therapy for those at high primary CVD risk but updated this in 2012 for patients only at high-risk of a 'recurrent CVD event' (secondary prevention). Current CPGs include lipid-lowering for those at high primary CVD risk. The RAND/UCLA method excludes medication underuse criteria for CKD, ARF/RHD, or BP lowering in those at high primary CVD risk. The other RAND/UCLA criteria duplicate the MAI method for medication appropriateness and overuse.	<ul style="list-style-type: none"> a patient with coronary heart disease is taking an antiplatelet agent, and an ACEI or ARB; a patient with heart failure and left ventricular systolic dysfunction is taking an ACEI or ARB; and a patient has received influenza and pneumococcal vaccination.

ACEI= Angiotensin-converting enzyme inhibitor; ARB= Angiotensin 2 receptor blocker; ARF= acute rheumatic fever; CKD= chronic kidney disease; CPG= clinical practice guideline; CVD= cardiovascular disease; RHD= rheumatic heart disease; T2DM= Type 2 diabetes mellitus. N/A= not available.

Table 3. Characteristics of participants with the assessment of medication underutilisation (AoU) at baseline.

Patient characteristics	AoU patients (n=353)
Location classification by ASGS-RA (2016)	
Major city (RA1)	17 /353 (4.8%)
Inner regional (RA2)	91 /353 (25.8%)
Outer regional (RA3)	133 /353 (37.7%)
Remote (RA4)	53 /353 (15.0%)
Very remote (RA5)	59 /353 (16.7%)
Mean age at baseline (SD) [years]	n=352 57.2 (15.4)
Sex (n,%)	
Male	150 /352 (42.6%)
Female	202 /352 (57.4%)
Ethnicity (n,%)	
Aboriginal and/or Torres Strait Islander	328 /352 (93.2%)
Non-Indigenous	24 /352 (6.8%)
Mean body mass index (BMI; kg/m²) (SD)	n=309 31.8 (11.6)
BMI<25 kg/m² (n,%)	60/309 (19.4%)
Pensioner/concessional (n, %)	290 /352 (82.4%)
CTG scripts eligible (n,%)	264 /352 (75.0%)
Engaged in Health Care Home (HCH) program (n, %) ^a	38 /353 (10.8%)
Number of medications per participant^{# b}	n=279
Mean (SD)	7.21 (8.0)
Median (IQR)	7 (5-9)
Prior medication review (MBS item 900) (n,%) ^c	39 /353 (11.1%)
Doctors' encounters prior to enrolment (per 12 months) (SD or IQR) ^d	n=331
Mean (SD)	8.60 (8.4)
Median (IQR)	7 (4-11)
Mean number of medication 'adherent days' (SD) ^e	n=279 6.01 (4.0)
Self-assessed health status (SF1) (n,%) ^{# f}	
Excellent	11 /243 (4.5%)
Very good	33 /243 (13.6%)
Good	104 /243 (42.5%)
Fair	63 /243 (25.9%)
Poor	29 /243 (11.9%)
Very poor	3 /243 (1.2%)

Recorded clinical diagnoses (n,%): #	
Diabetes mellitus	
Type 1	1 /353 (0.3%)
Type 2	220 /353 (62.3%)
Hypertension	218 /353 (61.8%)
Dyslipidaemia	189 /353 (53.5%)
Established or existing CVD [^]	116/353 (32.9%)
Coronary heart disease	99/353 (28.1%)
Peripheral vascular disease	11/353 (3.1%)
Cerebrovascular disease (stroke)	13/353 (3.7%)
Chronic kidney disease	124/353 (35.1%)
Rheumatic heart disease (RHD) or acute rheumatic fever (ARF)	8/353 (2.3%)
Chronic obstructive pulmonary disease (COPD)	32/353 (9.1%)
Depressive disorder	21/353 (6.0%)
Mean BP >= 140/90* [mmHg] (n,%)	21/263 (8.0%)
Dyslipidaemia ^g (n,%)*	228/257 (88.7%)
Comorbidity (1 or more chronic diseases) #	309/353 (87.5%)
Multi-morbidity (2 or more chronic diseases) #	269/353 (76.2%)
Number of chronic diseases:	n=353
Mean (SD)	2.24 (2.3)
Median (IQR)**	2 (2-3)
Biomedical parameters (n,%): ##	
Type 2 with HbA1c >8% or >65mmol/mol	76/165 (46.6%)
Type 2 with HbA1c >7% or >54 mmol/mol	106/165 (64.2%)
Albuminuria ^h	102/167 (61.1%)
eGFR (and CKD stage) ⁱ (n,%):	
eGFR ≥90 (Stage 1)	43 /274 (15.7%)
eGFR ≥60<90 (Stage 2)	92 /274 (33.6%)
eGFR ≥45<60 (Stage 3a)	30 /274 (11.0%)
eGFR ≥30<45 (Stage 3b)	14 /274 (5.1%)
eGFR ≥15<30 (Stage 4)	15 /274 (5.5%)
eGFR <15 (Stage 5)	80 /274 (29.2%)

BMI= body mass index; BP= blood pressure; CKD= chronic kidney disease. CTG= Close the Gap prescriptions (for Aboriginal peoples and Torres Strait Islanders) to waive or reduce the Pharmaceutical Benefits Scheme (PBS) patient contribution (co-payment). CVD= cardiovascular disease. MBS= Medicare Benefits Schedule.

SD = standard deviation (cluster adjusted);

IQR = inter-quartile range

*Refers to the mean of variables measured in the 12 months prior to patient enrolment into the study.

Sourced from the pharmacist's logbook.

Biomedical results were sourced from GRHANITE

[^] CVD= cardiovascular disease: It refers to any of the following: coronary heart disease, cerebrovascular disease, and peripheral vascular disease.

^a The Health Care Homes program was funded by the Australian Government to better coordinate the health care of patients with chronic disease and was only relevant to NT situated IPAC services. The HCH program was distinct from the *Community Pharmacy in Health Care Homes (HCH) Trial* program. All participants in this latter program were removed from the analysis.

^b Prior MBS claim was measured for the 12-month period prior to participant enrolment.

^c Denominator sourced from logbook data entered by pharmacists when reporting medication adherence, to source comparative data on non-MAI participants.

^d Medicare GP consultation claim items: vocational registration: 3, 23, 36, 44. Non-vocational registration: 52, 53, 54, 57.

^e A self-reported single-item question ('How many days in the last week have you taken this medication?') exploring the extent of non-adherence, assessed as a mean score for all medications. An 'adherent day' was defined as not missing any doses of prescribed medicines on that day. Pharmacists recorded the number of adherent days for each medication the patient was taking.

^f Derived from the first question of the Short Form (SF)-36 health related quality of life instrument that asks: '*In general, would you say your health is excellent, very good, good, fair, poor, or very poor?*'

^g Dyslipidaemia = Dyslipidaemia is defined by one or more of the following: Low Density Lipoprotein (LDL) ≥ 3.5 mmol/L; Total cholesterol (TC) ≥ 5.5 mmol/L; Triglycerides (TG) ≥ 2.0 mmol/L; High density lipoprotein (HDL) < 1.0 mmol/L for men and < 1.3 mmol/L for women. Data was sourced from GRHANITE information.

^h Albumin:creatinine ratio > 2.5 mg/mmol for males and > 3.5 mg/mmol for females. Data was sourced from GRHANITE information.

ⁱ Estimated glomerular filtration rate (eGFR). eGFR reference range: Normal or Stage 1: CKD > 89 , Stage 2: 60-89 Stage 3A: 45-59, Stage 3B: 30-44, Stage 4: 15-29, Stage 5: < 15 . (Units in ml/min/1.73m²). Data was sourced from GRHANITE information.

Table 4. Potential prescribing omissions (PPOs) for participants who had medication underuse assessed at both baseline (first assessment after enrolment) and at follow-up (end of the study) assessment (N=353).

Outcome measures for medication underuse	Baseline	Follow-up	p-value
Time from participant enrolment to baseline AOU			
Mean time (days), (SD)	24.4 (112.5)	-	-
Range (days)	0-189	-	-
Median time (days), (IQR)	2 (0-35)	-	-
Number of participants with AOU assessed >100 days since enrolment, N (%)	26 (7.4%)	-	-
Time from baseline AOU to end of study AOU			
Mean time (days), (SD)	-	266.7 (286.9)	-
Range (days)	-	61-446	-
Median time (days), (IQR)	-	266 (217-315)	-
Number of participants with AOU assessed >100 days since baseline assessment, N (%)	-	352 (99.7%)	-
Number of participants with at least one PPO (positively assessed)*			
	181/353 (51.3%)	76/353 (21.5%)	<0.001~
Number of participants with this number of PPOs:			
None	172/353 (48.7%)	277/353 (78.5%)	<0.001~
One	130/353 (36.8%)	59/353 (16.7%)	
Two	42/353 (11.9%)	13/353 (3.7%)	
Three	7/353 (2.0%)	4/353 (1.1%)	
Four	2/353 (0.6%)	0/353 (0%)	
Total number of PPOs	256	103	
Mean number of PPOs per participant (SD)	0.73 (1.3)	0.29 (0.9)	<0.001^
Mean number of PPOs per positively assessed participant* (SD)	1.41 (1.3)	1.36 (1.5)	0.789#

SD= standard deviation (cluster-adjusted). Bold p-value implies statistically significant change at the 0.05 level.

~ Cluster adjusted p-value (ACCHS cluster) determined using the . svy linearized : clogit Stata command (paired data).

^P-values (paired data) were derived from the cluster-adjusted confidence interval (ACCHS cluster) as this is equivalent to a paired t-test.

Cluster adjusted p-value (ACCHS cluster) determined using the . svy linearized : logit Stata command (unpaired data).

*A participant with at least one PPO has been expressed as a positively assessed participant.

PPO= potential prescribing omission

AOU= assessment of underutilisation

IQR= interquartile range.

Table 5: Description of potential prescribing omissions (PPOs) as identified in categories A to K at baseline (first assessment after enrolment) and at follow-up assessment (end of the study) for participants who had an assessment of underutilization (AOU) of medications and who remained in study till the end (n=353).

Underuse category	Clinical criteria	Type of PPO	Number of PPO types at baseline (%)	Number of PPO types at follow-up (%)	Number of individual PPO's at baseline (%)	Number of individual PPO's at follow-up (%)	Number of patients with PPO at baseline (%)	Number of patients with PPO at follow-up (%)	P-value
A	Patient with high calculated risk (>15%) of CVD								
		Absence of bp-lowering therapy	3 /246 (1.2%)	4 /97 (4.1%)	3 /256 (1.2%)	4 /103 (3.9%)			
		Absence of lipid-lowering therapy	14 /246 (5.7%)	10 /97 (10.3%)	14 /256 (5.5%)	10 /103 (9.7%)			
		Absence of both bp-lowering & lipid- lowering therapy	0 /246 (0%)	2 /97 (2.1%)	0 /256 (0%)	4 /103 (3.9%)			
		Subtotal	17 /246 (6.9%)	16 /97 (16.5%)	17 /256 (6.6%)	18 /103 (17.5%)	17/353 (4.8%)	16/353 (4.5%)	0.850
B	A patient in a clinically high- risk (>15%) category for CVD								
		Absence of bp-lowering therapy	10 /246 (4.1%)	3 /97 (3.1%)	10 /256 (3.9%)	3 /103 (2.9%)			
		Absence of lipid-lowering therapy	11 /246 (4.5%)	5 /97 (5.2%)	11 /256 (4.3%)	5 /103 (4.9%)			
		Absence of both bp-lowering & lipid- lowering therapy	10 /246 (4.1%)	4 /97 (4.1%)	20 /256 (7.8%)	8 /103 (7.8%)			
		Subtotal	31 /246 (12.6%)	12 /97 (12.4%)	41 /256 (16.0%)	16 /103 (15.5%)	31/353 (8.8%)	12/353 (3.4%)	0.002
C	A patient with an established diagnosis of CVD								
		Low-dose aspirin (75-150mg)	9 /246 (3.7%)	2 /97 (2.1%)	9 /256 (3.5%)	2 /103 (1.9%)			
		Clopidogrel (75mg)	0 /246 (0%)	0 /97 (0%)	0 /256 (0%)	0 /103 (0%)			

Underuse category	Clinical criteria	Type of PPO	Number of PPO types at baseline (%)	Number of PPO types at follow-up (%)	Number of individual PPO's at baseline (%)	Number of individual PPO's at follow-up (%)	Number of patients with PPO at baseline (%)	Number of patients with PPO at follow-up (%)	P-value
		Subtotal	9 /246 (3.7%)	2 /97 (2.1%)	9 /256 (3.5%)	2 /103 (1.9%)	9 /353 (2.6%)	2 /353 (0.6%)	0.052
D*	A patient with Type 2 diabetes and micro- or macro - albuminuria								
		ACEI	28 /246 (11.4%)	13 /97 (13.4%)	28 /256 (10.9%)	13 /103 (12.6%)			
		ARB	2 /246 (0.8%)	0 /97 (0%)	2 /256 (0.8%)	0 /103 (0%)			
		Subtotal	30 /246 (12.2%)	13 /97 (13.4%)	30 /256 (11.7%)	13 /103 (12.6%)	30/353 (8.5%)	13/353 (3.7%)	0.005
E*	A patient without diabetes who has CKD and macro-albuminuria								
		ACEI	4 /246 (1.6%)	3 /97 (3.1%)	4 /256 (1.6%)	3 /103 (2.9%)			
		ARB	2 /246 (0.81%)	0 /97 (0%)	2 /256 (0.8%)	0 /103 (0%)			
		Subtotal	6 /246 (2.4%)	3 /97 (3.1%)	6 /256 (2.3%)	3 /103 (2.9%)	6 /353 (1.7%)	3 /353 (0.9%)	0.330
F	A patient with heart failure with a reduced left ventricular ejection fraction								
		ACEI	3 /246 (1.2%)	2 /97 (2.1%)	3 /256 (1.2%)	2 /103 (1.9%)			
		ARB	0 /246 (0%)	0 /97 (0%)	0 /256 (0%)	0 /103 (0%)			
		Subtotal	3 /246 (1.2%)	2 /97 (2.1%)	3 /256 (1.2%)	2 /103 (1.9%)	3 /353 (0.9%)	2 /353 (0.6%)	0.570
G	A patient with T2DM who needs metformin								
		metformin	17 /246 (6.9%)	5 /97 (5.2%)	17 /256 (6.6%)	5 /103 (4.9%)			
		Subtotal	17 /246 (6.9%)	5 /97 (5.2%)	17 /256 (6.6%)	5 /103 (4.9%)	17/353 (4.8%)	5 /353 (1.4%)	0.012

Underuse category	Clinical criteria	Type of PPO	Number of PPO types at baseline (%)	Number of PPO types at follow-up (%)	Number of individual PPO's at baseline (%)	Number of individual PPO's at follow-up (%)	Number of patients with PPO at baseline (%)	Number of patients with PPO at follow-up (%)	P-value
H	A patient with T2DM who needs a second antihyperglycaemic drug								
		Sulfonylurea	1 /246 (0.4%)	1 /97 (1.0%)	1 /256 (0.4%)	1 /103 (1.0%)			
		DPP-4 inhibitor	4 /246 (1.6%)	4 /97 (4.1%)	4 /256 (1.6%)	4 /103 (3.9%)			
		GLP-1 agonist	0 /246 (0%)	0 /97 (0%)	0 /256 (0%)	0 /103 (0%)			
		Subtotal	5 /246 (2.0%)	5 /97 (5.2%)	5 /256 (2.0%)	5 /103 (4.9%)	5 /353 (1.4%)	5 /353 (1.4%)	>0.999
I	People for whom 23vPPV vaccine is indicated								
		>=15-49 years (without chronic disease- as per NT Schedule)	2 /246 (0.8%)	1 /97 (1.0%)	2 /256 (0.8%)	1 /103 (1.0%)			
		>=15-49 years with chronic cardiac, lung, liver, or other chronic disease	18 /246 (7.3%)	3 /97 (3.1%)	18 /256 (7.0%)	3 /103 (2.9%)			
		>=15-49 years without chronic disease but is alcohol dependent	0 /246 (0%)	0 /97 (0%)	0 /256 (0%)	0 /103 (0%)			
		>=15-49 years without chronic disease but is a smoker	5 /246 (2.03%)	0 /97 (0%)	5 /256 (2.0%)	0 /103 (0%)			
		>=50 years	34 /246 (13.8%)	11 /97 (11.3%)	34 /256 (13.3%)	11 /103 (10.7%)			
		Subtotal	59 /246 (24.0%)	15 /97 (15.5%)	59 /256 (23.1%)	15 /103 (14.6%)	59 /353 (16.7%)	15 /353 (4.3%)	<0.001
J	People with Acute Rheumatic Fever (ARF) or Rheumatic Heart Disease (RHD) who still require antibiotic prophylaxis								

Underuse category	Clinical criteria	Type of PPO	Number of PPO types at baseline (%)	Number of PPO types at follow-up (%)	Number of individual PPO's at baseline (%)	Number of individual PPO's at follow-up (%)	Number of patients with PPO at baseline (%)	Number of patients with PPO at follow-up (%)	P-value
		Benzathine penicillin	0 /246 (0%)	0 /97 (0%)	0 /256 (0%)	0 /103 (0%)			
		Oral penicillin	0 /246 (0%)	0 /97 (0%)	0 /256 (0%)	0 /103 (0%)			
		Subtotal	0 /246 (0%)	0 /97 (0%)	0 /256 (0%)	0 /103 (0%)	0 /357(0%)	0 /353 (0%)	-
K	Other								
		Other	69 /246 (28.1%)	24 /97 (24.7%)	69 /256 (27.0%)	24 /103 (23.3%)			
		Subtotal	69 /246 (28.1%)	24 /97 (24.7%)	69 /256 (27.0%)	24 /103 (23.3%)	65/353 (18.4%)	24/353 (6.8%)	<0.001
		TOTAL	246 /246 (100%)	97 /97 (100%)	256 /256 (100%)	103 /103 (100%)	181/353** (51.3%)	76/353** (21.5%)	<0.001

Bold p-value implies statistically significant change at the 0.05 level. P-value is cluster adjusted (ACCHS cluster) determined using the . svy linearized : clogit Stata command (paired data).

PPO= potential prescribing omission; ACEI= Angiotensin-converting enzyme inhibitor; ARB= Angiotensin 2 receptor blocker; ARF= acute rheumatic fever; CKD= chronic kidney disease; CVD= cardiovascular disease; RHD= rheumatic heart disease; T2DM= Type 2 diabetes mellitus.

*Category D and E pertain to participants with or without existing cardiovascular disease.

**The total number of patients exceeds the total number with at least one PPO, as each patient may have had a PPO in one or more categories.

Table 6: MAI subset- Type of 'other' potential prescribing omissions identified by IPAC pharmacists from Medication Appropriateness Index assessments (n=69, Cat K PPOs, from 353 patients assessed for a PPO)

'Other' PPOs	Condition
Anticoagulant or anti-platelet	stroke, atrial fibrillation
antiemetic	dyspepsia
antihypertensive	uncontrolled hypertension
antipsychotic	psychosis
antiviral	hepatitis B
beta blocker	Ischaemic heart disease
biphosphonate, calcium, denosumab, etc	osteoporosis
bronchodilator, anti-inflammatory	asthma; COPD
glycerol trinitrate	angina
insulin, other oral hypoglycaemic	T2DM
iron supplement	anaemia
laxatives	iatrogenic constipation
lipid lowering	dyslipidaemia
pain reliever	chronic pain
urate lowering, anti-inflammatory	gout
vaccine	zoster, influenza
vitamin D	vitamin D deficiency

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