

# **Integrated pharmacists in ACCHSs- Analysis of the assessment of clinical endpoints in Aboriginal and Torres Strait Islander patients with chronic disease (IPAC Project)**

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

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

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## ABSTRACT

### Objective

To assess the effect of integrated pharmacist interventions on intermediate clinical endpoints in Aboriginal and Torres Strait Islander adults with chronic disease attending Aboriginal Community Controlled Health Services (ACCHSs) compared with usual care (pre-intervention).

### Design and participants

The study was a non-randomised, prospective, pre and post quasi-experimental community-based, participatory, and pragmatic trial that integrated a registered pharmacist within an ACCHS located in Queensland, the Northern Territory or Victoria. The intervention comprised non-dispensing medicines-related services, collaborative and coordinated care, including the provision of medication management reviews. Participants were usual patients of the ACCHSs aged 18 years or older with a chronic disease. Participants consented to receive the intervention and were followed for up to 15 months.

### Outcome measures

De-identified participant data was electronically extracted from health records. Biomedical outcome measures comprised HbA1c in participants with Type 2 diabetes mellitus (T2DM), and systolic and diastolic blood pressure (SBP and DBP), total cholesterol (TC), low density lipoprotein cholesterol (LDL-C), high-density lipoprotein cholesterol (HDL-C), triglycerides (TG), estimated glomerular filtration rate (e-GFR), albumin-creatinine ratio (ACR), and absolute primary cardiovascular disease risk (CVD risk) for all participants.

### Statistical analysis

The following differences were calculated for paired measurements: (1) for HbA1c and ACR: the differences between the most recent observation in the 12 months prior to enrolment and the final observation during follow-up; (2) for SBP, DBP, TC, LDL-C, HDL-C, TG, ACR: the differences in the mean baseline values (12-month pre-intervention period representing usual care) from the mean follow-up value; (3) for e-GFR: mean annualised e-GFR difference as the most recent e-GFR value 12 months pre-enrolment and at end of study divided by follow-up time between assessments; (4) and for the absolute CVD 5-year risk according to the Framingham risk equation for those not at high risk according to clinical criteria: the difference between assessment at enrolment and at the end of the study.

Differences for all outcome measures except for e-GFR were statistically compared against zero using cluster-adjusted (ACCHS) regression analyses techniques. For e-GFR, annualised differences were statistically compared against  $-3 \text{ (ml/min/1.73 m}^2\text{)}$  a theoretically assumed value, using cluster-adjusted (ACCHS) regression analyses techniques. The effects of participant, health service, and intervention characteristics on differences of outcome measures were examined, including the influence of Home Medicines Review and other comprehensive reviews, using cluster (ACCHS) and length of follow-up time adjusted regression analyses.

### Results

Participants ( $n=1,456$ ) from 18 ACCHSs involving 26 integrated pharmacists were followed-up for a median of 285 (IQR: 219-352) days. At baseline, the mean age of participants within clinical endpoint groups defined by the availability of outcome measures stated above, ranged from 57- 58 years, and most (91-94%) were Aboriginal and/or Torres Strait Islander, 65 to 76% attended health services located in inner and outer regional locations, 59% to 75.4% had T2DM, and 87.5% to 90.2% had co-morbidity. Of the participants with data available for analysis, mean baseline HbA1c was 8.3% ( $n=539$ ), mean SBP was 133 ( $n=1,103$ ) with mean DBP of 80 mmHg ( $n=1,045$ ), dyslipidaemia only pertained to elevated mean triglycerides (2.39 mmol/L,  $n=730$ ), mean eGFR was consistent with Stage 3A of CKD ( $49.1 \text{ ml/min/1.73 m}^2$ ,  $n=895$ ), mean ACR levels were consistent with overt albuminuria ( $57.9 \text{ mg/mmol}$ ,  $n=475$ ), mean BMI was 32.4 ( $n=991$ ), with moderate CVD risk (10% to <15%,  $n=38$ ).

There was a significant improvement in HbA1c in participants with T2DM, with a 2.8 mmol/mol or 0.3% (unit) reduction ( $p=0.001$ , 95% CI  $-0.4\%$  to  $-0.1\%$ ). Significant reductions in diastolic BP ( $-0.8 \text{ mmHg}$ ,  $p=0.008$ ), total cholesterol ( $-0.15 \text{ mmol/L}$ ,  $p<0.001$ ), LDL-C ( $-0.08 \text{ mmol/L}$ ,  $p=0.001$ ), and triglyceride levels ( $-0.11 \text{ mmol/L}$ ,  $p=0.006$ ) were observed for the entire participant collective. The mean calculated absolute 5-year CVD risk was significantly reduced by 1% (95% CI:  $-1.8\%$  to  $-0.12\%$ ,  $p=0.027$ ). The mean annual eGFR significantly improved with an increase of  $1.9 \text{ mL/min/1.73 m}^2$  (95% CI: 0.1 to 3.7) from baseline ( $p<0.001$ ). When participants with less than 6-months of follow-up were excluded, the mean annual eGFR decline was  $-0.2 \text{ ml/min/1.73 m}^2$  (95% CI:  $-2.99$  to  $2.7$ ), significantly less than the predicted decline of  $-3$  ( $p=0.034$ ,  $n=720$ ). SBP significantly improved only for younger participants ( $<57$  years,  $-1.8 \text{ mmHg}$ , SD: 12.5,  $p=0.004$ ). There were no net improvements in HDL-C. ACR stabilised with a mean difference of  $3.8 \text{ mg/mmol}$  (95%CI:  $-6.3$  to  $13.8$ ,

p=0.42). No differential impact on clinical endpoints was identified by the type of medication management review ( $p>0.05$ ).

**Conclusion**

Integrated pharmacists embedded into usual care in a range of geographical settings, can significantly improve the control of CVD risk factors, glycaemic control in patients with T2DM, and reduce absolute CVD risk in Aboriginal and Torres Strait islander adults with chronic disease. This evaluation supports the integration of non-dispensing pharmacists within ACCHS settings more broadly.

Confidential

## 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).<sup>1</sup> 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, and inappropriate use of medications by Aboriginal peoples and Torres Strait Islanders persists when assessed within primary health care settings.<sup>2 3</sup> There are many reasons for this including health system factors such as poorer access to primary health care services,<sup>4</sup> culturally unsafe pharmaceutical support,<sup>5</sup> lack of health service integration,<sup>6</sup> disease profiles inconsistent with medicines listed on the PBS,<sup>7</sup> and suboptimal prescribing quality.<sup>8</sup> Patient factors include insufficient health literacy for optimal self-management of disease,<sup>9</sup> distrust of health services,<sup>10</sup> family and community obligations,<sup>11</sup> and belief in traditional medicines,<sup>12</sup> whilst condition-related factors include disproportionately high multimorbidity.<sup>13</sup> Socioeconomic factors may also affect the personal management of medicines such as adherence and storage.<sup>14</sup>

A whole of health system response is needed to tackle these factors. One strategy has been to integrate pharmacists within primary health care multidisciplinary teams so that patients and teams can receive better medication management support, direct care from a pharmacist, and a more joined-up experience of care. This strategy is intended to complement and extend the services provided as usual care by community pharmacists'. Increasingly, studies are reporting that the addition of pharmacists to healthcare teams enhances quality prescribing,<sup>15</sup> biomedical outcomes,<sup>16 17</sup> and reduces hospitalisation.<sup>18 19</sup> Co-location of pharmacists within general practice appears to enable greater communication, collaboration and relationship building among health professionals.<sup>20</sup> However, the impact of integrated pharmacists on health outcomes for patients with chronic disease has never been evaluated in Aboriginal health settings.

The Australian Government Department of Health, under the Pharmacy Trials Program (PTP, Tranche 2) funding as part of the Sixth Community Pharmacy Agreement (6CPA) sought to improve clinical outcomes for patients utilizing the full scope of pharmacist's role in

delivering primary health care services. This Program supported a project 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. The project explored if integrating a registered pharmacist as part of the primary health care (PHC) team within ACCHSs (the intervention) led to improvements in the quality of the care received by Aboriginal and Torres Strait Islander peoples with chronic diseases, when compared with prior (usual) care. Integration within ACCHSs meant that pharmacists had identified positions and core roles, shared access to clinical information systems, provided continuous clinical care to patients, received administrative and other supports from primary health care staff, and adhered to the governance, cultural, and clinical protocols within ACCHSs as part of their shared vision.

If pharmacists can influence prescribing quality within these settings, improvements in participant biomedical outcomes such as a reduction in HbA1c (in patients with diabetes), blood pressure, lipids, albumin- creatinine ratio, and absolute primary cardiovascular risk, may be evident over time. Reductions in these clinical endpoints are proxy or intermediate outcome measures in lieu of distal outcomes such as CVD events. For example, 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.<sup>21</sup> Reduction in HbA1c in patients with T2DM can significantly reduce diabetes-related complications such as deaths related to diabetes, myocardial infarction, and microvascular complications.<sup>22</sup> Lipid lowering (as measured with serum cholesterol) using statin therapy over 5 years reduces the risk of major CVD events such as coronary deaths, non-fatal myocardial infarction, coronary revascularisation, or stroke by 20%.<sup>23</sup> The development of end stage kidney disease (ESKD) can also be slowed if albuminuria is reduced by 30% such as from anti-hypertensive therapy.<sup>24</sup>

Improvements in intermediate clinical endpoints may result from improved patient access to medication management reviews as pharmacists providing this service can detect and resolve errors in prescribing, medication omissions, inappropriate medication choices, and adverse drug reactions and interactions.<sup>25</sup> If pharmacists support patients to better address

all the World Health Organisation (WHO) dimensions of medication adherence,<sup>26</sup> this may play a significant role in improving patient outcomes as ‘drugs don’t work in patients who don’t take them’.<sup>27</sup> Consistent with the chronic disease care model,<sup>28</sup> these influences may be more efficiently mobilised if pharmacists participate in chronic disease management plan development other team-care arrangements initiated by general practitioners and undertake active patient follow-up. Improved communication between integrated pharmacists and community pharmacy, as well as with tertiary care providers (such as hospitals when patients are discharged), may also facilitate improvements in biomedical outcomes as medication-related errors in the transition points of care are reduced.<sup>29</sup> [See *Supplementary file- IPAC Theory of change*]

The IPAC project commenced in 2018 and involved ACCHS as they deliver comprehensive primary health care to predominantly Aboriginal peoples and Torres Strait Islanders, and consequently do much more than just cure illness.<sup>30 31</sup> Primary clinical endpoints for the study were changes in HbA1c levels in those with T2DM, and changes in systolic and diastolic blood pressure (SBP and DBP), total cholesterol (TC), low density lipoprotein cholesterol (LDL-C), high-density lipoprotein cholesterol (HDL-C), triglycerides (TG), albumin-creatinine ratio (ACR), and absolute primary cardiovascular disease risk (CVD risk). Secondary clinical endpoints with regard to biomedical measures were changes in annualized estimated glomerular filtration rate (e-GFR).

This report describes the clinical endpoint outcomes for participants enrolled in the IPAC trial. Other secondary endpoints included prescribing indices (appropriateness, overuse and underuse), medication adherence, patient self-assessed health status, and health service utilisation indices, but these outcomes are reported elsewhere.<sup>32 33 34 35</sup>

## **METHOD**

### **Study Design**

The IPAC project was a pragmatic, community-based, participatory, non-randomised, prospective, pre and post quasi-experimental study (Trial Registration Number and Register: ACTRN12618002002268) that integrated a registered pharmacist within the ACCHS primary healthcare team for up to a 15-month period. A total of 26 registered pharmacists were

recruited and appointed within ACCHSs to deliver 12.5 full-time equivalent pharmacist services for the duration of the study within ACCHS services (n=18). These ACCHSs were recruited for the project across three jurisdictions: Victoria, Queensland and the Northern Territory (NT), and comprised 34% (18/53) of all ACCHSs in these jurisdictions.

The IPAC project methodology has been described in detail elsewhere,<sup>36</sup> with health services characteristics also summarized in a separate report.<sup>37</sup> Briefly, IPAC pharmacists delivered non-dispensing clinical medication-related services within ACCHSs through a coordinated, collaborative and integrated approach to improve the quality of care of patients (the intervention). The intervention phase of the IPAC study comprised the period from participant enrolment to the end of the study (31<sup>st</sup> October 2019).

### **Study participants**

Patients were eligible to participate in the study if they 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). Patients attending ACCHSs for their usual care who met the study inclusion criteria were recruited as participants by health service staff and pharmacists. A non-probabilistic sampling method was adopted to reflect the pragmatic study design where all patients who had relevant chronic disease conditions were invited to participate without setting criteria for study compliance or other restrictions.<sup>38</sup> Patients were consented into the study by pharmacists or other health service staff according to the cultural protocols of the ACCHS,<sup>39</sup> after which pharmacists provided supportive clinical care as part of the primary healthcare team to meet the individual needs of the participant. All participating health service sites included participant access to a GP. The decision to provide a medication review to a participant was based on usual clinical criteria consistent with MBS rules, and was a decision made by the GP, with or without consultation with the integrated pharmacist.

### **Study sites**



The majority of services (n=13 of 18) were located in outer regional and remote locations of Australia, and in regions of relative greater disadvantage for Indigenous Australians than other locations based on the Indigenous Relative Socioeconomic Outcomes (IRSEO) index.<sup>40</sup> Participating ACCHS sites were similar to other ACCHSs in their jurisdiction according to geographic location, and proportionate patient distribution by sex and Aboriginality [data not shown]. However, to minimize the risk of unreliable or missing data, only ACCHSs that had participated in continuing quality improvement activity for at least 24 months prior to enrolment were eligible for study inclusion.

In order to identify if incidental changes to health service systems during the intervention confounded the interpretation of study outcomes, additional health service information was sourced directly from each site through a 'health systems assessment' survey completed by two NACCHO project officers each visiting individual sites. Information was collected on service and client population size, number of episodes of care (annualised number of client contacts with the service, where all contacts with the same client on the same day are counted as one episode), number and types of staff, access to on-site specialist and allied health services, engagement with and the support received from community pharmacy, and systems for clinical management and chronic disease care.

By the end of the study, the vast majority of the broad health service level factors explored had not changed, as reported elsewhere.<sup>41</sup> Six ACCHSs were eligible for remote area support from community pharmacy through the Section 100 Pharmacy Support program that supports the quality assurance of medications dispensed from remote area Aboriginal health services.<sup>42</sup> This program did not usually require pharmacists to provide individual patient medication management services. Remote area support continued in these services during the intervention phase of the study. Five ACCHS sites also participated in the Health Care Homes (HCH) program funded by the Australian Government and designed to better coordinate the health care of patients with chronic disease,<sup>43</sup> with all located in the NT and predominantly in remote locations.

### **Integrated pharmacist interventions**

As a pragmatic trial, pharmacists functioned within existing and usual primary health care service delivery systems and were trained to deliver ten core roles during the intervention

phase. Pharmacists provided medication management reviews (to resolve identified medication -related problems and optimise prescribing quality), assessed adherence and medication appropriateness, provided medicines information and education and training, collaborated with healthcare teams, delivered preventive care, liaised with stakeholders such as community pharmacy, provided transitional care, and undertook a drug utilisation review to support quality improvement within the ACCHS. Their intervention targeted both consented patients (participants) and practices, with practice-specific activities directed to health professionals and systems within the service. Two types of medication management reviews were offered to participants– a Home Medicines Review (HMR, also known as Medicare item 900), and a non-HMR defined as a comprehensive medication management review comprising some or all the elements of a HMR, but not fulfilling all relevant MBS HMR criteria. Pharmacists also scheduled patient follow-up assessments 3-6 months after the completion of a medication management review to reinforce advice, monitor the impact of any changes made, and determine if additional supports were needed. As there was no MBS rebate for these follow-up pharmacist services, pharmacists may have also supported practice nurses and Aboriginal and Torres Strait Islander Health Practitioners to undertake an MBS rebated follow-up of participants for a health assessment or a chronic disease care plan that included a medication adherence check (rebated as items 10987 and 10997).<sup>44</sup> This follow-up service was consistent with usual practice within each ACCHS, but could be enhanced by integrated pharmacists.

Pharmacists had the flexibility to apply their core roles to meet participant and ACCHS needs, matching their activity with the existing service and staff infrastructure in a full range of clinical settings. Participants were not charged a fee for any of the services they received from the integrated pharmacist.<sup>45</sup>

As reported elsewhere, pharmacists completed a total of 639 HMRs and 757 non-HMRs during the period participants were enrolled, as well as 1,548 other follow-up assessments to either a HMR or non-HMR. Medicines information to health staff was provided on 1,715 occasions, with 358 occasions of formal education and training services such as workshops and the provision of written resources to both patients and health professionals.<sup>46</sup> There were 47 completed stakeholder liaison plans and 3,233 separate contacts with community

pharmacy. Transitional care support was provided on 1,901 occasions and predominantly involved community pharmacy, hospitals, and renal units in order to support medicines reconciliation (such as with patient discharge from hospital), dose administration aid supply, and dispensing of medicines. The number of team-based collaboration activities that were logged was 3,165 (predominantly involving general practitioners (GP), nurses and Aboriginal Health Practitioners), and 26 drug utilization reviews were completed.<sup>47</sup>

### **Pharmacists**

The Pharmaceutical Society of Australia (PSA) recruited pharmacists to be integrated within ACCHSs, in partnership with the National Aboriginal Community Controlled Health Organization (NACCHO). 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. Accreditation to conduct an HMR was preferred, however it was not mandatory. These criteria enabled the selection of pharmacists with skills aligned to the expected scope of practice for this project.

All pharmacists had access to participants electronic medical records held at the ACCHS to function as a member of the health care team. 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 correspondence from specialist clinicians, discussion with the individual patient or other clinical staff, and by liaising with community pharmacy.

### **Data collection**

De-identified participant data was collected from two existing clinical information systems (CIS) used by ACCHSs (Best Practice and Communicare) to manage patients' electronic health records and a bespoke online database (pharmacist logbook) to record information about pharmacist activity. Demographic, biomedical, and health service utilization indices were extracted from CISs in de-identified form using an electronic tool called GRHANITE. This tool required remote installation and regular extraction from IPAC sites for the term of the project.<sup>48</sup> Participant consent was recorded in the CIS by pharmacists. GRHANITE

extracted data only from 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). Definitions ensured the fit-for-purpose collection of clinical endpoint measures and MBS-related measures such as participant MBS 900 claims pre-enrolment. All ACCHSs consented to the installation of GRHANITE and de-identified data extractions. Each ACCHS successfully completed 'site acceptance testing' to confirm the extraction of fit-for purpose data. The integrity of the data extraction process was monitored with weekly data uploads. XML interface maintenance ensured that any vendor software upgrades to the CIS were aligned with data extract definitions.

Deidentified CIS participant identification numbers in the GRHANITE extractions were linked with participant data recorded by pharmacists in the logbook. 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 record activity details into the logbook including participant medication management reviews that were a HMR and/or a non-HMR, and the participant clinical diagnoses pertinent to patient eligibility criteria for the project. Information on the duration of participant chronic diseases was not collected.

The participants primary place of residence was not collected for privacy reasons, and so the location of the health service providing the intervention was used as a proxy. The geographical location of IPAC sites was defined to the Australian Statistical Geography Standard-Remoteness Area (ASGS-RA, 2016) which is a classification based on the physical distance of a location from the nearest urban centre.<sup>49</sup> The Indigenous Relative Socioeconomic Outcomes (IRSEO) index was used to define the relative advantage or disadvantage of geographical areas based on nine socioeconomic measures such as education, employment, housing and income for the Aboriginal and Torres Strait Islander

population. The measure is Indigenous-specific and assigns a score of one (1) for the most advantaged area and a score of 100 for the most disadvantaged area.<sup>50</sup> IRSEO data was sourced from publicly available datasets.<sup>51</sup>

The participants self-assessed health status was determined using 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?*'. An extra response option – 'very poor' – was added (as in the SF-8 survey) to reduce the potential for respondents to overstate their health status.<sup>52</sup> Responses to this single-item (SF-1) question have been shown to correlate well with multi-item tools measuring the same construct,<sup>53</sup> and are used in the National Aboriginal and Torres Strait Islander Social Survey.<sup>54</sup>

The extent of medication adherence for each participant was assessed using a self-reported indirect method of assessment with a single-item question: '*How many days in the last week have you taken this medication?*' This was asked for each medication the participant was taking. Pharmacists were trained to express the score as a proportion of the number of days the participant took the correct doses of the medication as prescribed in the preceding week. For example, if the patient took half the doses prescribed for the preceding week, this would be expressed as 50% of the days in the previous 7 days. An 'adherent day' was defined as not missing any doses of prescribed medicines on that day.<sup>55</sup> The mean number of adherent days in the preceding week ranged from 0-7 days, based on the mean score for all medications. This informed the proportion of days with the correct number of doses taken, which is a frequent summary statistic used for reporting medication adherence.<sup>56</sup> If the mean number of adherent days for participants was least 6 of 7 days, this approximated medication adherence for at least 80% of the days indicated.

Albuminuria was defined as a urinary albumin:creatinine ratio (ACR) >2.5 mg/mmol for males and >3.5mg/mmol for females.<sup>57 58</sup> Estimated glomerular filtration rate (eGFR) as reported in CIs was used without derivation from serum creatinine measures. Patients already at a clinically high risk for a CVD event were those with any of the following: diabetes mellitus and age >60 years, diabetes mellitus and microalbuminuria (urinary ACR

>2.5 mg/mmol for males and >3.5 mg/mmol for females), eGFR <45 mL/min per 1.73 m<sup>2</sup>, systolic blood pressure (BP) ≥180 mm Hg, diastolic BP ≥110 mm Hg, and serum total cholesterol >7.5 mmol/L.<sup>59</sup> Patients with existing CVD were defined as participants with a clinical diagnosis for any of the following: coronary heart disease, cerebrovascular disease, and peripheral vascular disease.<sup>60</sup>

Clinical endpoints such as blood pressure were measured by existing healthcare staff within ACCHSs as per usual care. Private laboratories conducted all pathology testing for ACCHSs using standardised enzymic methods through usual systems and were all accredited for testing by the National Association of Testing Authorities.<sup>61</sup> Additional point of care testing undertaken in some sites as part of usual care, complied with *Quality Assurance for Aboriginal and Torres Strait Islander Medical Services* (QAAMS) program requirements. The QAAMS program supported participating ACCHSs to ensure that such testing was conducted under a quality management framework delivering analytically sound performance.<sup>62</sup>

GRHANITE extracted relevant clinical endpoint data for each consented IPAC participant for the 12-month interval prior to participant enrolment into the study (representing pre-intervention usual care that was defined as baseline) and for the duration of the intervention until the end of the study date, set at 31<sup>st</sup> October 2019.

### **Clinical endpoints**

#### ***Haemoglobin A1C (HbA1C):***

The most recent HbA1c value in the 12 months prior to enrolment for participants with T2DM was compared with the follow-up result closest to the end of the study. The most recent value for this measure was considered clinically meaningful given that HbA1c is a measure of glycaemic control in the preceding 2 to 3 months of participant involvement in the study and free of daily fluctuations.<sup>63</sup>

#### ***Systolic and diastolic blood pressure, lipid profile (HDL-C, LD-L, TG, and TC) and ACR***

The mean of values in the 12 months (365 days) prior to participant study enrolment was considered baseline, whilst the mean of values in the period after enrolment until the end of the study, was considered the follow-up result. Given that the recommended frequency for

repeat ACR testing according to clinical practice guidelines is 2-yearly or annually,<sup>64</sup> for ACR, the most recent paired observations pre and post participant enrolment were compared due to the absence of repeat measures during the study period.

### ***e-GFR***

The outcome of eGFR change (ml/min per 1.73 m<sup>2</sup>) was defined as 'eGFR at end of study – eGFR at baseline'/follow-up time. The follow-up time was defined as the time between the most recent baseline eGFR value and the follow-up eGFR value closest to the end-of study date, as per the eGFR Follow-Up Study involving adult Indigenous Australians.<sup>65</sup> According to this study, one baseline and one follow-up estimate for eGFR (based on serum creatinine) is considered sufficient to estimate short-term kidney function decline (up to four years) and the decline is linear.<sup>66</sup> In the eGFR Follow-Up Study, the mean annual unstratified (by albuminuria) eGFR change was estimated at -3.0 (-3.6 to -2.5) ml/min/1.73<sup>2</sup> from participants (irrespective of baseline eGFR) with at least 6-months of follow-up between eGFR measures.<sup>67</sup> <sup>68</sup> This magnitude of expected decline was used as a standard with which to compare the observed annualised eGFR change for IPAC participants. The use of paired single eGFR measures for the duration of the study provided sufficient data points given that eGFR screening recommendations for those older than 30 years and/or with T2DM, were 2-yearly or annually (respectively).<sup>69</sup>

### ***Absolute cardiovascular (CV) risk score:***

The absolute CVD risk was calculated for each participant at baseline and the end of the study (derived from mean values for continuous variables) by using the National Vascular Disease Prevention Alliance (NVDPA) absolute cardiovascular disease risk tool (<http://www.cvdcheck.org.au/>).<sup>70</sup> This tool was based on the 1991 Framingham Risk Equation (FRE)<sup>71</sup> to estimate the 5-year risk of a primary cardiovascular event in those not already at clinically high-risk for CVD or were free of existing CVD at baseline. The tool uses a composite of sex, age, systolic blood pressure, total cholesterol to HDL-C ratio, and T2DM, plus smoking status measures (excluding left ventricular hypertrophy). This equation is recommended for people without existing CVD (primary risk) who are aged 30-74 years as outlined in clinical practice guidelines for the Aboriginal and Torres Strait Islander population.<sup>72 73</sup> It was not applied to those with existing CVD nor to those already at a clinically high risk for a CV event

(>15%) at baseline.<sup>74</sup> Absolute risk estimates were not adjusted upwards given the FRE is known to underestimate absolute CVD risk in the Aboriginal and Torres Strait Islander population as this is subject to clinical discretion.<sup>75</sup>

### **Covariates to clinical endpoints**

Changes in clinical endpoint's that could be attributable to a range of baseline participant, health service, and intervention-related characteristics (defined as covariates) were also examined. The participant-related covariates included: mean age at baseline; median length of time in the study (and/or length of time between endpoint measures); sex; baseline measures for medication adherence and the median number of medications, and baseline self-assessed health status. Health service-related characteristics included the IRSEO score of the health service location. Intervention-related characteristics investigated the influence of a HMR and non-HMR type of medication management reviews, as well as MBS rebates for item 10987 and 10997.

### **Sample size**

A sample size of 732 patients with chronic disease was estimated to achieve power in excess of 80% to detect (1) an absolute CVD risk reduction of 1% (1-point difference) from baseline if a standard deviation (SD) of 2.7% was assumed;<sup>76 77</sup> (2) a clinically relevant reduction of 10mmHg (SD 20 mmHg) in systolic blood pressure and (3) 5mmHg (SD 10 mmHg) in diastolic blood pressure;<sup>78 79</sup> (4) a reduction in total cholesterol (-0.3mmol/L; SD 1 mmol/l),<sup>80 81</sup> (5) an increase in high-density lipoproteins (0.1 mmol/L; SD 0.4 mmol/l),<sup>82 83</sup> and (6) a reduction in low-density lipoproteins (-0.3 mmol/L; SD 0.9 mmol/l);<sup>84</sup> (7) a reduction in triglycerides (-0.9mmol/L; SD 1.5 mmol/l);<sup>85 86</sup> and (8) a 30% decrease in ACR (SD: 23 mg/mmol);<sup>87 88</sup> with an overall level of significance of 0.05 (adjusted for multiple testing k=8) using two-sided one-sample paired t-tests.

A total sample size of 119 T2DM patients was estimated to achieve power in excess of 80% to detect a decrease in HbA1c (in % units) from baseline of at least 0.5% with an assumed SD for change of 1%<sup>89</sup> with an overall level of significance of 0.05 using two-sided one-sample paired t-tests. The sample size calculations allowed for an attrition rate (including missing values) of 50% and assumed a design effect of 1.75<sup>90 91</sup> to adjust for the cluster sampling



approach. Calculations were based on a comparison of mean values in a paired analysis, and were conducted with PASS 2008 (NCSS, Kaysville, Utah, USA).

### **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 (n=90). Health Care Homes (HCH) participants who were also concomitantly enrolled in another program known as the 'Community Pharmacy in Health Care Homes Trial'<sup>92</sup> were also removed from the analysis (n=47) due to the potential for confounding from the additional support given by community pharmacy to individuals in this program. The remaining HCH participants were retained in the analysis. For each clinical endpoint measure, there were participants with insufficient pathology data to enable paired data analyses (baseline compared with follow-up), who were consequently excluded from the analysis.

Participant characteristics and biomedical outcomes data was extracted from the JCU SQL Server database using the Navicat 15 for SQL Server (PremiumSoft) database management tool or from the pharmacist logbook as Microsoft Excel files. All data was subsequently analysed using a number of statistical programs including the SPSS Statistics Premium version 24 (IBM) statistical package, Stata/MP 13.0 (StataCorp LP), and Microsoft Excel 2016 (Microsoft). Categorical variables are presented as absolute and relative frequencies. Depending on their distribution, numerical variables are presented as mean and standard deviation (SD) or median and interquartile range (IQR) as indicated accordingly. Statistical analyses were cluster-adjusted as the study design involved cluster sampling using ACCHSs as the primary sampling units.

Differences were calculated for paired measurements of clinical outcome measures as described above. Differences for all clinical outcome measures except for e-GFR were statistically compared against zero using cluster-adjusted (ACCHS) regression analyses by applying the `svy : regress` Stata command. The observed mean eGFR decline per annum (annualised) was calculated as the number of days between eGFR measurements was not the same for all participants. For e-GFR, annualised differences were statistically compared against -3 (ml/min/1.73 m<sup>2</sup>) using a cluster-adjusted (ACCHS) regression analysis technique.

The value of -3 was the theoretically expected mean annual e-GFR (ml/min/1.73m<sup>2</sup>) linear decline expected without the intervention.<sup>93</sup> A sensitivity analysis was done for e-GFR change by excluding participants with a follow-up (days between paired assessments) of ≤180 days (6 months).

The effects of participant, health service, and intervention characteristics on all differences of clinical outcome measures (except for e-GFR) were examined using cluster (ACCHS) and length of follow-up time adjusted regression analyses (svy: regress command of Stata). For annualised e-GFR change such analyses were cluster (ACCHS) adjusted only. 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**

Of 1,733 patients who consented to participate in the study, the IPAC cohort included in the analysis after initial exclusions comprised 1,456 enrolled participants who remained in the study until the end (Figures 1-11) and were followed-up for a median of 285 (IQR: 219-352) days following enrolment.

A number of participants were excluded from the analysis if there was insufficient data for analysis (n=138), or if study enrolment was less than 90 days (n=40). Participants were also withdrawn from the study (n=99) if evidence of consent was missing (n=38), if there was concomitant enrolment in the Community Pharmacy in HCH program (n=47), or for other reasons (n=14). Of the 1,456 participants who remained in the study until the end, analyses were conducted if paired biomedical outcomes data at baseline and follow-up was available (Figures 1-10, and Table 1). Of participants with T2DM, HbA1c paired data was available from 54% (539/997). The proportion of participants with paired data for other clinical

endpoints were: systolic BP for 76% (1103/1456); diastolic BP for 72% (1045/1456); total cholesterol for 45% (660/1456); LDL-C for 39.5% (575/1456); HDL-C for 43% (622/1456); triglycerides for 50% (730/1456), ACR for 33% (475/1456); and eGFR for 61.5% (895/1456). The proportion of participants with paired data to estimate the primary CVD risk score was 27% (390/1456). After exclusion of those already at high clinical risk for a primary CVD event (n=288) and the remainder with only established CVD (n=27), plus those missing data necessary to assess these exclusions (n=37), this left 9.7% (38/390) of participants whose primary CVD risk was estimated (Figure 10). The median length of stay in the study for participants in all clinical endpoint groups ranged from 255 to 301 days, with the shortest stay being for the calculated CVD risk group (Table 1).

Demographic and other baseline participant characteristics were consistently similar across all clinical endpoint groups (Table 1). The mean age of participants at baseline ranged from 57- 58 years with the exception of the smaller cohort assessed for calculated CVD risk (mean 60 years; n=38). There were almost twice as many females as males, most participants (91-94%) were Aboriginal and/or Torres Strait Islander, and >80% were eligible for social support (pensioner or other concession card holders). Participants were similar across the groups with respect to the geographical location of the ACCHS they attended. Most participants (65 to 76%) attended health services located in inner and outer regional locations, and most of the remainder (22 to 30%) attended remote or very remotely located health services. Very few participants attended health services located in urban centres (0 to 3%).

The clinical endpoint groups with paired data were similar with regard to the mean number of prescribed medications (7.1 to 8.0) per person, the number of doctors encounters in the 12 months prior to enrolment (mean of 7.5 to 8.4), self-reported medication adherence (mean of 6.1 to 6.2 adherent days in the preceding week), and self-assessed health status (17.4% to 21.1% had 'excellent' to 'very good' health status). Similarly, the presence of co- or multimorbidity minimally varied between groups (87.5% to 90.2%, and 76.8% to 79.1% respectively). The proportion of participants with a clinical diagnosis of type 2 diabetes mellitus (T2DM) ranged from 59% to 75.4%, with the highest proportion being in the group tested for ACR. The range in the proportion of participants with a clinical diagnosis of

hypertension was 62.7% to 66.8%. The proportion of participants with dyslipidaemia (49.8% to 55.7%), chronic kidney disease (CKD, 37.4% to 46.8%), rheumatic heart disease or acute rheumatic fever (1.9% to 3.6%), chronic obstructive pulmonary disease (COPD, 5.8% to 9.2%) or depressive disorders (3.2% to 5.8%), also appeared similar between the clinical endpoint groups. Few participants across the groups (7.0% to 11.4%) had evidence of at least one medication management review in the 12 months prior to study enrolment (HMR based on MBS item 900 claims). Similarly, few participants were concomitantly engaged in the Health Care Homes (HCH) program (between 9.8% and 13.8% across the clinical endpoint groups), which is consistent with the remote geographical location of ACCHSs participating in this program. The smaller cohort who had their CVD risk calculated differed from the other groups by being proportionately more female (76.3%), from locations that were very remote (36.8%) and consequently also enrolled in the HCH program (18.4%), having fewer medications (mean of 5.3), and less multimorbidity (65.8%, Table 1).

At baseline, participants with T2DM had levels of glycaemia warranting further control measures (mean HbA1c of 8.3%, n=539). Participants as a whole were on average normotensive with a mean SBP of 133 (n=1,103) and mean DBP of 80 mmHg (n=1,045), whilst the only evidence for dyslipidaemia were elevated mean triglycerides (2.39 mmol/L, n=730). The calculated absolute 5-year CVD risk was classed as moderate (10% to <15%, n=38), the overall mean participant eGFR was consistent with Stage 3A of CKD (49.1 ml/min/1.73m<sup>2</sup>, n=895), and mean ACR levels were consistent with overt albuminuria (57.9 mg/mmol, n=475, Table 2). Participants were on average obese at baseline with a mean BMI of 32.4 (n=991, data not shown).

Changes in primary and secondary clinical endpoints from baseline are shown in Table 2. By the end of the study, there was a significant improvement in HbA1c in participants with T2DM, with a 2.8 mmol/mol or 0.3% (unit) reduction (p=0.001, 95% CI: -0.4% to -0.1%). Reductions in diastolic BP (-0.8mmHg, 95% CI: -1.4 to -0.2, p=0.008), total cholesterol (-0.15 mmol/L, 95% CI: -0.22 to -0.09, p<0.001), LDL-C (-0.08 mmol/L, 95% CI: -0.13 to -0.03, p=0.001), and triglyceride levels (-0.11 mmol/L, 95% CI: -0.20 to -0.01, p=0.006) were statistically significant for all participants. The mean calculated absolute 5-year CVD risk was significantly reduced by 1% (95% CI: -1.8% to -0.12%, p=0.027) but the risk remained at

a 'moderate' level for participants. The mean annual eGFR for all participants significantly improved with an increase of 1.9 mL/min/1.73 m<sup>2</sup> (95% CI: 0.08 to 3.74) from the mean eGFR at baseline and was significantly higher than the predicted rate of annual eGFR decline of -3.0 mL/min/1.73 m<sup>2</sup> (p<0.001). When participants with less than 6-months of follow-up were excluded, there was a decline in the mean annual eGFR by -0.2 mL/min/1.73 m<sup>2</sup> (95% CI: -2.99 to 2.68), that remained significantly lower than the predicted annual rate of eGFR decline (p=0.034, n=720).

Although there was a slight increase in HDL-C (0.01 mmol/L), this change was not significant (p=0.32). There were no net improvements in SBP or HDL-C, and the mean ACR stabilised from baseline to the end of the study with a mean difference of 3.8 mg/mmol (95%CI: -6.3 to 13.8, p=0.42).

Across all clinical endpoints, more participants tended to be recipients of a non-HMR than a HMR by the end of the study (Table 3) as was described elsewhere.<sup>94</sup> With the exception of the calculated CVD risk participant group, the proportion of non-HMR recipients in the clinical endpoint groups ranged from 40.4% to 50.4%, versus 30.9% to 38.3% who were HMR recipients. By the end of the study, the proportion of participants who had received an MBS follow-up service for medication adherence ranged from 43.3% to 63.5% across all clinical endpoint groups (Table 3).

The effect of participant, health service, and intervention covariates on each clinical endpoint is shown in Tables 4-11, and 13-15. Although SBP was not significantly reduced for the cohort as a whole, younger participants (<57 years) had a significantly greater mean reduction in SBP of -1.8 mmHg (SD: 12.5) from baseline to the end of the study when compared to those who were older (p=0.004, Table 5). A significantly greater mean DBP reduction of -1.4 mmHg (SD 7.5) was also seen for younger participants (<57 years) compared with those who were older (p=0.012, Table 6).

A significantly greater reduction in SBP of -1.6 mmHg (SD: 14.9) was evident for participants who stayed in the study for a median of 266 days or longer compared with shorter stays (n=588, p=0.03, Table 5). Participants with longer stays in the study (≥296 days) also had

significantly greater reductions in mean triglyceride levels of -0.20 mmol/L (SD: 1.34) compared to those with shorter than median stays (n=515, p=0.024, Table 10).

An increased length of stay in the study was associated with worsening of the eGFR. In participants who stayed in the study for a median of 296 days or longer (IQR: 234-359, n=450), the mean annual eGFR decline was -2.7 ml/min/1.73m<sup>2</sup> (SD 17.0), which was a significantly greater decline than for participants with a shorter than median stay (n=445, p<0.001, Table 13). Annual eGFR decline was even greater for participants with a minimum of 6 months between eGFR measures (as undertaken for sensitivity analysis). For these participants, a longer than median stay (≥317 days, IQR:252-366, n=372) in the study revealed an annual eGFR decline of -3.5ml/min/1.73m<sup>2</sup> (SD: 22.8), which was significantly greater than for participants with a shorter than median stay (n=348, p=0.003, Table 14).

The selected health service-related covariate (IRSEO score <median of 60) was identified as exerting an influence on clinical endpoints only for total cholesterol. The total cholesterol level of participants attending health services in more advantaged locations was reduced by -0.20mmol/L (SD 0.51) which was significantly greater than for participants attending services in disadvantaged locations (p=0.014, Table 7).

The intervention-related covariate MBS follow-up service that included assessments for medication adherence from items 10987/10997 was an influence only for participant triglyceride levels. A reduction in mean triglycerides of -1.8 mmol/L (SD 1.01) was significantly more likely in those who received this service (p=0.027, Table 10), compared to those who had not.

The influence of medication management reviews on clinical endpoints did not differ by the type of review (p>0.05), with two exceptions. The first was a significantly greater reduction in absolute CVD risk score observed for HMR recipients by -2.4% units (SD 1.1, for n=8) compared with non-HMR recipients of -0.5% units (SD 1.9, for n=22, p=0.039, Table 15), but the participant sample size was very small. The second was for participants with a minimum of 6 months between eGFR measures. HMR recipients in this subset had a significantly greater mean annual eGFR decline (-2.9 ml/min/1.73m<sup>2</sup>, SD 19.3, n=258) than non-HMR

recipients whose eGFR improved rather than declined ( $+2.2$  ml/min/ $1.73\text{m}^2$ , SD 30.1,  $n=314$ ,  $p=0.035$ , Table 14).

There was a suggestion that participants with a poorer self-assessed health status had more favourable changes to both their HDL-C and ACR levels over time compared to the other participants, but these improvements were of borderline significance ( $p=0.048$ , Table 9 and  $p=0.047$ , Table 11, respectively). No effect on clinical endpoints was evident for any of the other covariates examined.

## DISCUSSION

The IPAC study was set in ACCHS primary health care settings and is the first to explore the impact of integrated pharmacists on a range of intermediate clinical endpoints regarding Aboriginal and Torres Strait Islander adult patients with chronic disease. Compared with usual care (in the 12 months preceding the intervention), this study found that participants had significant improvements post- intervention in most primary and secondary clinical endpoints after a median of 285 days, compared with usual care pre-intervention. The intervention significantly improved glycaemic control in participants with T2DM and also brought about improvements in diastolic BP, total cholesterol, LDL-C, triglycerides, mean annual eGFR, and mean calculated absolute 5-year CVD risk in all study participants. Systolic BP significantly improved in those younger than 57 years of age. No change was observed in participant HDL-C levels, whilst ACR levels did not change during the study. The type of medication management review (HMR or non-HMR) received by participants did not influence the majority of clinical endpoints.

These clinical improvements were evident in a population with a substantial chronic disease burden that occurred at a relatively younger age than other Australians.<sup>95</sup> Almost all participants were Aboriginal and/or Torres Strait Islander, and most had polypharmacy ( $\geq 5$  medications) and clinical diagnoses of T2DM, and/or hypertension. Approximately half had a clinical diagnosis of dyslipidaemia, and more than one-third had CKD. The mean participant baseline clinical endpoints were outside the target range for HbA1c, eGFR, ACR, and triglycerides, whilst mean BP and other lipids were within the normal range for the cohort as a whole.

Glycaemic control in participants with T2DM significantly improved with a mean -0.3% (2.8 mmol/mol) decrease in HbA1c after a median of 284 days (9.3 months). This change was consistent with the -0.18% to -2.1% HbA1c decrease (difference between intervention and control groups) observed over a mean of 9.4 months in 24 of 26 other studies that investigated pharmacist interventions in patients with T2DM.<sup>96</sup> HbA1c reductions of -0.6% to -1.1% for those with T2DM were also reported in another systematic review of the effect of pharmacist interventions.<sup>97</sup> This review also found no association between the duration of pharmacist intervention and change in HbA1c, which concurs with IPAC study findings.<sup>98</sup>

Even a modest HbA1c drop may translate to a reduction in micro and macrovascular complications in people with T2DM if sustained population wide. According to the UK Prospective Diabetes Study (UKPDS) *any improvement* in HbA1c in those with T2DM reduced the risk of diabetes complications, with little evidence of a threshold of effect. The quantum of impact was such that for each 1% reduction in HbA1c, the risk of microvascular complications was reduced by 37%, the risk of myocardial infarction by 14%, and the risk of death related to diabetes was reduced by 21%.<sup>99</sup> These benefits were realised over a 10-year observation period in a treated population *without* pre-existing CVD.

However, IPAC participants at baseline differed from the UKPDS population by having a higher BMI, a lack of baseline glycaemic control, a higher prevalence of macroalbuminuria, and 31% already had pre-existing CVD.<sup>100</sup> Therefore, these predispositions better aligned with the ACCORD study cohort with T2DM who were at high risk for CVD events.<sup>101</sup> This study found that patients benefited from a modest lowering of HbA1c, but not from intensive lowering, as those with HbA1c lowered to a median of 6.4% had a 35% higher risk of death from CVD causes.<sup>102 103</sup> This suggests that the safest range for HbA1c in those with T2DM at greatest risk of CVD events appears to be between 7.0-8.0%.<sup>104</sup> However, Clinical Practice Guidelines (CPGs) tend to recommend a uniform HbA1c target for all patients with T2DM, adjusting glycaemic therapy so that HbA1c is maintained to  $\leq 7\%$ .<sup>105</sup> The modest, but significant HbA1c reduction observed in the IPAC trial may reflect the more appropriate clinical efforts that target individual needs, rather than meeting generic CPG targets. For



example, at the individual level, a 0.5% HbA1c reduction is considered a clinically significant change to aim for, whilst also taking into account the imprecision of the test.<sup>106</sup>

Optimising glycaemic control for Aboriginal peoples and Torres Strait Islanders with diabetes is complex as little empirical evidence exists to guide target-setting. The Aboriginal and/or Torres Strait Islander population is known to have an earlier age of onset and a higher risk of complications from diabetes, complicated by a reduced access to primary health care than other Australians.<sup>107</sup> This means there is a greater propensity to disease progression over time, and a need for earlier and sustained glycaemic control measures to minimise longer-term complications.<sup>108</sup> Clinicians need to make judicious treatment decisions when individualising glycaemic targets, to balance the risks and benefits associated with treatment, and manage social and other factors affecting this population.

The net drop in HbA1c observed in this study may be attributed to more efficient and enhanced collaborations between clinicians and integrated pharmacists to optimise prescribing decisions. Other studies, also conducted within Aboriginal primary health care settings but not involving a pharmacist, reported significant and similar drops in HbA1c (-0.4%) in Aboriginal and Torres Strait Islander patients with diabetes after one year. Patients attended health services where staff were better supported to adhere to clinical guidelines through systems changes and regular systems improvement cycles.<sup>109</sup> However, it is unlikely that these health system influences within IPAC sites acted to confound the impact of integrated pharmacists.<sup>110</sup> Health system assessment measures were explored pre and post intervention at IPAC sites, and the few changes identified were most likely explained by improvements generated by integrated pharmacist activity.<sup>111</sup>

The net mean reduction in diastolic BP for participants was significant but modest at 0.8mmHg, whilst systolic BP was significantly reduced by a mean -1.8mmHg for participants aged under 57 years of age, with a mean -1.6mmHg for those with a longer duration in the study ( $\geq 266$  days). These net reductions occurred for the cohort as a whole from a baseline where two-thirds had a clinical diagnosis of hypertension but the mean systolic and diastolic BP was within the normal range. This BP change was smaller than reported in other studies following pharmacist interventions. Pooled analysis from 33 randomised controlled studies

that examined pharmacist medication management reviews conducted within ambulatory clinics (defined as settings with care mostly provided by general practitioners), showed a mean SBP and DBP reduction of -8.3 (range -1.5 to -22.6 mmHg) and -4.5 (range -0.2 to -12.9) mmHg respectively, between intervention and control groups over a mean follow-up period of 8.5 months.<sup>112</sup> Another analysis of 17 randomised controlled studies investigated collaborative and integrated pharmacist interventions for patients with T2DM over a mean follow-up of 9.4 months, and reported SBP and DBP reductions from -3.3mmHg to -23.0 mmHg and -0.2 to -9.1 mmHg respectively.<sup>113</sup> An analysis of 13 randomised and non-randomised controlled studies of pharmacist interventions targeted to patients diagnosed with hypertension reported a net mean SBP reduction of -7.5mmHg, and DBP reduction of -3.4mmHg over a mean follow-up of 7.6 months.<sup>114</sup>

Even the small but significant average DBP and SBP reductions shown for IPAC participants may attenuate the incidence of CVD events for Aboriginal and Torres Strait islander peoples if such reductions were population-wide, particularly for those with chronic disease. The benefits that accrue from BP reduction are not just limited to those with hypertension, which is why population-wide BP reduction strategies are recommended for the primary prevention of CVD events.<sup>115</sup> A population-wide reduction in DBP of a mere 2mmHg is estimated to reduce the prevalence of hypertension and CHD risk by 17% and 6% respectively, and combined with BP reductions in those needing medical treatment, could double or triple the impact of medical treatment alone.<sup>116</sup> A mere 1 mmHg reduction in SBP may substantially reduce heart failure (with 20 fewer cases for every 100,000 African-Americans per year), as well as CHD, and stroke incidence.<sup>117</sup>

The net effect of BP reduction in the IPAC study most likely emanated from the observed targeted improvements to prescribing quality and participant medication adherence, as reported elsewhere. Prescribing quality significantly improved following the IPAC intervention with reductions in inappropriate prescribing for BP lowering and diabetes medications,<sup>118</sup> a significant reduction in underprescribing of BP-lowering medications for those with T2DM and albuminuria,<sup>119</sup> and significant improvements in patient self-reported medication adherence.<sup>120</sup> Integrated pharmacists also delivered team-based care to optimise chronic disease management (such as case conferences) and preventive health

assessments, and attended patient group meetings to deliver preventive health messages such as advice on dietary and lifestyle improvements.<sup>121</sup>

The mean total cholesterol and LDL-C was normal or already well controlled at baseline for participants as a whole, but also reduced significantly following intervention. Total cholesterol reduced by 3.3% (to -0.15mmol/L) compared with baseline over a mean 314 days of follow-up. LDL-C reduced by 3.4% (to -0.08 mmol/L), whilst mean triglycerides that were elevated at baseline, reduced by 4.6% (to -0.11 mmol/L) over a mean 295 days of follow-up. HDL-C levels did not increase following the intervention.

This reduction in LDL-C levels was slightly less than reported by other studies that assessed the impact of pharmacist interventions in the general or dyslipidaemic population. The mean LDL-C reduction identified in a metaanalysis of 9 randomised and non-randomised studies of pharmacist interventions for dyslipidaemic patients ranged from -1.4 to - 0.08 mmol/L in intervention groups over a mean of nearly 10 months follow-up. Like the present study, no impact on HDL-C levels was found.<sup>122</sup> Another meta-analysis of the impact of medication management reviews in the general population also showed a small (mean effect size of -0.23 to -0.39 mmol/l) reduction in LDL-C from 11 pooled studies in both ambulatory and community pharmacy settings when differences between intervention and control groups were compared over a mean of 9-months follow-up. In this analysis, the increase in lipid control was attributed to the positive effects of medication management reviews.<sup>123</sup>

The improvements in IPAC participant TC, LDL-C and TG levels were most likely mediated by significant improvements in prescribing quality and reduced medication omissions like lipid lowering drugs for those clinically at high risk for CVD, as was shown in other IPAC study reports.<sup>124 125</sup> The small magnitude of the change in LDL-C post-intervention may have been a function of the already low baseline LDL-C of participants. Statins are particularly effective at lowering LDL-C levels, but for patients already on statins, only a 6% further reduction in LDL-C is achievable for every doubling of the statin dose such as a change from 20mg to 40mg of atorvastatin.<sup>126</sup> Based on subset analysis for the IPAC project, 72% of participants were already prescribed lipid-lowering medication at baseline,<sup>127</sup> meaning that further LDL-

C reductions beyond what was observed may have been difficult to achieve or clinically unnecessary.

Nevertheless, for those already on statins, reducing LDL-C levels by a further 0.51 mmol/l from the LDL-C at baseline over a year, can significantly reduce the residual risk for major CVD events by an additional 15% (on top of the existing 20% relative risk reduction per 1 mmol/L LDL-C reduction from statin therapy).<sup>128 129</sup> This suggests that any population-wide reduction in LDL-C, even if small in magnitude such as demonstrated in the IPAC study, may have broader benefits in reducing major CVD events for Aboriginal and Torres Strait Islander peoples. Lipid lowering therapy should also be targeting those at highest CVD risk and not just those with elevated LDL-C levels.<sup>130</sup>

The reductions in LDL-C were not influenced by the selected patient, service, or intervention characteristics that were examined. This indicates that certain subsets of participants did not benefit more than others, nor was the change influenced by the type of medication review received. A similar LDL-C reduction was evident in participants who had a HMR compared to those who received a non-HMR.

The mean annual eGFR decline in IPAC participants was slowed significantly compared with the pre-intervention period. Participant eGFR change was compared to the standard established by the eGFR Follow-Up Study with an estimated rate of mean annual change in the progression of eGFR decline of -3.0ml/min (irrespective of baseline eGFR).<sup>131</sup> This study longitudinally followed 550 Aboriginal and/or Torres Strait Islander peoples recruited from ambulatory health care settings across remote and non-remote locations. At baseline, the cohort had a mean age of 46.3 years overall, but a subset of those with an eGFR <60 ml/min/1.73m<sup>2</sup> (n=85) had a mean age of 60.1 years, BMI of 27.8 kg/m<sup>2</sup>, mean eGFR of 46.2 ml/min/1.73m<sup>2</sup>, and a mean ACR of 73.5 mg/mmol, indicating that this subset had similar characteristics to the IPAC participant cohort. The annual rate of eGFR decline for the subset with baseline eGFR <60 ml/min/1.73m<sup>2</sup> was -5.0 ml/min/1.73m<sup>2</sup>, and for those with ACR > 30 mg/mmol it was -6.0 ml/min/1.73m<sup>2</sup> (irrespective of baseline eGFR strata).<sup>132</sup> Thus, without intervention, IPAC participants were at risk of a much higher rate of eGFR decline per year than the selected expected rate. This further affirms that the progression of kidney

disease significantly slowed as a result of the intervention for IPAC participants. This benefit persisted after removing from the analysis those participants with less than 6-months of follow-up,<sup>133</sup> as eGFR was significantly less likely to decline in IPAC participants with shorter follow-up times.

A decline in eGFR of  $-5 \text{ ml/min/1.73m}^2$  over 2 years predicts a 1.5 and 1.2 times higher risk of ESKD and CVD events respectively, as shown in an analysis from the USA involving participants from mixed ethnic groups.<sup>134</sup> The eGFR Follow-Up study showed that those with a slower rate of kidney disease progression (a  $5 \text{ ml/min/1.73m}^2$  higher eGFR) had an 18% risk reduction (hazard ratio 95% confidence interval 0.75-0.91) in combined renal endpoints over a median of 3 years (adjusted for aged, sex, and ACR) that included death from renal causes, and initiation of renal replacement therapy.<sup>135</sup> This suggests that the magnitude of the slowing in annual eGFR decline observed in IPAC study participants was clinically significant, and could delay the onset of these events if the impact of the intervention was sustained.

Slowing of the eGFR decline in IPAC participants was achieved in the absence of a significant reduction in mean ACR level upon follow-up. An increase in the ACR is usually an early indicator of CKD progression. An increasing ACR is also linearly associated with increasing risk for ESKD and both CVD and non-CVD related deaths when compared to those with a stable ACR, according to a large 2-year observational study that adjusted for baseline ACR, age, and a range of CVD risk factors.<sup>136</sup> So, whilst a higher ACR is also predictive of eGFR decline as shown for the Aboriginal and Torres Strait Islander population,<sup>137</sup> a reduction in ACR can prevent kidney disease progression.<sup>138</sup> Indeed, a 30% drop in ACR over 2 years was shown to be associated with a 22% relative risk reduction in ESKD in a large meta-analysis of prospective cohort studies.<sup>139</sup> In spite of this association, a third to half of ESKD outcomes in this meta-analysis developed *without any increase* in albuminuria, especially for those with high baseline albuminuria,<sup>140</sup> because even stable albuminuria remains a CVD and ESKD risk factor.<sup>141</sup> However, the management of CVD risk factors in those with CKD ( $\text{eGFR } 15\text{-}59 \text{ ml/min/1.73m}^2$ ) and T2DM can still reduce all-cause and CVD mortality, even without a change in ACR.<sup>142</sup> This was shown in a study including Aboriginal peoples with diabetes and micro or macroalbuminuria who were treated with an angiotensin converting enzyme

inhibitor (ACEI) plus other agents to reach blood pressure targets (including attempts to control glucose and lipid levels). Deaths were reduced from renal and non-renal causes, even though ACR and eGFR did not decline. Survival benefits persisted in those with overt albuminuria, even with stabilization of their ACR.<sup>143</sup> Only 11.6 people needed to be treated over a mean 3.39 years to avoid one death.<sup>144</sup>

Strategies to slow the rate of CKD progression (by slowing eGFR decline) are vital for Aboriginal peoples and Torres Strait Islanders as they have 10 times higher rates of end-stage kidney disease (ESKD) than other Australians and at much younger ages.<sup>145</sup> An improved use of ACEI, angiotensin-2 receptor blockers (ARB), and statins may have slowed eGFR decline and stabilised the ACR in IPAC participants. This is because ACEI or ARB treatments are known to reduce progression of albuminuria, the risk of ESKD, and CVD events in those with CKD.<sup>146</sup> Statins can significantly slow the rate of annual eGFR decline by  $-0.09 \text{ ml/min/1.73m}^2$ <sup>147</sup> to  $-0.19 \text{ ml/min/1.73m}^2$ <sup>148</sup> in those with baseline eGFR <60 ml/min/1.73m<sup>2</sup> as well as to reduce proteinuria. The improvements in lipids, the rate of eGFR decline, and ACR stabilization in the IPAC study likely followed improvements in prescribing quality, medication adherence, and participant access to medication management reviews.

Very few other studies have reported the impact of pharmacist interventions (in any setting) on eGFR and ACR clinical endpoints for patients with or without CKD. Of 36 studies included in a systemic review of pharmacist interventions in ambulatory care settings, only four reported ACR clinical endpoints and all showed no change.<sup>149</sup> A short study duration, small sample size, patients at low risk for CKD progression, and an inability to provide sufficient patient follow-up, may explain most of these research findings.

The mean 5-year CVD risk of IPAC participants was significantly reduced by an absolute 1% (or 8.4% relative risk reduction) over 255 days suggesting a clinically significant potential for primary CVD prevention. This composite risk measure could only be calculated from a small number of participants because most were already classified as 'high' risk for CVD (>15% in the next 5 years) for clinical reasons or due to existing CVD. A 1% absolute risk reduction in CVD events translates to a substantial population-wide impact over 5 years, as only 100

people need to receive the integrated pharmacist intervention to prevent one from developing a CVD event in that time. Integrated pharmacist influences on risk factors such as BP and lipids most likely explains this outcome as all participants in this small cohort were smokers (data not shown).

CVD risk was predicted by six other pharmacist intervention studies involving patients with T2DM, with only two demonstrating a significant decline.<sup>150</sup> Another systematic review of pharmacist interventions in general practice settings demonstrated a significant decline in predicted CVD risk in one of two studies.<sup>151</sup> In Aboriginal health settings, other types of interventions, such as electronic decision support tools for clinicians, have been used to enhance the primary prevention of CVD and reduce predicted CVD risk. One study increased the proportion of patients tested for certain CVD risk factors but had no statistically significant impact on clinical endpoints such as reductions in mean SBP, LDL-C, or a lowering of the calculated 5-year CVD risk.<sup>152</sup>

A major strength of the IPAC study was the large number of enrolled Aboriginal and/or Torres Strait Islander participants who remained till the study end (n=1,456), with initial exclusions undertaken for ethical reasons and to minimise confounding. Only one participant opted to withdraw from the study (reasons not given). After this, the vast majority of participant exclusions were due to missing data for paired clinical endpoint analysis, with numbers closely following the 50% attrition rate estimated apriori to determine the sample size. The study was therefore sufficiently powered to show the expected changes in clinical endpoints within pragmatic, real-life, ACCHS settings to inform on external validity. It is unusual for a clinical interventional study to enrol so many adult Aboriginal and Torres Strait Islander participants with chronic disease, suggesting that the community-based participatory research and pragmatic study design was a success factor,<sup>153</sup> as was shown in other large-scale (but non-interventional) studies.<sup>154</sup>

Medication management reviews were the most likely mechanism through which pharmacists influenced clinical endpoints. Such reviews have elsewhere been shown to improve prescribing quality,<sup>155</sup> improve CVD risk factors,<sup>156</sup> reduce underuse and overuse of medications,<sup>157</sup> and support patients with medication adherence and chronic disease self-

management.<sup>158</sup> IPAC Integrated pharmacists significantly increased participant access to these reviews. Elsewhere, we reported that the proportion of participants who received an HMR increased 3.9 times after a median of 284 days enrolment in the IPAC study compared with usual care pre-intervention. Integrated pharmacists needed to assess only 5 participants for one to receive a HMR.<sup>159</sup> Non-HMR services were also provided by integrated pharmacists as patients most in need of a HMR were known to be missing out on this service.<sup>160</sup> In the present analysis, we showed that clinical endpoints improved irrespective of the type of medication management review received by participants. This is an important observation given that non-HMRs served to enhance participants' access to a comprehensive medication management review (most were conducted within the health service setting) where participants were 'at risk of forgoing a HMR'.<sup>161</sup>

Other likely factors that served to enhance pharmacist integration and participant access to medication management reviews include a pharmacist workforce trained to target high-value pharmacotherapies specifically for the Aboriginal and Torres Strait Islander population, a receptive clinical environment that fostered their integration within the primary health care team, trusting and responsive relationships with prescribers, and access to patients' medical records.<sup>162 163 164 165</sup> When prescribers are unsupported in challenging health service environments, quality improvement in intermediate clinical endpoint measures can be impeded.<sup>166</sup>

## **Limitations**

Whilst this study had many strengths, there are several limitations that require consideration. Participants were not randomly assigned to receive the intervention but were sampled according to their eligibility as if the intervention was part of usual care. Internal validity may have been compromised if it was likely that participants enrolled in the study were more responsive to the advice of pharmacists and had less progressive chronic disease than those not enrolled but who also attended the same ACCHS. The characteristics of adult patients with chronic disease who were not enrolled in the study were not assessed, nor was it possible to assess the proportion of those who declined to participate. However, participant characteristics suggest they were at very high risk of disease progression over time. Of the enrolled participants, most had a substantial degree of



comorbidity, only a minority self-rated their health as very good to excellent (fewer than reported by Aboriginal and Torres Strait Islander adults with poorly controlled T2DM in a separate study<sup>167</sup> and the national average for adults<sup>168</sup>), no more than 11% had a prior medication management review, and there was suboptimal control of glycaemia with a mean eGFR indicating progressive CKD. Participants were from a population known to be at high risk for CKD progression to ESKD and at a rapid rate, within 2 years of follow-up.<sup>169</sup> Due to participants' severe chronic disease, the average number of doctors' visits for them 12 months prior to the intervention (7.5 to 8.4 visits) was above the average number of attendances per annum for all Australians at general practices (6.1 visits).<sup>170</sup> Selection bias may also have been minimised because of the large sample sizes (participants and sites) and representativeness of ACCHSs (they comprised one-third of all services in the jurisdictions involved in the study). The potential bias from sampling clusters from within ACCHSs was also minimised by statistical adjustment in the analysis of all clinical endpoint measures.

Without an external and randomised control group, it is possible that participant clinical endpoints improved independently of the IPAC intervention. This temporal trend might be mediated directly if participants had less progressive disease or from the effect of regression to the mean, or indirectly by other factors influencing medication management reviews. The possibility that participants had less progressive disease was clinically unlikely as already mentioned. However, the effect of regression to the mean may explain the observed improvements in BP and other endpoints, being a particular limitation of pre-post intervention studies without a control group. Regression to the mean occurs from the influence of chance on highly variable measurements, where long-term (average values) are less extreme than baseline values.<sup>171</sup> Most regression to the mean occurs from measurements taken within 3-6 months after baseline measurements.<sup>172</sup> The clinical endpoints analysed in this study used mean measures over a 12-month baseline time-period which is likely to have mitigated the influence of regression to the mean. In addition, participant baseline mean BP was not elevated which suggests that regression to the mean could have caused a 'headwind effect' if the effects of the intervention (to reduce average BP) were minimised from the opposing influence of upward regression to the mean.<sup>173 174</sup> This was demonstrated in a systematic review of 86 trials reporting change in BP where upward regression to the mean observed in those with low baseline BP levels acted to

counteract the BP reduction treatment effects.<sup>175</sup> Therefore, this effect may have biased mean differences towards the null value, thereby underestimating the observed impact of the IPAC intervention on BP change. Regression to the mean can also occur irrespective of how clinical endpoint values are measured.<sup>176</sup> Any information bias arising from the imprecision in BP measurements which could not be standardised for pragmatic reasons, or from laboratory measures, would have been non-differential, which in general implies a bias towards the null value.

EGFR changes over time from baseline were measured against an independently validated rate of annual eGFR decline that was applicable to the type of population included in the IPAC study. The significantly slowed eGFR decline that was observed relative to this expected decline offers empirical support in favour of the intervention effect, even in the absence of a control group. We also found that the quantum of clinical endpoint changes reported in the present study are similar to the findings of other trials that investigated pharmacist interventions in ambulatory care settings, even though these studies were randomised and externally controlled.

Indirect influences may have independently increased participant access to HMRs. As reported elsewhere, ACCHS characteristics and service activity did not change in ways that were independent of integrated pharmacists to otherwise explain the increase in HMR access.<sup>177</sup> Moreover, in qualitative analysis, clinicians and participants reported that the intervention had increased their access to medication reviews.<sup>178</sup> Substantial and significant increases in HMR access also occurred over a short time during this study, which also make it unlikely that this was mediated by external factors.<sup>179</sup>

The influence of potentially confounding programs on participants was removed from the analysis. This included participants concurrently enrolled in the *Community Pharmacy in Health Care Homes* Trial program that was undertaken around the same time as the IPAC project.<sup>180</sup> The few IPAC participants concurrently enrolled in the broader HCH program were not in receipt of additional community pharmacy support beyond usual care and were therefore not excluded. Moreover, the IPAC pharmacist was integrated within those services also operating as a HCH trial site, meaning that the HCH program could not have

acted as a confounder independently of the pharmacist. Non-HMRs were also a unique outcome of the IPAC project and cannot be attributed to external and independent influences.

A 50% attrition rate due to missing follow-up data was anticipated when deriving estimates of the sample size required to power the study. Follow-up of patients with chronic disease is a known challenge within primary health care settings and particularly with regard to underserved populations.<sup>181</sup> To minimise this data loss, only ACCHSs with experience in continuing quality improvement activity were eligible for study inclusion. Indeed, the proportion of participants who had a recorded result for clinical endpoints in the previous 12 months was higher in IPAC sites than reported by ACCHSs nationally based on key performance indicator data quality assurance reporting. A higher proportion of T2DM IPAC participants had a recorded eGFR test result over the previous 12 months (81.5%, 722/886, data not reported) than reported by all ACCHSs nationally (58% in 2017).<sup>182</sup> This was also observed for ACR testing and for HbA1c testing (62.5%, 554/886 of IPAC participants compared with 50% nationally, and 74.2%, 657/886 of IPAC participants, compared with 64% nationally, respectively).<sup>183</sup> National quality assurance reporting includes reports from all ACCHS including those services that would not have met the site inclusion criteria for the IPAC study, that are generally smaller sites. It is important to note that this site inclusion criterion was set only to maximise data collection for trial purposes. It is possible that the intervention may have had an even greater effect within services requiring more support to improve the quality of care for their patients with chronic disease.

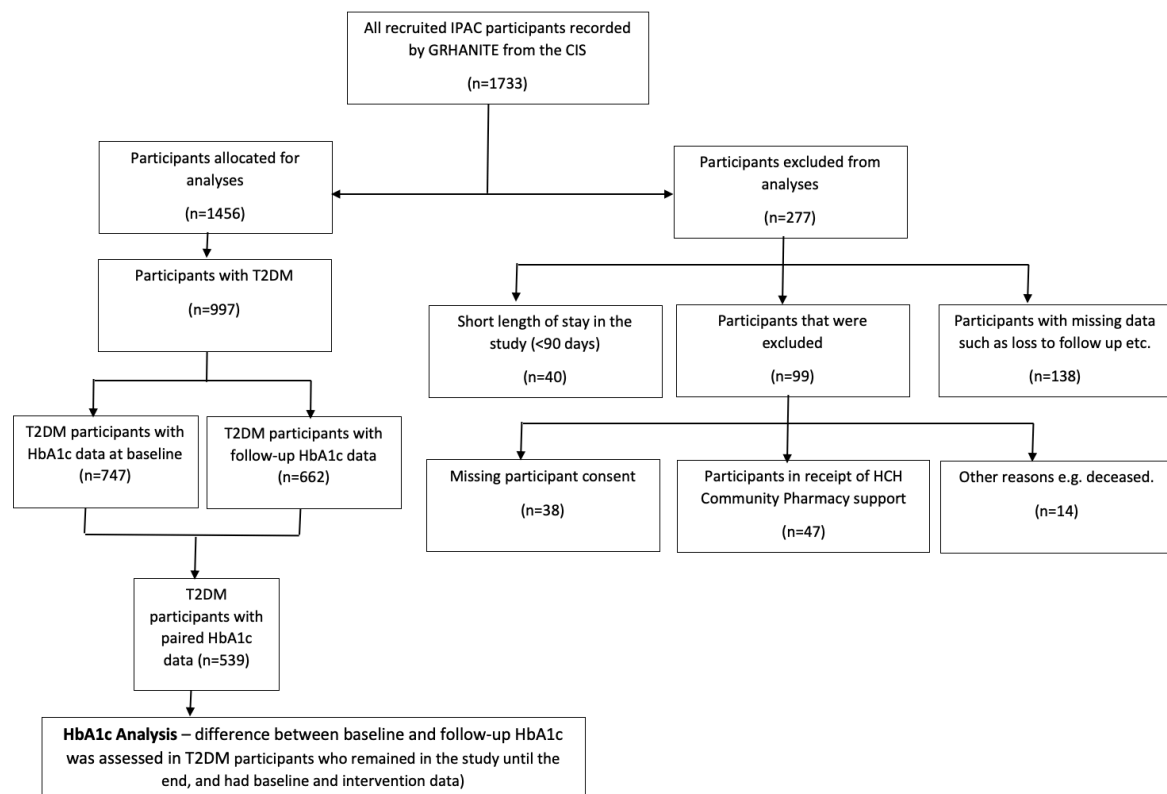
The outcomes attributed to the support provided by integrated pharmacists are generalisable to the broader ACCHS adult patient population with chronic disease who are at risk of developing medication related problems. This is because all study participants were usual patients accessing ACCHSs, were general patients rather than disease subgroups (with the exception of T2DM), a large number of ACCHSs participated in the study, and the study design was pragmatic being consistent with usual care. The lack of randomisation facilitated the recruitment of a large number of participants which also acted to optimise the external validity of the effects of the intervention.

Despite these limitations, no previous studies, to our knowledge, have evaluated the impact of integrated pharmacist services within Aboriginal health settings. This evaluation linked the observed clinical endpoint improvements to measured activities arising from the intervention such as medication management reviews, impacts on participant adherence, and practice-based activity that enhanced team care. According to the perspectives of stakeholders involved in the project, integrated pharmacists could have also influenced the quality of care in other intangible ways that are difficult to measure. These include the development of trust between the pharmacist, patients, healthcare providers, and external stakeholders such as community pharmacy that could have acted to improve the quality of care.<sup>184</sup> As a whole, the collection of multiple clinical endpoint improvements that were observed, support the effectiveness of integrated pharmacists within ACCHSs.

## **CONCLUSION**

The IPAC study is the first work to investigate the impact of integrated pharmacist interventions with regard to Indigenous peoples by enrolling adult Aboriginal and Torres Strait Islander participants with chronic disease. It may be the largest prospective study that investigated the impact of integrated pharmacists using intermediate clinical endpoints in primary health care settings. The intervention comprised non-dispensing medicines-related services, collaborative and coordinated care, including the provision of medication management reviews by pharmacists integrated within Aboriginal community-controlled health services. The IPAC study findings show that integrated pharmacists embedded into usual care in a range of geographical settings, can significantly improve the control of CVD risk factors, improve glycaemic control in patients with T2DM, and reduce absolute CVD risk in Aboriginal and Torres Strait islander adults with chronic disease. This evaluation supports the integration of non-dispensing pharmacists within ACCHS settings more broadly. This will increase Aboriginal peoples and Torres Strait Islanders access to comprehensive medication management support to significantly reduce CVD risk factors in this already high-risk population.

**Figure 1. Flow diagram for *HbA1c* outcome analysis in participants with Type 2 diabetes mellitus enrolled in the IPAC study**



*CIS= Clinical information systems*

*GRHANITE= Data extraction tool*

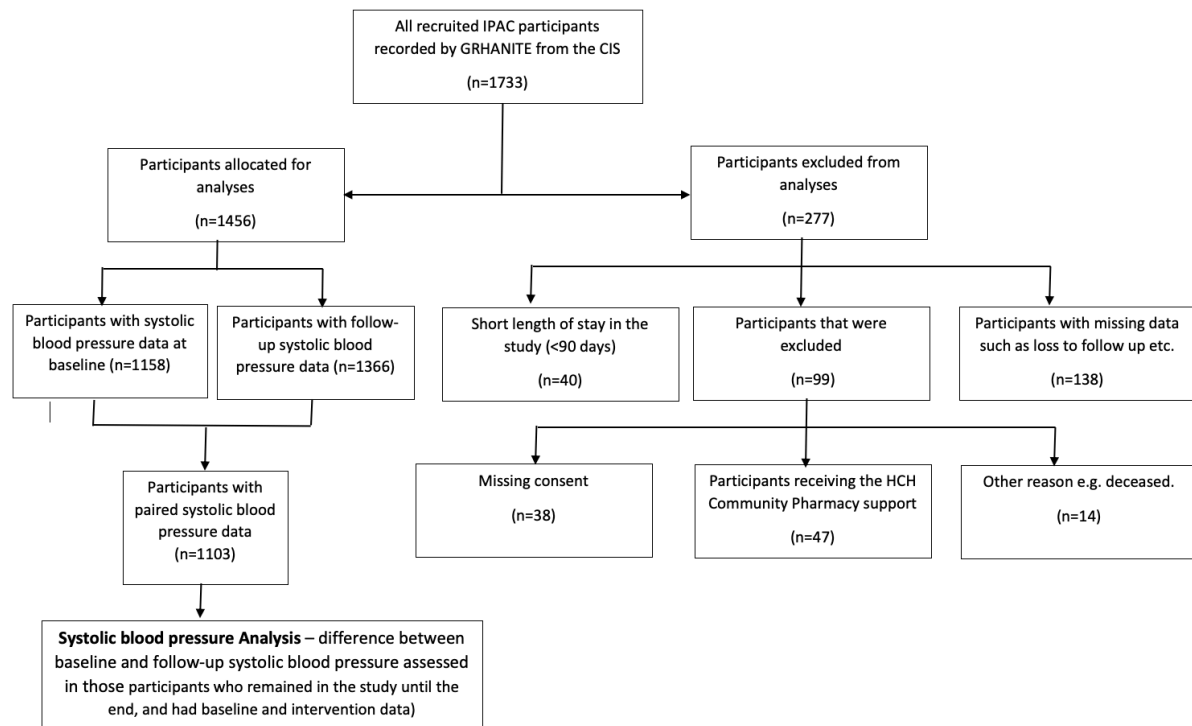
*HbA1c= Haemoglobin A1c*

*HCH= Health Care Homes*

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

*T2DM= Type 2 diabetes mellitus*

**Figure 2. Participant flow diagram for *systolic blood pressure (SBP)* outcome analysis in the IPAC study cohort**



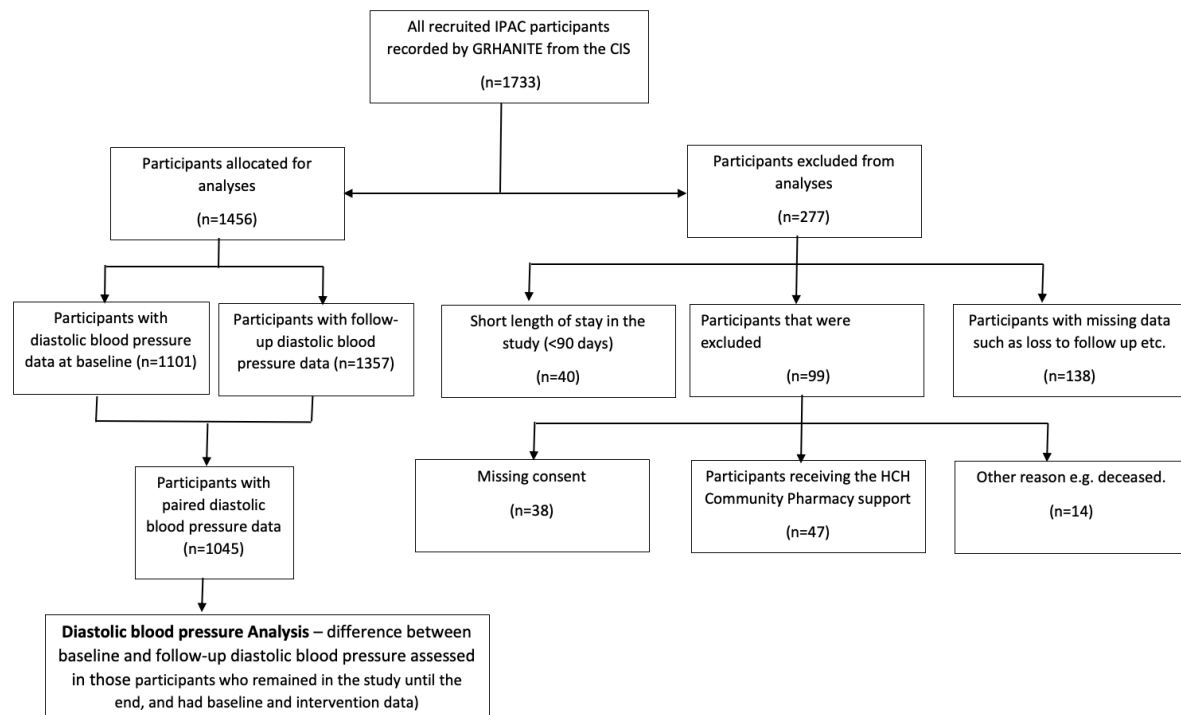
*CIS= Clinical information systems*

*GRHANITE= Data extraction tool*

*HCH= Health Care Homes*

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

**Figure 3. Participant flow diagram for *diastolic blood pressure (DBP)* outcome analysis in the IPAC study cohort**



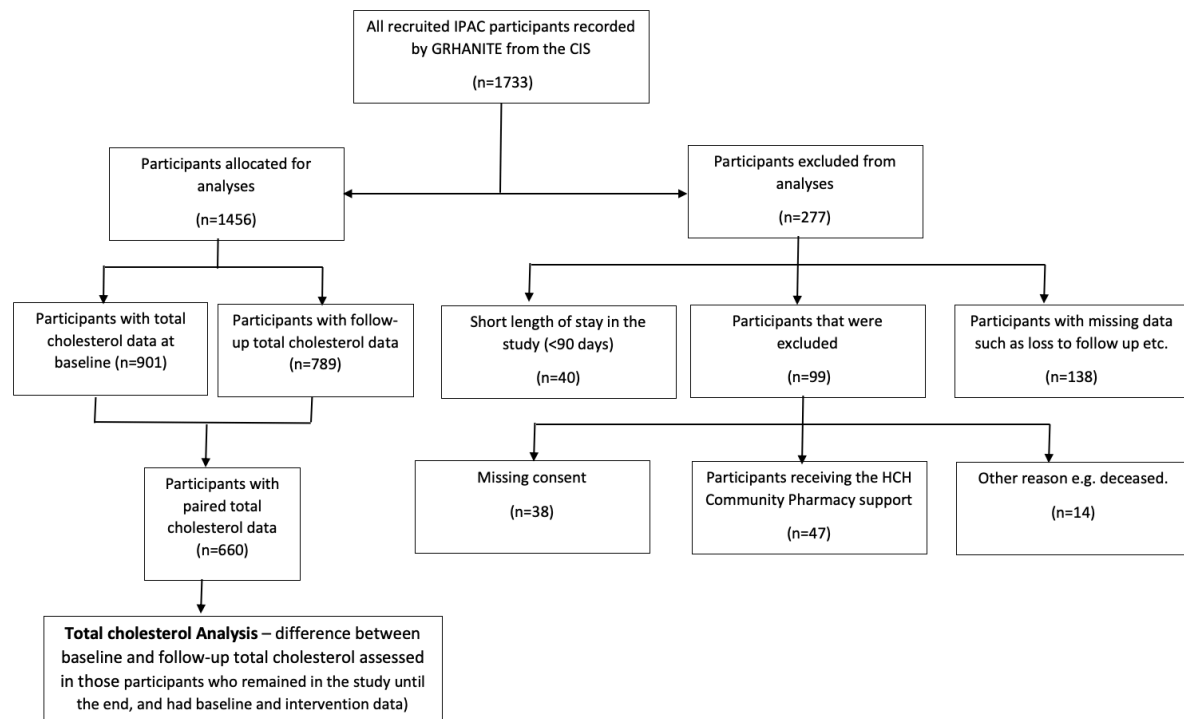
*CIS= Clinical information systems*

*GRHANITE= Data extraction tool*

*HCH= Health Care Homes*

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

**Figure 4. Participant flow diagram for *total cholesterol (TC)* outcome analysis in the IPAC study cohort**



*CIS= Clinical information systems*

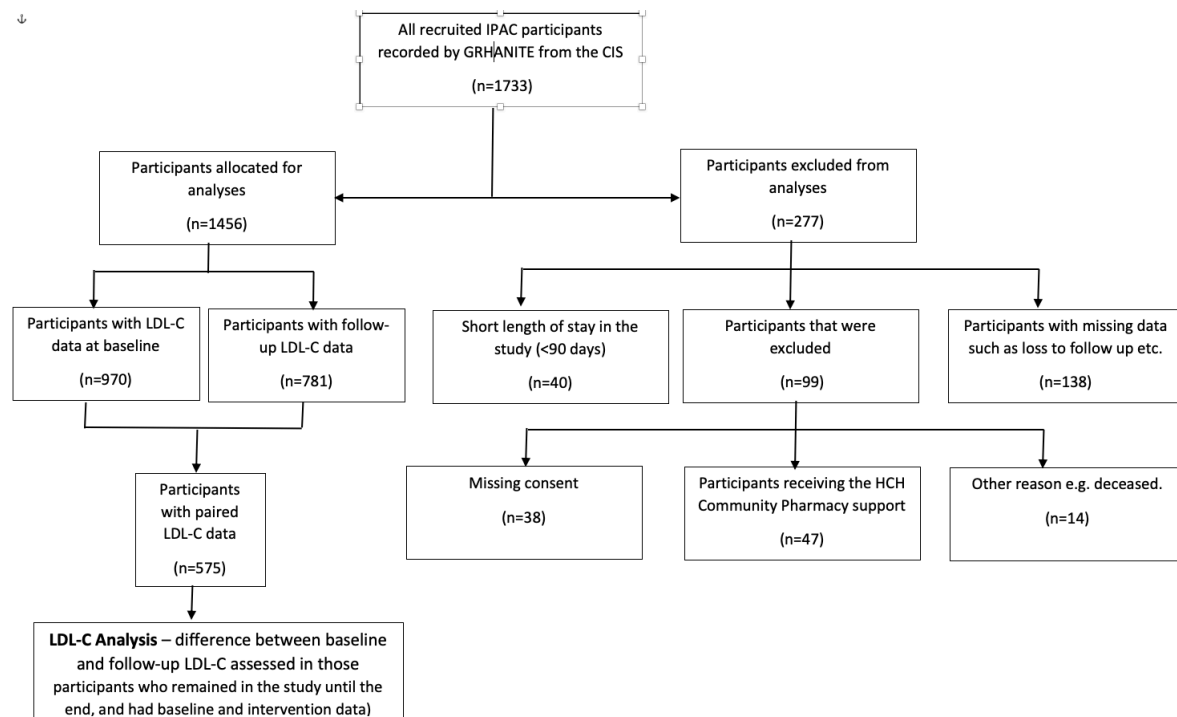
*GRHANITE= Data extraction tool*

*HCH= Health Care Homes*

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



**Figure 5. Participant flow diagram for low density lipoprotein cholesterol (LDL-C) outcome analysis in the IPAC study cohort**



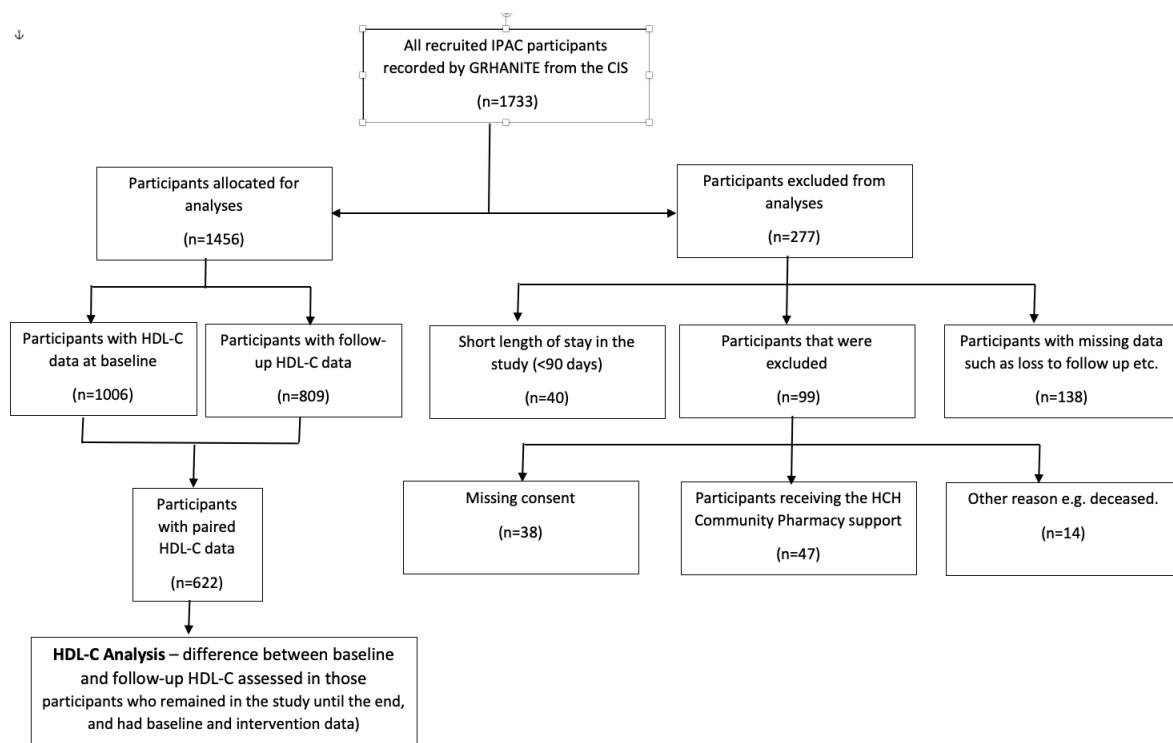
*CIS= Clinical information systems*

*GRHANITE= Data extraction tool*

*HCH= Health Care Homes*

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

**Figure 6. Participant flow diagram for *high density lipoprotein cholesterol (HDL-C)* outcome analysis in the IPAC study cohort**



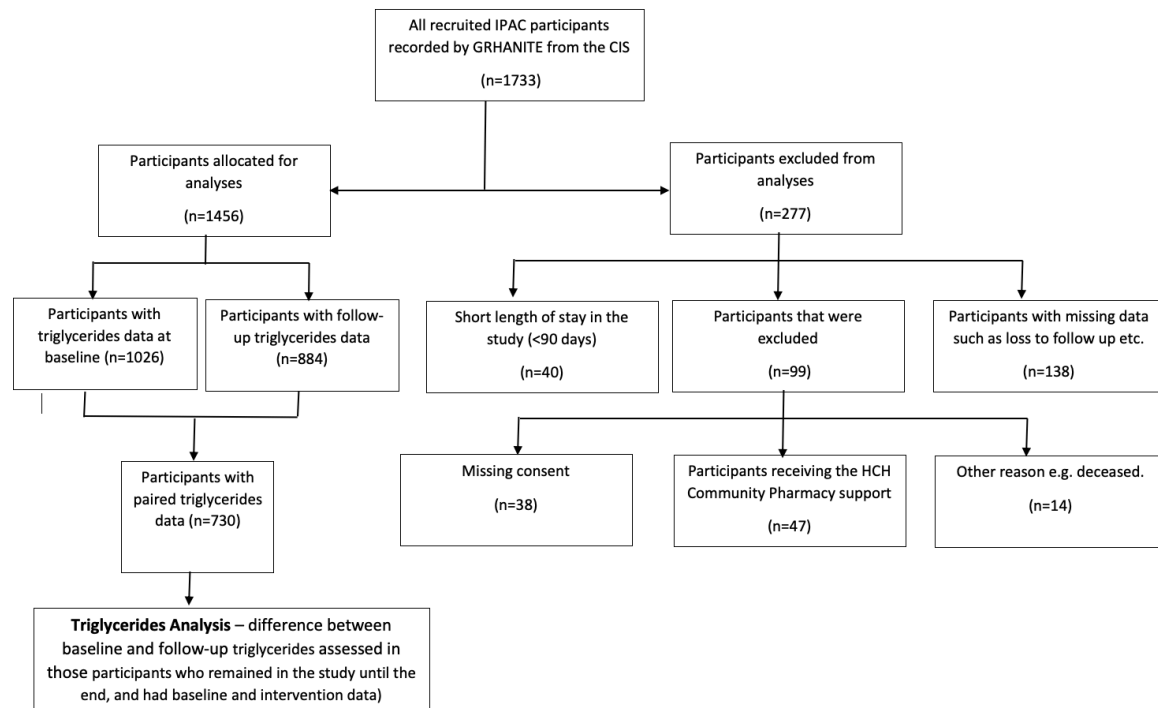
*CIS= Clinical information systems*

*GRHANITE= Data extraction tool*

*HCH= Health Care Homes*

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

**Figure 7. Participant flow diagram for *triglycerides (TG)* outcome analysis in the IPAC study cohort**



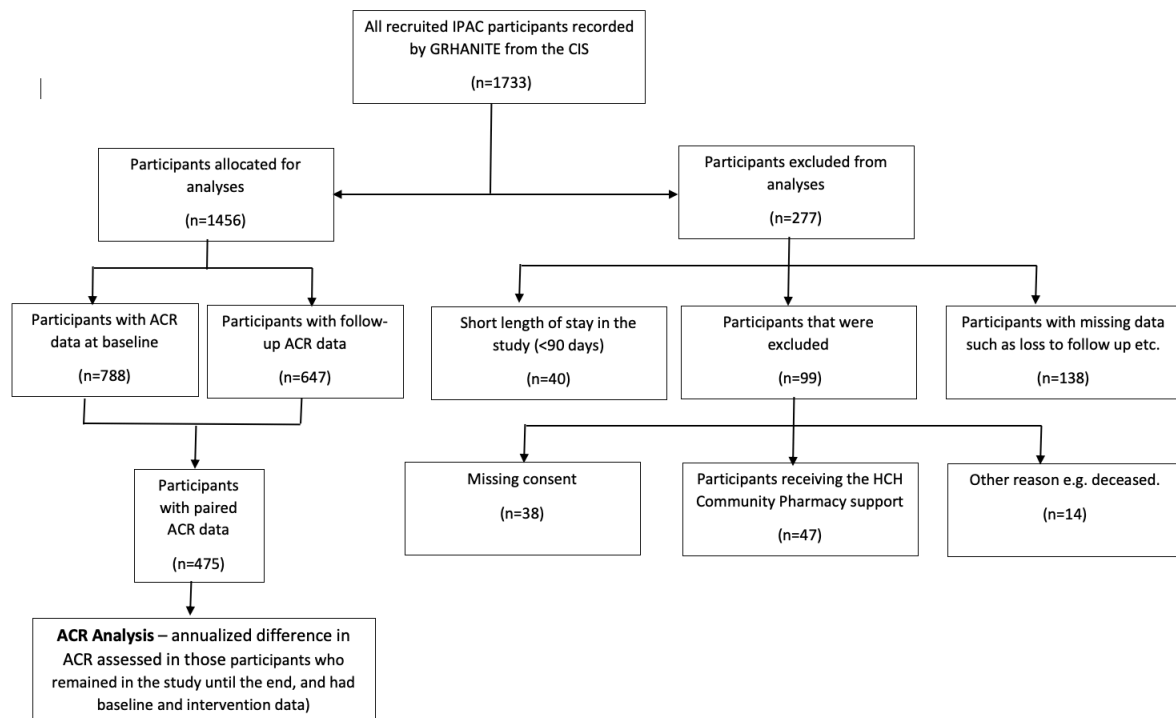
*CIS= Clinical information systems*

*GRHANITE= Data extraction tool*

*HCH= Health Care Homes*

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

**Figure 8. Participant flow diagram for *albumin-creatinine ratio (ACR)* outcome analysis in the IPAC study cohort**



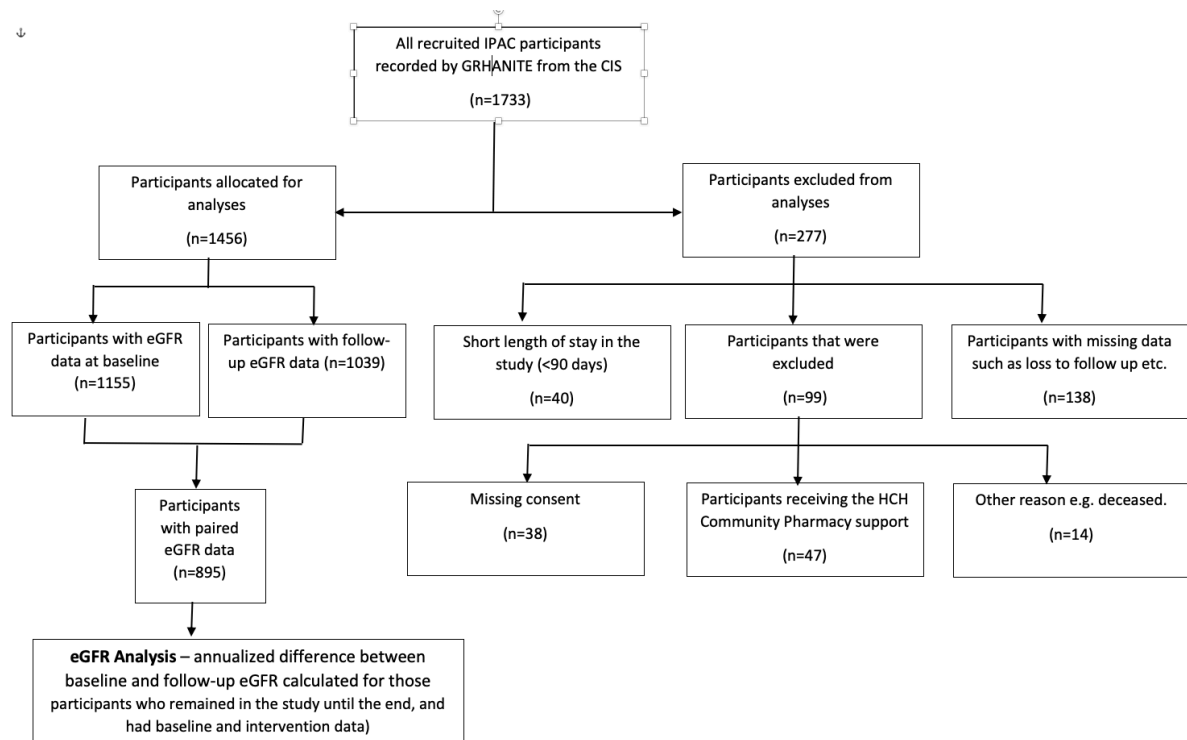
*CIS= Clinical information systems*

*GRHANITE= Data extraction tool*

*HCH= Health Care Homes*

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

**Figure 9. Participant flow diagram for estimated Glomerular Filtration Rate (eGFR) outcome analysis in the IPAC study cohort**



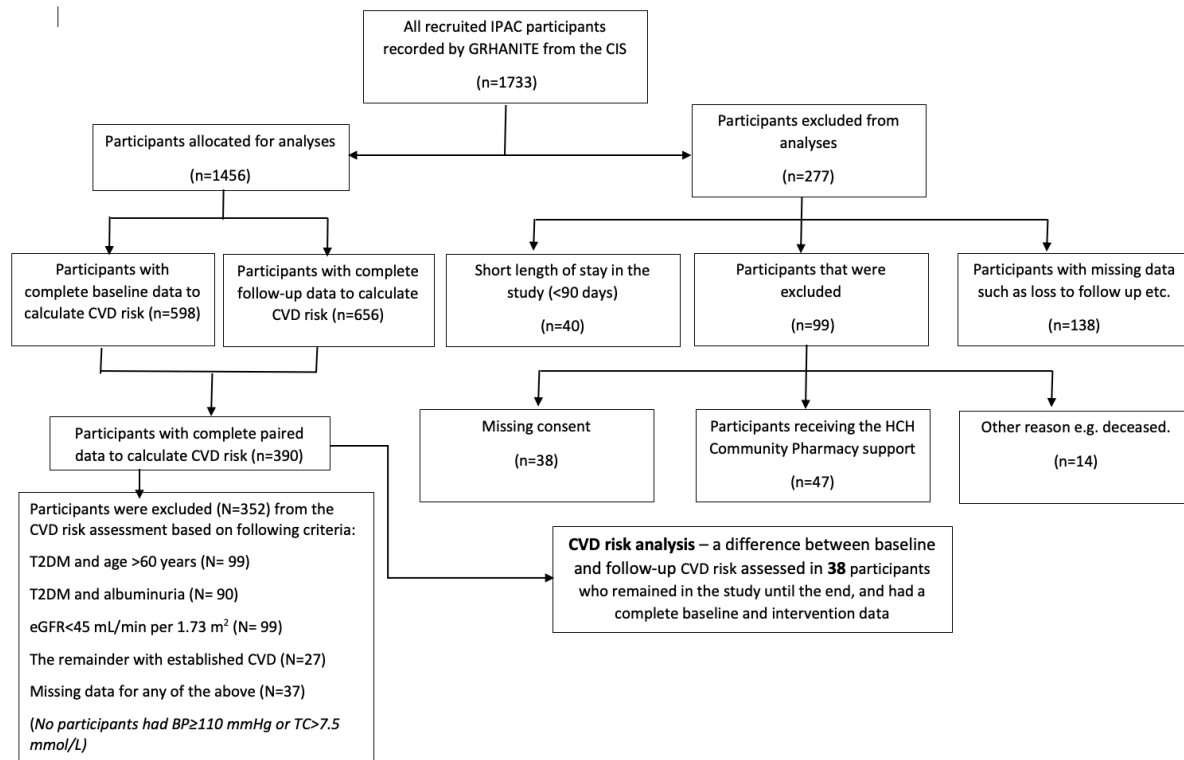
CIS= Clinical information systems

GRHANITE= Data extraction tool

HCH= Health Care Homes

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

**Figure 10. Participant flow diagram for *calculated absolute cardiovascular disease risk (CVD risk)* outcome analysis in the IPAC study cohort**



BP= blood pressure

CIS= Clinical Information Systems

CVD= cardiovascular disease

e-GFR= estimated glomerular filtration rate

GRHANITE= Data extraction tool

HCH= Health Care Homes

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

T2DM= Type 2 diabetes mellitus

TC= total cholesterol

**Table 1: Baseline characteristics of participants with Type 2 diabetes mellitus (T2DM, n=997) and the whole IPAC participant cohort (n=1,456) disaggregated into subsets with complete and paired pre and post-intervention biomedical outcome measures.**

Patient characteristics	HbA1c in participants with T2DM (n=539)	SBP (n=1,103)	DBP (n=1,045)	TC (n=660)	LDL-C (n=575)	HDL-C (n=622)	TG (n=730)	ACR (n=475)	eGFR (n=895)	Estimated primary CVD risk* (n=38)
<b>Location classification by ASGS-RA (2016)</b>										
Major city (RA1)	5/539 (0.9%)	34/1103 (3.1%)	34/1045 (3.3%)	0/660 (0%)	1/575 (0.2%)	2/622 (0.3%)	0/730 (0%)	2/475 (0.4%)	26/895 (2.9%)	0/38 (0%)
Inner regional (RA2)	147/539 (27.3%)	381/1103 (34.5%)	377/1045 (36.1%)	113/660 (17.1%)	138/575 (24.0%)	144/622 (23.2%)	176/730 (24.1%)	89/475 (18.7%)	276/895 (30.8%)	7/38 (18.2%)
Outer regional (RA3)	240/539 (44.5%)	344/1103 (31.2%)	325/1045 (31.1%)	367/660 (55.6%)	271/575 (47.1%)	285/622 (45.8%)	344/730 (47.1%)	247/475 (52.0%)	367/895 (41.0%)	16/38 (42.1%)
Remote (RA4)	60/539 (11.1%)	155/1103 (14.1%)	124/1045 (11.9%)	55/660 (8.3%)	51/575 (8.9%)	66/622 (10.6%)	85/730 (11.6%)	41/475 (8.6%)	90/895 (10.1%)	1/38 (2.6%)
Very remote (RA5)	87/539 (16.1%)	189/1103 (17.1%)	185/1045 (17.7%)	125/660 (18.9%)	114/575 (19.8%)	125/622 (20.1%)	125/730 (17.1%)	96/475 (20.2%)	136/895 (15.2%)	14/38 (36.8%)
<b>Mean age at baseline (SD) [years]</b>	n=539 58.2 (20.9)	n= 1103 56.9 (36.5)	n=1045 56.9 (34.3)	n= 660 58.5 (25.7)	n= 575 58.3 (19.2)	n= 622 57.9 (22.4)	n=730 58.6 (24.3)	n=475 57.7 (21.1)	n=895 58.2 (26.9)	n=38 59.8 (7)
<b>Sex (n,%)</b>										
Male	188/539 (34.9%)	428/1103 (38.8%)	406/1045 (38.9%)	241/660 (36.5%)	216/575 (37.6%)	237/622 (38.1%)	280/730 (38.4%)	180/475 (37.9%)	346/895 (38.7%)	9/38 (23.7%)
Female	351/539 (65.1%)	675/1103 (61.2%)	639/1045 (61.1%)	419/660 (63.5%)	359/575 (62.4%)	385/622 (61.9%)	450/730 (61.6%)	295/475 (62.1%)	549/895 (61.3%)	29/38 (76.3%)
<b>Ethnicity (n,%)</b>	n=539	n=1101	n=1044	n=658	n=574	n=621	n=729	n=474	n=892	
Aboriginal and/or Torres Strait Islander	508/539 (94.3%)	1005/1101(91.3%)	953/1044 (91.3%)	617/658 (93.8%)	528/574 (92.0%)	571/621 (91.9%)	676/729 (92.7%)	453/474 (95.6%)	819/892 (91.8%)	37/38 (97.4%)
Non-Indigenous	31/539 (5.7%)	96/1101 (8.7%)	91/1044 (8.7%)	41/658 (6.2%)	46/574 (8.0%)	50/621 (8.1%)	53/729 (7.3%)	21/474 (4.4%)	73/892 (8.2%)	1/38 (2.6%)
<b>Pensioner/concessional (n, %)</b>	439/539 (81.5%)	891/1103 (80.8%)	839/1045 (80.3%)	573/660 (86.8%)	472/575 (82.1%)	513/622 (82.5%)	611/730 (83.7%)	403/475 (84.8%)	747/895 (83.5%)	28/38 (73.7%)
<b>CTG scripts eligible (n,%)</b>	418/539 (77.6%)	778/1103 (70.5%)	759/1045 (72.6%)	493/660 (74.7%)	425/575 (73.9%)	450/622 (72.4%)	553/730 (75.8%)	362/475 (76.2%)	682/895 (76.2%)	27/38 (71.1%)
<b>Patient engaged in Health Care Home program (n, %) <sup>a</sup></b>	72/539 (13.4%)	134/1103 (12.2%)	119/1045 (11.4%)	86/660 (13.0%)	71/575 (12.4%)	86/622 (13.8%)	86/730 (11.8%)	64/475 (13.5%)	96/895 (10.7%)	7/38 (18.4%)
<b>Number of medications<sup>#</sup></b>	n=441	n= 835	n=792	n= 558	n= 470	n= 508	n=606	n=399	n=722	n=32
Mean (SD)	8.0 (10.5)	7.1 (11.6)	7.2 (11.0)	7.3 (7.1)	7.4 (8.7)	7.3 (9)	7.6 (9.8)	7.4 (7.8)	7.6 (10.7)	5.3 (4.8)

Patient characteristics	HbA1c in participants with T2DM (n=539)	SBP (n=1,103)	DBP (n=1,045)	TC (n=660)	LDL-C (n=575)	HDL-C (n=622)	TG (n=730)	ACR (n=475)	eGFR (n=895)	Estimated primary CVD risk* (n=38)
Median (IQR)	8 (6-10)	7 (5-9)	7 (5-9)	7 (5-9)	7 (5-10)	7 (5-9)	7 (5-10)	7 (5-9)	7 (5-10)	5 (3-7)
Prior medication review (MBS item 900) <sup>c</sup> (n,%)	57/539 (10.6%)	114/1103 (10.3%)	113/1045 (10.8%)	46/660 (7.0%)	53/575 (9.2%)	54/622 (8.7%)	71/730 (9.7%)	38/475 (8.0%)	100/895 (11.2%)	4/38 (10.5%)
Doctors' encounters prior to enrolment (per 12 months) <sup>d</sup>	n=516	n= 1016	n=961	n= 629	n= 547	n= 591	n=701	n=445	n=839	n=36
Mean (SD)	7.8 (14.1)	7.5 (22.3)	7.5 (22.6)	8 (17.6)	7.8 (14)	7.8 (13.9)	8.4 (15.9)	7.8 (16.0)	8.2 (18.8)	6.9 (5.4)
Median (IQR)	6 (3-10)	6 (3-10)	6 (3-10)	6 (3-10)	6 (3-10)	6 (3-10)	6 (4-11)	6 (3-10)	6 (3-11)	5 (4-9)
Mean number of medication 'adherent days' (SD) <sup>e</sup>	n=441	n= 835	n=792	n= 558	n= 470	n= 508	n= 606	n=399	n=722	n=32
	6.1 (4.2)	6.1 (5.8)	6.1 (4.2)	6.1 (3.5)	6.2 (2.2)	6.1 (3.8)	6.2 (3.4)	6.2 (3.4)	6.2 (3.5)	6.3 (1.7)
Self-assessed health status score (SF1): <sup>#f</sup> (n,%)	n=388	n=787	n=746	n=484	n=414	n=448	n=533	n=336	n=636	n=31
Excellent	20/388 (5.2%)	33/787 (4.2%)	34/746 (4.6%)	26/484 (5.4%)	15/414 (3.6%)	18/448 (4.0%)	27/533 (5.1%)	19/336 (5.6%)	27/636 (4.2%)	1/31 (3.2%)
Very good	54/388 (13.9%)	104/787 (13.2%)	104/746 (13.9%)	76/484 (15.7%)	60/414 (14.5%)	65/448 (14.5%)	85/533 (15.9%)	50/336 (14.9%)	98/636 (15.4%)	4/31 (12.9%)
Good	162/388 (41.8%)	327/787 (41.6%)	305/746 (40.9%)	200/484 (41.3%)	177/414 (42.8%)	185/448 (41.3%)	222/533 (41.7%)	129/336 (38.4%)	260/636 (40.9%)	12/31 (38.7%)
Fair	106/388 (27.3%)	229/787 (29.1%)	214/746 (28.7%)	135/484 (27.9%)	121/414 (29.2%)	132/448 (29.5%)	146/533 (27.4%)	101/336 (30.1%)	183/636 (28.8%)	11/31 (35.5%)
Poor	42/388 (10.8%)	77/787 (9.8%)	72/746 (9.7%)	40/484 (8.3%)	37/414 (8.9%)	44/448 (9.8%)	46/533 (8.6%)	34/336 (10.1%)	54/636 (8.5%)	3/31 (9.7%)
Very poor	4/388 (1.0%)	17/787 (2.2%)	17/746 (2.3%)	7/484 (1.5%)	4/414 (1.0%)	4/448 (0.9%)	7/533 (1.3%)	3/336 (0.9%)	14/636 (2.2%)	0/31 (0%)
Recorded clinical diagnoses: <sup>#</sup> (n,%)										
Type 2 diabetes mellitus	539/539(100%)	651/1103 (59.0%)	616/1045 (59.0%)	430/660 (65.2%)	380/575 (66.1%)	418/622 (67.2%)	482/730 (66.0%)	358/475 (75.4%)	562/895 (62.8%)	10/38 (26.3%)
Hypertension	360/539 (66.8%)	703/1103 (63.7%)	657/1045 (62.9%)	415/660 (62.9%)	365/575 (63.5%)	401/622 (64.5%)	458/730 (62.7%)	310/475 (65.3%)	574/895 (64.1%)	22/38 (57.9%)
Dyslipidaemia	300/539 (55.7%)	550/1103 (49.9%)	520/1045 (49.8%)	335/660 (50.8%)	290/575 (50.4%)	324/622 (52.1%)	367/730 (50.3%)	245/475 (51.6%)	446/895 (49.8%)	16/38 (42.1%)
Patients with established or existing CVD <sup>g</sup>	168/539 (31.2%)	363/1103 (32.9%)	344/1045 (32.9%)	221/660 (33.5%)	191/575 (33.2%)	209/622 (33.6%)	249/730 (34.1%)	153/475 (32.2%)	291/895 (32.5%)	0/38 (0%)
Chronic kidney disease	252/539 (46.8%)	456/1103 (41.3%)	429/1045 (41.1%)	278/660 (42.1%)	236/575 (41.0%)	261/622 (42.0%)	292/730 (40.0%)	220/475 (46.3%)	369/895 (41.2%)	18/38 (47.4%)



Patient characteristics	HbA1c in participants with T2DM (n=539)	SBP (n=1,103)	DBP (n=1,045)	TC (n=660)	LDL-C (n=575)	HDL-C (n=622)	TG (n=730)	ACR (n=475)	eGFR (n=895)	Estimated primary CVD risk* (n=38)
Patients with a diagnosis of rheumatic heart disease (RHD) or Acute rheumatic fever (ARF)	10/539 (1.9%)	32/1103 (2.9%)	27/1045 (2.6%)	19/660 (2.9%)	13/575 (2.3%)	13/622 (2.1%)	18/730 (2.5%)	15/475 (3.2%)	23/895 (2.6%)	1/38 (2.6%)
Chronic obstructive pulmonary disease (COPD)	31/539 (5.8%)	87/1103 (7.9%)	82/1045 (7.9%)	61/660 (9.2%)	46/575 (8.0%)	50/622 (8.0%)	56/730 (7.7%)	35/475 (7.4%)	63/895 (7.0%)	6/38 (15.8%)
Depressive disorder	17/539 (3.2%)	64/1103 (5.8%)	60/1045 (5.7%)	36/660 (5.5%)	28/575 (4.9%)	30/622 (4.8%)	35/730 (4.8%)	20/475 (4.2%)	42/895 (4.7%)	0/38 (0%)
Patients with comorbidity (1 or more chronic diseases)	482/539 (89.4%)	967/1103 (87.7%)	914/1045 (87.5%)	577/660 (87.4%)	518/575 (90.1%)	561/622 (90.2%)	645/730 (88.4%)	423/475 (89.1%)	787/895 (87.9%)	33/38 (86.8%)
Patients with multi-morbidity (2 or more chronic diseases)	422/539 (78.3%)	851/1103 (77.2%)	804/1045 (76.9%)	507/660 (76.8%)	452/575 (78.6%)	490/622 (78.9%)	563/730 (77.1%)	368/475 (77.5%)	693/895 (77.4%)	25/38 (65.8%)
<b>Median (IQR) length of stay in the study [days]</b>	284 (232-350)	266 (210-325)	268 (210-325)	314 (239-360)	295 (239-351)	294 (237-350)	296 (237-356)	301 (238-365)	296 (234-359)	255 (203-316)

SD = cluster-adjusted standard deviation (ACCHS cluster); IQR = inter-quartile range;

ACR= albumin-creatinine ratio

BP= blood pressure;

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.

DBP= diastolic blood pressure

eGFR= estimated glomerular filtration rate

HbA1C= glycated haemoglobin

HDL-C= high density lipoprotein cholesterol

LDL-C= low density lipoprotein cholesterol

MBS= Medicare Benefits Schedule.

SBP= systolic blood pressure

TC= total cholesterol

TG= triglycerides

\* Sourced from the pharmacist's logbook.

\* Estimated 5-year risk of a primary cardiovascular event according to the Framingham risk equation for those not at high risk according to clinical criteria (<http://www.cvdcheck.org.au/>)<sup>185</sup>

<sup>a</sup> Health Care Homes (HCH) program funded by the Australian Government designed to better coordinate the health care of patients with chronic disease

<sup>b</sup> Denominator was sourced from logbook data entered by pharmacists with regard to the medication adherence of participants.

<sup>c</sup> Prior MBS item 900 claim measured for the 12-month period prior to participant enrolment. This rebate pertains to a Home Medicines Review (HMR).

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

<sup>e</sup> 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.

<sup>f</sup> 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?'

<sup>g</sup> CVD= cardiovascular disease: It refers to any of the following: coronary heart disease, cerebrovascular disease, and peripheral vascular disease.

**Table 2. Mean difference in primary and secondary clinical endpoints in IPAC study participants using paired pre and post-intervention measures, adjusted for health service cluster and the length of follow-up time.**

Variable	Value pre-enrolment mean (SD)	Value during follow-up mean (SD)	Mean difference mean (SD, 95% CI)	p-value <sup>^</sup>
<b>Primary clinical endpoints</b>				
<b>HbA1c*</b> , mmol/mol [%units] (n=539 with a clinical diagnosis of T2DM)	66.8 (37.2) [8.3% (5.5%)]	64.0 (39.5) [8.0% (5.8%)]	-2.8 (19.5, -4.5 to -1.0) [-0.3% (3.9%, -0.4% to -0.1%)]	<b>0.001</b>
<b>SBP</b> , mmHg (n=1103)	132.7 (33.2)	132.0 (29.9)	-0.7 (16.6, -1.7 to 0.4)	0.16
<b>DBP</b> , mmHg (n=1045)	80.0 (35.6)	79.2 (29.1)	-0.8 (9.4, -1.4 to -0.2)	<b>0.008</b>
<b>TC</b> , mmol/L <sup>#</sup> (n=660)	4.51 (1.80)	4.35 (2.06)	-0.15 (0.77, -0.22 to -0.09)	<b>&lt;0.001</b>
<b>LDL-C</b> , mmol/L <sup>#</sup> (n=575)	2.35 (1.20)	2.27 (1.20)	-0.08 (0.48, -0.13 to -0.03)	<b>0.001</b>
<b>HDL-C</b> , mmol/L <sup>#</sup> (n=622)	1.05 (0.5)	1.06 (0.5)	0.01 (0.25, -0.02 to 0.03)	0.32
<b>TG</b> , mmol/L <sup>#</sup> (n=730)	2.39 (2.43)	2.29 (2.21)	-0.11 (1.08, -0.20 to -0.01)	<b>0.006</b>
<b>ACR</b> , mg/mmol* n=475	57.9 (183.1)	61.7 (224.5)	3.8 (102.4, -6.32 to 13.83)	0.42
<b>CVD 5-year risk</b> , %units (n=38)	11.9 (7.2)	10.9 (5.4)	-1.0 (2.6, -1.8 to -0.12)	<b>0.027</b>
<b>Secondary clinical endpoints</b>				
<b>eGFR* (no minimum follow-up time)</b> , ml/min/1.73m <sup>2</sup> (n=895)	49.1 (159.2)	48.4 (160.4)	1.9 (25.7, 0.1 to 3.7)**	<b>&lt;0.001</b>
<b>eGFR* (6-month minimum follow-up time)</b> , ml/min/1.73m <sup>2</sup> (n=720)	49.6 (140.6)	48.1 (145.4)	-0.2 (36.0, -2.99 to 2.7)**	<b>0.034</b>

Bold p-values imply statistically significant change at the 0.05 level.

<sup>^</sup>P-values (paired data) were derived from the cluster-adjusted (ACCHS cluster) comparison of differences against zero and were determined using the svy linearized : regress Stata command. The follow-up time in days between the enrolment date and the end of study date was added to all cluster-adjusted linear regression models.

SD = cluster-adjusted standard deviation (ACCHS cluster)

\*Refers to last observation pre-enrolment and at follow-up. Unit conversion from IFCC (International Federation of Clinical Chemistry, mmol/mol) to DCCT (Diabetes Control and Complications Trial, %) units using the <https://www.diabetes.co.uk/hba1c-units-converter.html> units converter. 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/1.73m<sup>2</sup>), sourced from the National Guide (3<sup>rd</sup> Edn).<sup>186</sup> Albumin:creatinine ratio normal reference range: >2.5 mg/mmol for males and >3.5mg/mmol for females. Macroalbuminuria is defined as >25mg/mmol in males and >35 mg/mmol in females. Absolute CVD 5-year risk sourced from the National Guide (3<sup>rd</sup> Edn).<sup>187</sup>

\*\*Mean annualised difference. P-value (paired data) were derived from the cluster-adjusted (ACCHS cluster) comparison of annualised differences against -3, as this is equivalent to a paired t-test. The value of -3 is the expected mean annual eGFR (ml/min/1.73m<sup>2</sup>) linear decline in Aboriginal and Torres Strait Islander adults (see Tables 12-14).

<sup>#</sup> Dyslipidaemia is defined by one or more of the following: Low Density Lipoprotein (LDL) ≥3.5mmol/L; Total cholesterol (TC) ≥5.5mmol/L; Triglycerides (TG) ≥2.0mmol/L; High density lipoprotein (HDL) <1.0 mmol/L for men and <1.3 mmol/L for women [Source: National Aboriginal and Torres Strait Islander Health Measure Survey, 2012-13].<sup>188</sup>

ACR= albumin-creatinine ratio

BP= blood pressure;

CVD= cardiovascular disease.

DBP= diastolic blood pressure

eGFR= estimated glomerular filtration rate

HbA1C= glycated haemoglobin

HDL-C= high density lipoprotein cholesterol

LDL-C= low density lipoprotein cholesterol

SBP= systolic blood pressure

TC= total cholesterol

TG= triglycerides

T2DM= type 2 diabetes mellitus

**Table 3. Number and proportion of participants with clinical endpoint measures who were in receipt of medication management reviews, and services based on MBS item 10987 and 10997 (follow-up) during the intervention (intervention-related characteristics for covariate analysis).**

	HbA1c* N=539 (n,%)	SBP N=1103 (n,%)	DBP N=1045 (n,%)	TC N=660 (n,%)	LDL-C N=575 (n,%)	HDL-C N=622 (n,%)	TG N=730 (n,%)	ACR N=475 (n,%)	eGFR N=895 (n,%)	CVD-risk N=38 (n,%)
<b>Non-HMR</b>	248 (46.0)	527 (47.8)	527 (50.4)	279 (42.3)	281 (48.9)	311 (50.0)	339 (46.4)	192 (40.4)	396 (44.2)	22 (57.9)
<b>HMR</b>	177 (32.8)	344 (31.2)	344(32.9)	251 (38.0)	184 (32.0)	192 (30.9)	246 (33.7)	182 (38.3)	316 (35.3)	8 (21.1)
<b>MBS item 10987/10997</b>	288 (53.4)	484 (43.9)	453 (43.3)	419 (63.5)	341 (59.3)	375 (60.3)	410 (56.2)	284 (59.8)	456 (50.9)	19 (50.0)

\*From participants with T2DM.

HMR= Home Medicines Review. A completed HMR represents a comprehensive medication management review that fulfils the criteria for a Medicare Benefits Scheme (MBS) claim for item 900, as sourced from the integrated pharmacist's logbook.

Non-HMR= a comprehensive medication management review that was not an HMR, as sourced from the integrated pharmacist's logbook.

MBS items 10987 and 10997 provide a rebate for a service by a practice nurse or an Aboriginal and Torres Strait Islander Health Practitioner (e.g. staff within ACCHSs) that includes a follow-up the assessment of the medication adherence of an Indigenous patient.

ACR= albumin-creatinine ratio

BP= blood pressure;

CVD= cardiovascular disease.

CVD-risk= Estimated 5-year risk of a primary cardiovascular event according to the Framingham risk equation for those not at high risk according to clinical criteria.<sup>189</sup>

DBP= diastolic blood pressure

eGFR= estimated glomerular filtration rate

HbA1C= glycated haemoglobin

HDL-C= high density lipoprotein cholesterol

LDL-C= low density lipoprotein cholesterol

SBP= systolic blood pressure

TC= total cholesterol

TG= triglycerides

T2DM= type 2 diabetes mellitus

**Table 4: Mean difference in HbA1c in participants with a clinical diagnosis of Type 2 diabetes mellitus (T2DM, n=539) using paired pre and post-intervention measures, stratified by selected participant, health service, and intervention characteristics, and adjusted for health service cluster and the length of follow-up time.**

Time:

T2DM patients with paired data for HbA1c (n=539)	HbA1c (mmol/mol) [%units]*			P-value
	Last observation pre-enrolment	Last observation at follow-up	Difference	
	Mean (SD) 66.8 (37.2) [8.3% (5.5%)]	Mean (SD) 64.0 (39.5) [8.0% (5.8%)]	Mean (SD, 95% CI) -2.8 (19.5, -4.5 to -1.0) [-0.3% (3.9%, -0.4% to -0.1%)]	0.001^
Participant-related characteristics				
Median age at baseline =58 years	Mean (SD)	Mean (SD)	Mean (SD)	0.79^^
<Median (n=249)	71.5 (34.7)	68.5 (44.2)	-3.0 (20.5)	
≥Median (n=290)	62.7 (30.7)	60.2 (20.4)	-2.5 (17.0)	
Median length of time between measurements =196 days#	Mean (SD)	Mean (SD)	Mean (SD)	0.24^^
<Median (n=269)	67.4 (29.5)	63.1 (34.4)	-4.3 (16.4)	
≥Median (n=270)	66.2 (31.2)	64.9 (27.9)	-1.3 (19.7)	
Sex	Mean (SD)	Mean (SD)	Mean (SD)	0.44^^
Male (n=351)	66.9 (33.7)	64.5 (31.9)	-2.4 (16.9)	
Female (n=188)	66.5 (24.7)	63.2 (30.2)	-3.3 (15.1)	
Number of adherent days (baseline score)	Mean (SD)	Mean (SD)	Mean (SD)	0.95^^
0-5 days (n=87)	75.0 (28.0)	72.0 (24.3)	-3.0 (17.7)	
6-7 days (n=354)	65.1 (33.9)	62.4 (39.5)	-2.7 (20.7)	
Median number of medications =8	Mean (SD)	Mean (SD)	Mean (SD)	0.11^^
<Median (n=234)	67.5 (31.5)	63.4 (35.2)	-4.1 (21.4)	
≥Median (n=207)	66.6 (33.2)	65.4 (29.6)	-1.2 (13.0)	
Self -assessed health status at baseline (SF1)	Mean (SD)	Mean (SD)	Mean (SD)	0.76^^
'Good, Fair, Poor, Very Poor' (n=314)	68.3 (33.7)	65.7 (30.1)	-2.6 (16.0)	
'Excellent' or 'very good' (n=74)	62.2 (15.5)	60.1 (12.9)	-2.1 (13.8)	
Health service-related characteristics				
Patient attended a health service with a median IRSEO score	Mean (SD)	Mean (SD)	Mean (SD)	0.95^^
< 60 (n=244)	65.1 (42.2)	62.4 (54.7)	-2.7 (17.2)	
>= 60 (n=295)	68.2 (34.4)	65.4 (25.8)	-2.8 (20.6)	
Intervention-related characteristics				
Patient who had a HMR compared to patient who had a non-HMR	Mean (SD)	Mean (SD)	Mean (SD)	0.27^^
Non-HMR (n=248)	66.8 (28.4)	63.7 (29.9)	-3.1 (21.0)	
HMR (n=177)	66.2 (41.2)	65.6 (37.3)	-0.6 (20.8)	
Patients who received an MBS service for item 10987 or 10997 during the follow-up period**	Mean (SD)	Mean (SD)	Mean (SD)	0.91^^
No (n=251)	67.4 (22.2)	64.3 (38.0)	-3.1 (20.6)	
Yes (n=288)	66.2 (40.7)	63.7 (30.6)	-2.5 (17.0)	

Bold p-values imply statistically significant change at the 0.05 level.

^P-value (paired data) was derived from the cluster-adjusted (ACCHS cluster) comparison of HbA1c differences against zero and was determined using the `svy linearized : regress` Stata command.

^^Cluster adjusted p-values (ACCHS cluster) were determined using the `svy linearized : regress` Stata command with differences of HbA1c as the outcome measure. The follow-up time in days between the enrolment date and the end of study date was added to all cluster-adjusted linear regression models.

\*Unit conversion from IFCC (International Federation of Clinical Chemistry, mmol/mol) to DCCT (Diabetes Control and Complications Trial, %) units using the <https://www.diabetes.co.uk/hba1c-units-converter.html> units converter.

\*\*MBS items 10987 and 10997 provide a rebate for a service by a practice nurse or an Aboriginal and Torres Strait Islander Health Practitioner (e.g. staff within ACCHSs) that includes a follow-up the assessment of the medication adherence of an Indigenous patient.

# The median length of stay in the study was 284 days (IQR:232-350).

SD= cluster adjusted standard deviation (ACCHS cluster).

Health service= Aboriginal community-controlled health service (ACCHS)

HMR= Home Medicines Review. A completed HMR represents a comprehensive medication management review that fulfils the criteria for a Medicare Benefits Scheme (MBS) claim for item 900, as sourced from the integrated pharmacist's logbook.

IRSEO= Indigenous Relative Socioeconomic Outcomes index. The IRSEO reflects relative advantage or disadvantage at the Indigenous Area level, where a score of one (1) represents the most advantaged area and a score of 100 represents the most disadvantaged area.<sup>190</sup>

MBS= Medicare Benefits Schedule

Non-HMR= a comprehensive medication management review that was not an HMR, as sourced from the integrated pharmacist's logbook.

SF1= 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?'*

T2DM= type 2 diabetes mellitus

**Table 5: Mean difference in *systolic blood pressure* (SBP) in IPAC study participants (n=1,103) using paired pre and post-intervention measures, stratified by selected participant, health service, and intervention characteristics, and adjusted for health service cluster and the length of follow-up time.**

IPAC participants with paired data for systolic blood pressure (n=1,103)	Systolic blood pressure (mm Hg)			P-value
	Mean value pre-enrolment	Mean value during follow-up	Difference	
	Mean (SD) 132.7 (33.2)	Mean (SD) 132.0 (29.9)	Mean (SD, 95% CI) -0.7 (16.6, -1.7 to 0.4)	
<b>Participant-related characteristics</b>				
Median age at baseline =57 years	Mean (SD)	Mean (SD)	Mean (SD)	<b>0.004<sup>^^</sup></b>
<Median (n=515)	131.6 (28.1)	129.8 (21.1)	-1.8 (12.5)	
≥Median (n=588)	133.6 (29.8)	133.9 (27.4)	0.3 (11.2)	
Median length of stay in the study =266 days (IQR: 210-325)	Mean (SD)	Mean (SD)	Mean (SD)	<b>0.03<sup>^^</sup></b>
<Median (n=545)	132.0 (22.4)	132.3 (19.4)	0.3 (8.4)	
≥Median (n=558)	133.4 (30.9)	131.8 (23.4)	-1.6 (14.9)	
Sex	Mean (SD)	Mean (SD)	Mean (SD)	0.36 <sup>^^</sup>
Female (n=675)	131.6 (33.8)	131.2 (23.4)	-0.4 (15.3)	
Male (n=428)	134.5 (20.7)	133.4 (20.7)	-1.1 (11.4)	
Number of adherent days ( <i>baseline score</i> )	Mean (SD)	Mean (SD)	Mean (SD)	0.70 <sup>^^</sup>
0-5 days (n=172)	132.2 (22.3)	131.8 (26.0)	-0.4 (8.4)	
6-7 days (n=663)	132.7 (23.2)	132.0 (18.5)	-0.7 (12.4)	
Median number of medications =7	Mean (SD)	Mean (SD)	Mean (SD)	0.74 <sup>^^</sup>
<Median (n=375)	132.2 (27.1)	131.2 (21.3)	-1.0 (13.9)	
≥Median (n=460)	133.0 (25.7)	132.6 (21.5)	-0.4 (11.8)	
Self-assessed health status at baseline (SF1)	Mean (SD)	Mean (SD)	Mean (SD)	0.94 <sup>^^</sup>
'Good, Fair, Poor, Very Poor' (n=650)	132.7 (24.5)	132.2 (22.7)	-0.5 (11.5)	
'Excellent' or 'very good' (n=137)	132.0 (23.0)	131.0 (17.3)	-1.0 (12.2)	
<b>Health service-related characteristics</b>				
Patient attended a health service with a median IRSEO score (=60)	Mean (SD)	Mean (SD)	Mean (SD)	0.40 <sup>^^</sup>
< 60 (n=525)	133.8 (41.2)	132.4 (32.1)	-1.4 (17.2)	
≥ 60 (n=578)	131.7 (28.9)	131.7 (26.5)	-0.0 (12.0)	
<b>Intervention-related characteristics</b>				
Patient who had a HMR compared to patient who had a non-HMR	Mean (SD)	Mean (SD)	Mean (SD)	0.84 <sup>^^</sup>
Non-HMR (n=527)	131.9 (25.3)	131.6 (20.7)	-0.3 (11.9)	
HMR (n=344)	133.2 (22.3)	132.7 (18.6)	-0.5 (7.8)	
Patients who received an MBS service for item 10987 or 10997 during the follow-up period**	Mean (SD)	Mean (SD)	Mean (SD)	0.62 <sup>^^</sup>
No (n=619)	133.5 (29.9)	132.7 (19.9)	-0.8 (17.7)	
Yes (n=484)	131.6 (24.2)	131.1 (22.0)	-0.5 (10.3)	

Bold p-values imply statistically significant change at the 0.05 level.

^P-value (paired data) was derived from the cluster-adjusted (ACCHS cluster) comparison of SBP differences against zero and was determined using the svy linearized : regress Stata command.

^^Cluster adjusted p-values (ACCHS cluster) were determined using the svy linearized : regress Stata command with differences of SBP as the outcome measure. The follow-up time in days between the enrolment date and the end of study date was added to all cluster-adjusted linear regression models.

\*\*MBS items 10987 and 10997 provide a rebate for a service by a practice nurse or an Aboriginal and Torres Strait Islander Health Practitioner (e.g. staff within ACCHSs) that includes a follow-up the assessment of the medication adherence of an Indigenous patient.

SD= cluster adjusted standard deviation (ACCHS cluster).

Health service= Aboriginal community-controlled health service (ACCHS)

HMR= Home Medicines Review. A completed HMR represents a comprehensive medication management review that fulfils the criteria for a Medicare Benefits Scheme (MBS) claim for item 900, as sourced from the integrated pharmacist's logbook.

IRSEO= Indigenous Relative Socioeconomic Outcomes index. The IRSEO reflects relative advantage or disadvantage at the Indigenous Area level, where a score of one (1) represents the most advantaged area and a score of 100 represents the most disadvantaged area.<sup>191</sup>

MBS= Medicare Benefits Schedule

Non-HMR= a comprehensive medication management review that was not an HMR, as sourced from the integrated pharmacist's logbook.

SF1= 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?'

**Table 6: Mean difference in *diastolic blood pressure* (DBP) in IPAC study participants (n=1,045) using paired pre and post-intervention measures, stratified by selected participant, health service, and intervention characteristics, and adjusted for health service cluster and the length of follow-up time.**

IPAC participants with paired data for diastolic blood pressure (n=1,045)	Diastolic blood pressure (mm Hg)			P-value
	Mean value pre-enrolment	Mean value during follow-up	Difference	
	Mean (SD)	Mean (SD)	Mean (SD, 95% CI)	
	80.0 (35.6)	79.2 (29.1)	-0.8 (9.4, -1.4 to -0.2)	<b>0.008<sup>^</sup></b>
<b>Participant-related characteristics</b>				
Median age at baseline =57 years	Mean (SD)	Mean (SD)	Mean (SD)	<b>0.012<sup>^^</sup></b>
<Median (n=515)	82.7 (18.8)	81.3 (16.8)	-1.4 (7.5)	
≥Median (n=588)	77.5 (25.9)	77.3 (20.8)	-0.2 (6.4)	
Median length of stay in the study =268 days (IQR:210-325)	Mean (SD)	Mean (SD)	Mean (SD)	0.052 <sup>^^</sup>
<Median (n=522)	79.5 (20.6)	79.3 (16.0)	-0.2 (8.0)	
≥Median (n=523)	80.4 (29.7)	79.0 (27.4)	-1.4 (7.3)	
Sex	Mean (SD)	Mean (SD)	Mean (SD)	0.92 <sup>^^</sup>
Female (n=639)	78.8 (28.8)	78.1 (20.7)	-0.7 (10.1)	
Male (n=406)	81.6 (19.8)	80.8 (20.2)	-0.8 (6.0)	
Number of adherent days (baseline score)	Mean (SD)	Mean (SD)	Mean (SD)	0.77 <sup>^^</sup>
0-5 days (n=159)	81.4 (11.4)	81.0 (11.7)	-0.4 (5.0)	
6-7 days (n=633)	79.2 (25.2)	78.6 (24.7)	-0.6 (7.6)	
Median number of medications =7	Mean (SD)	Mean (SD)	Mean (SD)	0.40 <sup>^^</sup>
<Median (n=351)	80.9 (15.0)	80.1 (13.1)	-0.8 (7.5)	
≥Median (n=441)	78.6 (25.2)	78.2 (23.1)	-0.4 (6.3)	
Self-assessed health status at baseline (SF1)	Mean (SD)	Mean (SD)	Mean (SD)	0.16 <sup>^^</sup>
'Good, Fair, Poor, Very Poor' (n=608)	79.7 (22.2)	79.0 (22.2)	-0.7 (6.2)	
'Excellent' or 'very good' (n=138)	78.4 (14.1)	78.1 (12.9)	-0.3 (4.5)	
<b>Health service-related characteristics</b>				
Patient attended a health service with a median IRSEO score (=60)	Mean (SD)	Mean (SD)	Mean (SD)	0.47 <sup>^^</sup>
< 60 (n=510)	80.0 (49.7)	78.8 (42.9)	-1.2 (9.0)	
≥ 60 (n=535)	79.9 (9.3)	79.5 (9.3)	-0.4 (4.6)	
<b>Intervention-related characteristics</b>				
Patient who had a HMR compared to patient who had a non-HMR	Mean (SD)	Mean (SD)	Mean (SD)	0.52 <sup>^^</sup>
Non-HMR (n=527)	80.4 (15.5)	79.7 (13.3)	-0.7 (4.4)	
HMR (n=344)	78.9 (23.9)	78.0 (18.4)	-0.9 (9.2)	
Patients who received an MBS service for item 10987 or 10997 during the follow-up period**	Mean (SD)	Mean (SD)	Mean (SD)	0.86 <sup>^^</sup>
No (n=592)	80.6 (26.8)	79.8 (21.9)	-0.8 (9.7)	
Yes (n=453)	79.1 (23.4)	78.4 (21.3)	-0.7 (6.4)	

Bold p-values imply statistically significant change at the 0.05 level.



^P-value (paired data) was derived from the cluster-adjusted (ACCHS cluster) comparison of DBP differences against zero and was determined using the svy linearized : regress Stata command.

^^Cluster adjusted p-values (ACCHS cluster) were determined using the svy linearized : regress Stata command with differences of DBP as the outcome measure. The follow-up time in days between the enrolment date and the end of study date was added to all cluster-adjusted linear regression models.

\*\*MBS items 10987 and 10997 provide a rebate for a service by a practice nurse or an Aboriginal and Torres Strait Islander Health Practitioner (e.g. staff within ACCHSs) that includes a follow-up the assessment of the medication adherence of an Indigenous patient.

SD= cluster adjusted standard deviation (ACCHS cluster).

Health service= Aboriginal community-controlled health service (ACCHS)

HMR= Home Medicines Review. A completed HMR represents a comprehensive medication management review that fulfils the criteria for a Medicare Benefits Scheme (MBS) claim for item 900, as sourced from the integrated pharmacist's logbook.

IRSEO= Indigenous Relative Socioeconomic Outcomes index. The IRSEO reflects relative advantage or disadvantage at the Indigenous Area level, where a score of one (1) represents the most advantaged area and a score of 100 represents the most disadvantaged area.<sup>192</sup>

MBS= Medicare Benefits Schedule

Non-HMR= a comprehensive medication management review that was not an HMR, as sourced from the integrated pharmacist's logbook.

SF1= 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?'

**Table 7: Mean difference in *total cholesterol* (TC) in IPAC study participants (n=660) using paired pre and post-intervention measures, stratified by selected participant, health service, and intervention characteristics, and adjusted for health service cluster and the length of follow-up time.**

IPAC participants with paired data for total cholesterol (n=660)	Total cholesterol (mmol/L)			P-value
	Mean value pre-enrolment	Mean value during follow-up	Difference	
	Mean (SD)	Mean (SD)	Mean (SD, 95% CI)	
	4.51 (1.80)	4.35 (2.06)	-0.15 (0.77, -0.22 to -0.09)	<0.001^
Participant-related characteristics				
Median age at baseline =59 years	Mean (SD)	Mean (SD)	Mean (SD)	0.08^^
<Median (n=315)	4.63 (1.77)	4.43 (1.77)	-0.20 (0.89)	
≥Median (n=345)	4.39 (1.11)	4.28 (1.49)	-0.11 (0.76)	
Median length of stay in the study =314 days (IQR:239-360)	Mean (SD)	Mean (SD)	Mean (SD)	0.08^^
<Median (n=328)	4.42 (1.45)	4.33 (1.81)	-0.10 (0.91)	
≥Median (n=332)	4.59 (1.46)	4.38 (1.28)	-0.21 (0.73)	
Sex	Mean (SD)	Mean (SD)	Mean (SD)	0.33^^
Female (n=419)	4.58 (1.64)	4.46 (1.84)	-0.11 (0.61)	
Male (n=241)	4.39 (0.93)	4.16 (1.55)	-0.22 (1.4)	
Number of adherent days (baseline score)	Mean (SD)	Mean (SD)	Mean (SD)	0.42^^
0-5 days (n=110)	4.83 (1.05)	4.61 (1.05)	-0.21 (0.94)	
6-7 days (n=448)	4.42 (1.48)	4.30 (1.9)	-0.12 (1.06)	
Median number of medications =7	Mean (SD)	Mean (SD)	Mean (SD)	0.28^^
<Median (n=244)	4.75 (1.56)	4.55 (1.56)	-0.20 (1.09)	
≥Median (n=314)	4.31 (1.24)	4.22 (1.24)	-0.09 (0.53)	
Self -assessed health status at baseline (SF1)	Mean (SD)	Mean (SD)	Mean (SD)	0.49^^
'Good, Fair, Poor, Very Poor' (n=382)	4.49 (1.76)	4.34 (2.35)	-0.15 (0.98)	
'Excellent' or 'very good' (n=102)	4.34 (1.31)	4.26 (0.61)	-0.08 (0.91)	
Health service-related characteristics				
Patient attended a health service with a median IRSEO score (=60)	Mean (SD)	Mean (SD)	Mean (SD)	0.014^^
< 60 (n=291)	4.55 (1.19)	4.35 (1.54)	-0.20 (0.51)	
>= 60 (n=369)	4.47 (1.92)	4.35 (2.5)	-0.12 (0.77)	
Intervention-related characteristics				
Patient who had a HMR compared to patient who had a non-HMR	Mean (SD)	Mean (SD)	Mean (SD)	0.10^^
Non-HMR (n=279)	4.54 (2.0)	4.43 (2.34)	-0.11 (0.84)	
HMR (n=251)	4.43 (1.9)	4.30 (2.53)	-0.13 (0.95)	
Patients who received an MBS service for item 10987 or 10997 during the follow-up period**	Mean (SD)	Mean (SD)	Mean (SD)	0.57^^
No (n=241)	4.50 (1.09)	4.37 (1.24)	-0.13 (0.62)	
Yes (n=419)	4.51 (2.05)	4.35 (2.25)	-0.17 (0.61)	

Bold p-values imply statistically significant change at the 0.05 level.

^P-value (paired data) was derived from the cluster-adjusted (ACCHS cluster) comparison of total cholesterol differences against zero and was determined using the `svy linearized : regress` Stata command.

^^Cluster adjusted p-values (ACCHS cluster) were determined using the `svy linearized : regress` Stata command with differences of total cholesterol as the outcome measure. The follow-up time in days between the enrolment date and the end of study date was added to all cluster-adjusted linear regression models.

\*\*MBS items 10987 and 10997 provide a rebate for a service by a practice nurse or an Aboriginal and Torres Strait Islander Health Practitioner (e.g. staff within ACCHSs) that includes a follow-up the assessment of the medication adherence of an Indigenous patient.

SD= cluster adjusted standard deviation (ACCHS cluster).

Health service= Aboriginal community-controlled health service (ACCHS)

HMR= Home Medicines Review. A completed HMR represents a comprehensive medication management review that fulfils the criteria for a Medicare Benefits Scheme (MBS) claim for item 900, as sourced from the integrated pharmacist's logbook.

IRSEO= Indigenous Relative Socioeconomic Outcomes index. The IRSEO reflects relative advantage or disadvantage at the Indigenous Area level, where a score of one (1) represents the most advantaged area and a score of 100 represents the most disadvantaged area.<sup>193</sup>

MBS= Medicare Benefits Schedule

Non-HMR= a comprehensive medication management review that was not an HMR, as sourced from the integrated pharmacist's logbook.

SF1= 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?'*

**Table 8: Mean difference in *low density lipoprotein cholesterol* (LDL-C) in IPAC study participants (n=575) using paired pre and post-intervention measures, stratified by selected participant, health service, and intervention characteristics, and adjusted for health service cluster and the length of follow-up time.**

IPAC participants with paired data for low density lipoprotein cholesterol (n=575)	Low density lipoprotein cholesterol (mmol/L)			P-value
	Mean value pre-enrolment	Mean value during follow-up	Difference	
	Mean (SD)	Mean (SD)	Mean (SD, 95% CI)	
	2.35 (1.20)	2.27 (1.20)	-0.08 (0.48, -0.13 to -0.03)	0.001^
Participant-related characteristics				
Median age at baseline =59 years	Mean (SD)	Mean (SD)	Mean (SD)	0.36^^
<Median (n=279)	2.49 (1.17)	2.39 (0.84)	-0.10 (0.67)	
≥Median (n=296)	2.22 (0.86)	2.16 (1.03)	-0.06 (0.52)	
Median length of stay in the study =295 days (IQR: 239-351)	Mean (SD)	Mean (SD)	Mean (SD)	0.83^^
<Median (n=287)	2.33 (0.85)	2.28 (1.19)	-0.05 (0.85)	
≥Median (n=288)	2.37 (0.85)	2.26 (0.85)	-0.11 (0.51)	
Sex	Mean (SD)	Mean (SD)	Mean (SD)	0.27^^
Female (n=359)	2.40 (1.14)	2.34 (1.14)	-0.05 (0.38)	
Male (n=216)	2.28 (1.18)	2.15 (1.03)	-0.13 (0.88)	
Number of adherent days (baseline score)	Mean (SD)	Mean (SD)	Mean (SD)	0.48^^
0-5 days (n=86)	2.70 (1.21)	2.56 (1.39)	-0.14 (0.74)	
6-7 days (n=384)	2.27 (0.98)	2.20 (1.37)	-0.06 (0.78)	
Median number of medications =7	Mean (SD)	Mean (SD)	Mean (SD)	0.23^^
<Median (n=194)	2.60 (1.25)	2.49 (0.97)	-0.11 (0.7)	
≥Median (n=276)	2.17 (0.66)	2.11 (0.83)	-0.06 (0.5)	
Self -assessed health status at baseline (SF1)	Mean (SD)	Mean (SD)	Mean (SD)	0.08^^
'Good, Fair, Poor, Very Poor' (n=339)	2.35 (1.29)	2.24 (1.29)	-0.11 (0.74)	
'Excellent' or 'very good' (n=75)	2.25 (0.95)	2.26 (0.78)	0.01 (0.43)	
Health service-related characteristics				
Patient attended a health service with a median IRSEO score (=60)	Mean (SD)	Mean (SD)	Mean (SD)	0.05^^
< 60 (n=264)	2.35 (0.97)	2.26 (0.81)	-0.09 (0.49)	
>= 60 (n=311)	2.35 (1.23)	2.28 (1.41)	-0.07 (0.53)	
Intervention-related characteristics				
Patient who had a HMR compared to patient who had a non-HMR	Mean (SD)	Mean (SD)	Mean (SD)	0.76^^
Non-HMR (n=281)	2.38 (1.34)	2.31 (1.34)	-0.07 (0.67)	
HMR (n=184)	2.27 (0.68)	2.17 (1.36)	-0.09 (1.09)	
Patients who received an MBS service for item 10987 or 10997 during the follow-up period**	Mean (SD)	Mean (SD)	Mean (SD)	0.66^^
No (n=234)	2.41 (0.92)	2.34 (0.76)	-0.06 (0.76)	
Yes (n=341)	2.31 (1.11)	2.22 (1.29)	-0.09 (0.37)	

Bold p-values imply statistically significant change at the 0.05 level.

^P-value (paired data) was derived from the cluster-adjusted (ACCHS cluster) comparison of low density lipoprotein cholesterol differences against zero and was determined using the `svy linearized : regress Stata` command.

^^Cluster adjusted p-values (ACCHS cluster) were determined using the `svy linearized : regress Stata` command with differences of low density lipoprotein cholesterol as the outcome measure. The follow-up time in days between the enrolment date and the end of study date was added to all cluster-adjusted linear regression models.

\*\*MBS items 10987 and 10997 provide a rebate for a service by a practice nurse or an Aboriginal and Torres Strait Islander Health Practitioner (e.g. staff within ACCHSs) that includes a follow-up the assessment of the medication adherence of an Indigenous patient.

SD= cluster adjusted standard deviation (ACCHS cluster).

Health service= Aboriginal community-controlled health service (ACCHS)

HMR= Home Medicines Review. A completed HMR represents a comprehensive medication management review that fulfils the criteria for a Medicare Benefits Scheme (MBS) claim for item 900, as sourced from the integrated pharmacist's logbook.

IRSEO= Indigenous Relative Socioeconomic Outcomes index. The IRSEO reflects relative advantage or disadvantage at the Indigenous Area level, where a score of one (1) represents the most advantaged area and a score of 100 represents the most disadvantaged area.<sup>194</sup>

MBS= Medicare Benefits Schedule

Non-HMR= a comprehensive medication management review that was not an HMR, as sourced from the integrated pharmacist's logbook.

SF1= 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?'*

**Table 9: Mean difference in *high density lipoprotein cholesterol* (HDL-C) in IPAC study participants (n=622) using paired pre and post-intervention measures, stratified by selected participant, health service, and intervention characteristics, and adjusted for health service cluster and the length of follow-up time.**

IPAC participants with paired data for high density lipoprotein cholesterol (n=622)	High density lipoprotein cholesterol (mmol/L)			P-value
	Mean value pre-enrolment	Mean value during follow-up	Difference	
	Mean (SD)	Mean (SD)	Mean (SD, 95% CI)	
	1.05 (0.5)	1.06 (0.5)	0.01 (0.25, -0.02 to 0.03)	0.32 <sup>^</sup>
<b>Participant-related characteristics</b>				
Median age at baseline =58 years	Mean (SD)	Mean (SD)	Mean (SD)	0.59 <sup>^^</sup>
<Median (n=284)	1.02 (0.34)	1.02 (0.34)	0.00 (0.34)	
≥Median (n=338)	1.08 (0.18)	1.09 (0.18)	0.01 (0.18)	
Median length of stay in the study =294 days (IQR: 237-350)	Mean (SD)	Mean (SD)	Mean (SD)	0.43 <sup>^^</sup>
<Median (n=304)	1.02 (0.35)	1.04 (0.17)	0.02 (0.17)	
≥Median (n=318)	1.08 (0.36)	1.08 (0.36)	0.00 (0.36)	
Sex	Mean (SD)	Mean (SD)	Mean (SD)	0.89 <sup>^^</sup>
Female (n=385)	1.08 (0.2)	1.09 (0.35)	0.00 (0.17)	
Male (n=237)	1 (0.31)	1 (0.36)	0.00 (0.36)	
Number of adherent days (baseline score)	Mean (SD)	Mean (SD)	Mean (SD)	0.97 <sup>^^</sup>
0-5 days (n=100)	1.09 (0.5)	1.10 (0.4)	0.01 (0.5)	
6-7 days (n=408)	1.04 (0.2)	1.05 (0.2)	0.01 (0.2)	
Median number of medications =7	Mean (SD)	Mean (SD)	Mean (SD)	0.94 <sup>^^</sup>
<Median (n=216)	1.07 (0.29)	1.07 (0.29)	0.01 (0.29)	
≥Median (n=292)	1.04 (0.34)	1.05 (0.34)	0.01 (0.34)	
Self-assessed health status at baseline (SF1)	Mean (SD)	Mean (SD)	Mean (SD)	<b>0.048<sup>^^</sup></b>
'Good, Fair, Poor, Very Poor' (n=365)	1.05 (0.38)	1.06 (0.38)	0.01 (0.38)	
'Excellent' or 'very good' (n=83)	1.02 (0.18)	1.05 (0.18)	0.03 (0.18)	
<b>Health service-related characteristics</b>				
Patient attended a health service with a median IRSEO score (=60)	Mean (SD)	Mean (SD)	Mean (SD)	0.97 <sup>^^</sup>
< 60 (n=280)	1.06 (0.33)	1.06 (0.33)	0.00 (0.33)	
≥ 60 (n=342)	1.04 (0.37)	1.06 (0.37)	0.01 (0.18)	
<b>Intervention-related characteristics</b>				
Patient who had a HMR compared to patient who had a non-HMR	Mean (SD)	Mean (SD)	Mean (SD)	0.61 <sup>^^</sup>
Non-HMR (n=311)	1.04 (0.35)	1.04 (0.35)	0.01 (0.18)	
HMR (n=192)	1.03 (0.28)	1.05 (0.14)	0.02 (0.28)	
Patients who received an MBS service for item 10987 or 10997 during the follow-up period**	Mean (SD)	Mean (SD)	Mean (SD)	0.07 <sup>^^</sup>
No (n=247)	1.04 (0.31)	1.03 (0.31)	-0.01 (0.31)	
Yes (n=375)	1.06 (0.19)	1.08 (0.19)	0.02 (0.19)	

Bold p-values imply statistically significant change at the 0.05 level.

^P-value (paired data) was derived from the cluster-adjusted (ACCHS cluster) comparison of high density lipoprotein cholesterol differences against zero and was determined using the `svy linearized : regress Stata` command.

^^Cluster adjusted p-values (ACCHS cluster) were determined using the `svy linearized : regress Stata` command with differences of high density lipoprotein cholesterol as the outcome measure. The follow-up time in days between the enrolment date and the end of study date was added to all cluster-adjusted linear regression models.

\*\*MBS items 10987 and 10997 provide a rebate for a service by a practice nurse or an Aboriginal and Torres Strait Islander Health Practitioner (e.g. staff within ACCHSs) that includes a follow-up the assessment of the medication adherence of an Indigenous patient.

SD= cluster adjusted standard deviation (ACCHS cluster).

Health service= Aboriginal community-controlled health service (ACCHS)

HMR= Home Medicines Review. A completed HMR represents a comprehensive medication management review that fulfils the criteria for a Medicare Benefits Scheme (MBS) claim for item 900, as sourced from the integrated pharmacist's logbook.

IRSEO= Indigenous Relative Socioeconomic Outcomes index. The IRSEO reflects relative advantage or disadvantage at the Indigenous Area level, where a score of one (1) represents the most advantaged area and a score of 100 represents the most disadvantaged area.<sup>195</sup>

MBS= Medicare Benefits Schedule

Non-HMR= a comprehensive medication management review that was not an HMR, as sourced from the integrated pharmacist's logbook.

SF1= 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?'*

**Table 10: Mean difference in *triglycerides* (TG) in IPAC study participants (n=730) using paired pre and post-intervention measures, stratified by selected participant, health service, and intervention characteristics, and adjusted for health service cluster and the length of follow-up time.**

IPAC participants with paired data for triglycerides (n=730)	Triglycerides (mmol/L)			P-value
	Mean value pre-enrolment	Mean value during follow-up	Difference	
	Mean (SD)	Mean (SD)	Mean (SD, 95% CI)	
	2.39 (2.43)	2.29 (2.21)	-0.11 (1.08, -0.20 to -0.01)	0.006^
Participant-related characteristics				
Median age at baseline =59 years	Mean (SD)	Mean (SD)	Mean (SD)	0.26^^
<Median (n=347)	2.60 (3.17)	2.47 (2.61)	-0.12 (0.93)	
≥Median (n=383)	2.21 (1.17)	2.12 (0.98)	-0.09 (1.17)	
Median length of stay in the study =296 days (IQR: 237-356)	Mean (SD)	Mean (SD)	Mean (SD)	0.024^^
<Median (n=365)	2.35 (1.91)	2.33 (1.91)	-0.02 (0.96)	
≥Median (n=365)	2.44 (1.91)	2.24 (1.34)	-0.20 (1.34)	
Sex	Mean (SD)	Mean (SD)	Mean (SD)	0.99^^
Female (n=450)	2.40 (2.12)	2.30 (1.91)	-0.10 (1.06)	
Male (n=280)	2.38 (1.67)	2.27 (1.67)	-0.11 (1.51)	
Number of adherent days (baseline score)	Mean (SD)	Mean (SD)	Mean (SD)	0.89^^
0-5 days (n=111)	2.65 (3.16)	2.55 (2.84)	-0.10 (0.84)	
6-7 days (n=495)	2.34 (2.00)	2.25 (1.56)	-0.09 (1.11)	
Median number of medications =7	Mean (SD)	Mean (SD)	Mean (SD)	0.54^^
<Median (n=246)	2.33 (1.57)	2.22 (1.57)	-0.11 (0.78)	
≥Median (n=360)	2.45 (1.90)	2.37 (1.9)	-0.08 (1.33)	
Self -assessed health status at baseline (SF1)	Mean (SD)	Mean (SD)	Mean (SD)	0.31^^
'Good, Fair, Poor, Very Poor' (n=421)	2.43 (2.46)	2.32 (1.88)	-0.12 (0.78)	
'Excellent' or 'very good' (n=112)	2.18 (1.59)	2.18 (2.66)	0.00 (1.90)	
Health service-related characteristics				
Patient attended a health service with a median IRSEO score (=61)	Mean (SD)	Mean (SD)	Mean (SD)	0.71^^
< 61 (n=364)	2.37 (2.29)	2.24 (1.72)	-0.12 (0.76)	
>= 61 (n=366)	2.42 (2.87)	2.33 (2.49)	-0.09 (1.34)	
Intervention-related characteristics				
Patient who had a HMR compared to patient who had a non-HMR	Mean (SD)	Mean (SD)	Mean (SD)	0.47^^
Non-HMR (n=339)	2.42 (2.95)	2.40 (2.39)	-0.02 (1.29)	
HMR (n=246)	2.37 (1.73)	2.24 (2.2)	-0.13 (0.78)	
Patients who received an MBS service for item 10987 or 10997 during the follow-up period**	Mean (SD)	Mean (SD)	Mean (SD)	0.027^^
No (n=320)	2.24 (1.61)	2.23 (1.25)	-0.01 (0.89)	
Yes (n=410)	2.51 (2.23)	2.33 (1.82)	-0.18 (1.01)	

Bold p-values imply statistically significant change at the 0.05 level.



^P-value (paired data) was derived from the cluster-adjusted (ACCHS cluster) comparison of triglyceride differences against zero and was determined using the svy linearized : regress Stata command.

^^Cluster adjusted p-values (ACCHS cluster) were determined using the svy linearized : regress Stata command with differences of triglycerides as the outcome measure. The follow-up time in days between the enrolment date and the end of study date was added to all cluster-adjusted linear regression models.

\*\*MBS items 10987 and 10997 provide a rebate for a service by a practice nurse or an Aboriginal and Torres Strait Islander Health Practitioner (e.g. staff within ACCHSs) that includes a follow-up the assessment of the medication adherence of an Indigenous patient.

SD= cluster adjusted standard deviation (ACCHS cluster).

Health service= Aboriginal community-controlled health service (ACCHS)

HMR= Home Medicines Review. A completed HMR represents a comprehensive medication management review that fulfils the criteria for a Medicare Benefits Scheme (MBS) claim for item 900, as sourced from the integrated pharmacist's logbook.

IRSEO= Indigenous Relative Socioeconomic Outcomes index. The IRSEO reflects relative advantage or disadvantage at the Indigenous Area level, where a score of one (1) represents the most advantaged area and a score of 100 represents the most disadvantaged area.<sup>196</sup>

MBS= Medicare Benefits Schedule

Non-HMR= a comprehensive medication management review that was not an HMR, as sourced from the integrated pharmacist's logbook.

SF1= 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?'*

**Table 11: Mean annualised difference in *albumin-creatinine ratio* (ACR) in IPAC study participants (n=475) using paired pre and post-intervention measures, stratified by selected participant, health service, and intervention characteristics, and adjusted for health service cluster and the length of follow-up time.**

IPAC participants with paired data for albumin-creatinine ratio (n=475)	ACR (mg/mmol)			P-value
	Last observation pre-enrolment	Last observation at follow-up	Difference	
	Mean (SD)	Mean (SD)	Mean (SD, 95% CI)	
	57.9 (183.1)	61.7 (224.5)	3.8 (102.4, -6.3 to 13.8)	0.42 <sup>^</sup>
<b>Participant-related characteristics</b>				
Median age at baseline =58 years	Mean (SD)	Mean (SD)	Mean (SD)	0.78 <sup>^^</sup>
<Median (n=230)	58.5 (162.3)	61.0 (187.3)	2.4 (94.5)	
≥Median (n=245)	57.4 (134.6)	62.4 (185.6)	5.0 (108.0)	
Median length of stay in the study =301 days (IQR: 238-365)	Mean (SD)	Mean (SD)	Mean (SD)	0.17 <sup>^^</sup>
<Median (n=237)	61.1 (178.6)	69.1 (200.8)	8.0 (44.6)	
≥Median (n=238)	54.8 (126.5)	54.3 (142.4)	-0.5 (111.1)	
Sex	Mean (SD)	Mean (SD)	Mean (SD)	0.49 <sup>^^</sup>
Female (n=295)	57.4 (159.4)	63.7 (184.8)	6.3 (85.9)	
Male (n=180)	58.8 (137.3)	58.4 (141.9)	-0.4 (107.3)	
Number of adherent days (baseline score)	Mean (SD)	Mean (SD)	Mean (SD)	0.90 <sup>^^</sup>
0-5 days (n=69)	83.7 (132.1)	88.4 (119.6)	4.7 (113.8)	
6-7 days (n=330)	56.3 (183.5)	59.5 (210.7)	3.2 (67.2)	
Median number of medications =7	Mean (SD)	Mean (SD)	Mean (SD)	0.83 <sup>^^</sup>
<Median (n=160)	54.1 (134.1)	58.1 (153.0)	4.0 (64.5)	
≥Median (n=239)	65.7 (160.8)	68.8 (180.9)	3.1 (85.0)	
Self-assessed health status at baseline (SF1)	Mean (SD)	Mean (SD)	Mean (SD)	<b>0.047<sup>^^</sup></b>
'Good, Fair, Poor, Very Poor' (n=267)	68.4 (204.3)	67.1 (235.3)	-1.3 (81.7)	
'Excellent' or 'very good' (n=69)	33.4 (106.3)	50.2 (191.1)	16.8 (83.1)	
<b>Health service-related characteristics</b>				
Patient attended a health service with a median IRSEO score (=61)	Mean (SD)	Mean (SD)	Mean (SD)	0.78 <sup>^^</sup>
< 61 (n=233)	47.5 (119.1)	49.5 (135.9)	2.0 (27.5)	
≥ 1 (n=242)	68.1 (194.5)	73.5 (252.0)	5.4 (140.0)	
<b>Intervention-related characteristics</b>				
Patient who had a HMR compared to patient who had a non-HMR	Mean (SD)	Mean (SD)	Mean (SD)	0.08 <sup>^^</sup>
Non-HMR (n=192)	71.3 (185.3)	70.0 (223.2)	-1.3 (77.6)	
HMR (n=182)	45.1 (89.2)	56.7 (139.8)	11.6 (70.2)	
Patients who received an MBS service for item 10987 or 10997 during the follow-up period**	Mean (SD)	Mean (SD)	Mean (SD)	0.62 <sup>^^</sup>
No (n=191)	43.8 (192.1)	50.1 (215.6)	6.3 (55.3)	
Yes (n=284)	67.5 (143.2)	69.5 (197.2)	2.0 (123.0)	

Bold p-values imply statistically significant change at the 0.05 level.

^P-value (paired data) was derived from the cluster-adjusted (ACCHS cluster) comparison of differences in albumin creatinine ratio against zero and was determined using the svy linearized : regress Stata command.

^^Cluster adjusted p-values (ACCHS cluster) were determined using the svy linearized : regress Stata command with differences in albumin creatinine ratios as the outcome measure. The follow-up time in days between the enrolment date and the end of study date was added to all cluster-adjusted linear regression models.

\*\*MBS items 10987 and 10997 provide a rebate for a service by a practice nurse or an Aboriginal and Torres Strait Islander Health Practitioner (e.g. staff within ACCHSs) that includes a follow-up the assessment of the medication adherence of an Indigenous patient.

SD= cluster adjusted standard deviation (ACCHS cluster).

Health service= Aboriginal community-controlled health service (ACCHS)

HMR= Home Medicines Review. A completed HMR represents a comprehensive medication management review that fulfils the criteria for a Medicare Benefits Scheme (MBS) claim for item 900, as sourced from the integrated pharmacist's logbook.

IRSEO= Indigenous Relative Socioeconomic Outcomes index. The IRSEO reflects relative advantage or disadvantage at the Indigenous Area level, where a score of one (1) represents the most advantaged area and a score of 100 represents the most disadvantaged area.<sup>197</sup>

MBS= Medicare Benefits Schedule

Non-HMR= a comprehensive medication management review that was not an HMR, as sourced from the integrated pharmacist's logbook.

SF1= 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?'*

**Table 12. Mean annualised difference in *estimated glomerular filtration rate* (eGFR) in IPAC study participants (n=895) using paired pre and post-intervention measures (cluster adjusted) and sensitivity analysis by follow-up time.**

IPAC participants with paired data	Estimated glomerular filtration rate (eGFR) (mL/min/1.73m <sup>2</sup> ) n=895					P-value <sup>^</sup>
	Last observation pre-enrolment	Last observation at follow-up	Observed crude difference	Follow-up time (days) *	Observed mean annualised difference	
<b>No minimum follow-up time</b> N=895 Mean (SD), [95% CI]	49.1 (159.2)	48.4 (160.4)	-0.8 (21.8) [-2.3 to 0.8]	298 (320) Range: 27-661	1.90 (25.7), [0.08 to 3.74]	<b>&lt;0.001</b>
<b>6-month minimum follow-up time</b> N=720** Mean (SD), [95% CI]	49.6 (140.6)	48.1 (145.4)	-1.5 (31.9) [-4.0 to 1.0]	340 (271) Range: 180-661	-0.16 (36.0), [-2.99 to 2.68]	<b>0.034</b>

Bold p-values imply statistically significant change at the 0.05 level.

<sup>^</sup>P-values (paired data) were derived from the cluster-adjusted (ACCHS cluster) comparison of annualised differences in eGFR against -3 and were determined using the svy linearized : regress Stata command. The value of -3 was the theoretically expected mean annual eGFR (mL/min/1.73m<sup>2</sup>) linear decline.

\* Follow-up time is the number of days between two measurements. It was defined as the time between the most recent baseline eGFR value and the follow-up eGFR value closest to the end-of study date (31/10/2019).

\*\* Participants with <6 months (≤180 days) days between two eGFR measurements were excluded.

**Table 13: Mean annualised difference in *estimated glomerular filtration rate* (eGFR) in IPAC study participants (n=895) using paired pre and post-intervention measures, stratified by selected participant, health service, and intervention characteristics, and adjusted for health service cluster, *with no minimum follow-up time*.**

IPAC participants with paired data for estimated glomerular filtration rate (n=895)	Estimated glomerular filtration rate (mL/min/1.73m <sup>2</sup> )					P-value
	Last observation pre-enrolment	Last observation at follow-up	Observed crude difference	Follow-up time (days)*	Observed mean annualised difference	
	Mean (SD) 49.1 (159.2)	Mean (SD) 48.4 (160.4)	Mean (SD, 95% CI) -0.8 (21.8, -2.3 to 0.8)	Mean (SD, range) 298 (320, 27-661)	Mean (SD, 95% CI) 1.9 (25.7, 0.1 to 3.7)	<0.001^
Participant-related characteristics						
Median age at baseline =59 years	Mean (SD)	Mean (SD)	Mean (SD)	Mean (SD), range	Mean (SD)	0.34^^
<Median (n=446)	45.7 (171.5)	43.6 (181.6)	-2.1 (40.1)	296 (299, 40-661)	0.2 (46.7)	
≥Median (n=449)	52.5 (81.4)	53.1 (84.8)	0.6 (23.3)	300 (203, 27-650)	3.6 (34.5)	
Median length of stay = 296 days (IQR: 234-359)	Mean (SD)	Mean (SD)	Mean (SD, 95% CI)	Mean (SD), range	Mean (SD)	<0.001^^
<Median (n=445)	47.0 (109.7)	49.3 (105.5)	2.3 (15.8)	240 (150, 27-601)	6.5 (27.4)	
≥Median (n=450)	51.2 (131.5)	47.5 (140.0)	-3.7 (18.0)	356 (163, 43-661)	-2.7 (17.0)	
Sex	Mean (SD)	Mean (SD)	Mean (SD)	Mean (SD), range	Mean (SD)	0.98^^
Female (n=549)	47.0 (124.2)	46.1 (124.2)	-0.9 (23.4)	295 (284, 34-661)	1.9 (30.7)	
Male (n=346)	52.5 (102.3)	51.9 (104.2)	-0.6 (22.3)	304 (225, 27-650)	1.9 (37.4)	
Number of adherent days (baseline score)	Mean (SD)	Mean (SD)	Mean (SD)	Mean (SD), range	Mean (SD)	0.80^^
0-5 days (n=128)	42.9 (79.2)	41.3 (80.33)	-1.6 (32.8)	310 (232, 44-661)	-0.3 (46.4)	
6-7 days (n=594)	51.1 (121.9)	49.6 (124.3)	-1.5 (29.3)	306 (324, 27-650)	0.9 (36.6)	
Median number of medications =7	Mean (SD)	Mean (SD)	Mean (SD)	Mean (SD), range	Mean (SD)	0.06^^
<Median (n=292)	46.3 (103)	46.2 (102.5)	-0.1 (25.6)	305 (263, 40-661)	4.2 (38.5)	
≥Median (n=430)	51.9 (112)	49.5 (109.9)	-2.4 (24.9)	310 (257, 27-650)	-1.7 (28.8)	
Self -assessed health status at baseline (SF1)	Mean (SD)	Mean (SD)	Mean (SD)	Mean (SD), range	Mean (SD)	0.67^^
'Good, Fair, Poor, Very Poor' (n=511)	49.1 (126.6)	48.4 (119.8)	-0.7 (22.2)	294 (258, 40-650)	1.7 (32.3)	
'Excellent' or 'very good' (n=125)	47.9 (54.8)	45.4 (59.3)	-2.5 (17.3)	300 (139, 27-609)	0.3 (27.4)	
Health service-related characteristics						
Patient attended a health service with a median IRSEO score (=61)	Mean (SD)	Mean (SD)	Mean (SD)	Mean (SD), range	Mean (SD)	0.13^^
< 61 (n=420)	53.9 (186.49)	52.2 (194.7)	-1.7 (12.3)	314 (311, 27-661)	0.6 (14.8)	
>= 61 (n=475)	44.9 (128.59)	45.0 (124.2)	0.1 (24.0)	285 (259, 34-650)	3.1 (30.3)	
Intervention-related characteristics						
Patient who had a HMR compared to patient who had a non-HMR	Mean (SD)	Mean (SD)	Mean (SD)	Mean (SD), range	Mean (SD)	0.61^^
Non-HMR (n=396)	48.9 (119.4)	48.7 (111.4)	-0.2 (19.7)	292 (245, 34-613)	1.3 (25.1)	
HMR (n=316)	48.9 (112.0)	46.2 (115.6)	-2.7 (21.3)	305 (251, 43-650)	0.1 (27.7)	
Patients who received an MBS service for item 10987 or 10997 during the follow-up period**	Mean (SD)	Mean (SD)	Mean (SD)	Mean (SD), range	Mean (SD)	0.93^^
No (n=439)	57.6 (136.2)	57.1 (132.0)	-0.5 (16.1)	287 (350, 34-622)	2.0 (32.3)	
Yes (n=456)	41.0 (61.9)	40.0 (61.9)	-1.0 (23.5)	309 (333, 27-661)	1.8 (27.6)	

Bold p-values imply statistically significant change at the 0.05 level.

^P-values (paired data) were derived from the cluster-adjusted (ACCHS cluster) comparison of annualised differences in eGFR against -3 and were determined using the `svy linearized : regress Stata` command. The value of -3 was the theoretically expected mean annual eGFR (ml/min/1.73m<sup>2</sup>) linear decline.

^^Cluster adjusted p-values (ACCHS cluster) were determined using the `svy linearized : regress Stata` command with differences of annualised eGFR as the outcome measure.

\* Follow-up time is the number of days between two measurements. It was defined as the time between the most recent baseline eGFR value and the follow-up eGFR value closest to the end-of study date (31/10/2019).

\*\*MBS items 10987 and 10997 provide a rebate for a service by a practice nurse or an Aboriginal and Torres Strait Islander Health Practitioner (e.g. staff within ACCHSs) that includes a follow-up the assessment of the medication adherence of an Indigenous patient.

SD= cluster adjusted standard deviation (ACCHS cluster).

Health service= Aboriginal community-controlled health service (ACCHS)

HMR= Home Medicines Review. A completed HMR represents a comprehensive medication management review that fulfils the criteria for a Medicare Benefits Scheme (MBS) claim for item 900, as sourced from the integrated pharmacist's logbook.

IRSEO= Indigenous Relative Socioeconomic Outcomes index. The IRSEO reflects relative advantage or disadvantage at the Indigenous Area level, where a score of one (1) represents the most advantaged area and a score of 100 represents the most disadvantaged area.<sup>198</sup>

MBS= Medicare Benefits Schedule

Non-HMR= a comprehensive medication management review that was not an HMR, as sourced from the integrated pharmacist's logbook.

SF1= 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?'*

**Table 14: Mean annualised difference in *estimated glomerular filtration rate* (eGFR) in IPAC study participants (n=720) using paired pre and post-intervention measures, stratified by selected participant, health service, and intervention characteristics, and adjusted for health service cluster, *with 6-months minimum follow-up time*.**

IPAC participants with paired data for estimated glomerular filtration rate (n=720)	Estimated glomerular filtration rate (mL/min/1.73m <sup>2</sup> )					P-value
	Last observation pre-enrolment	Last observation at follow-up	Observed crude difference	Follow-up time (days)*	Observed mean annualised difference	
	Mean (SD) 49.6 (140.6)	Mean (SD) 48.1 (145.4)	Mean (SD, 95% CI) -1.5 (31.9, -4.0 - 1.0)	Mean (SD, range) 340 (271, 180-661)	Mean (SD, 95% CI) -0.2 (36.0, -2.99 to 2.7)	0.034 <sup>^</sup>
Participant-related characteristics						
Median age at baseline =59 years	Mean (SD)	Mean (SD)	Mean (SD)	Mean (SD), range	Mean (SD)	0.93 <sup>^^</sup>
<Median (n=359)	45.6 (155.4)	43.6 (164.8)	-2.0 (47.4)	337 (296, 180-661)	0.001 (51.2)	
≥Median (n=361)	53.7 (68.4)	52.7 (77.9)	-1.0 (24.7)	343 (137, 181-650)	-0.3 (30.4)	
Median length of stay = 317 days (IQR: 252-366)	Mean (SD)	Mean (SD)	Mean (SD, 95% CI)	Mean (SD), range	Mean (SD)	0.003 <sup>^^</sup>
<Median (n=348)	47.9 (100.4)	49.1 (94.7)	1.2 (24.6)	295 (116, 180-601)	3.4 (32.2)	
≥Median (n=372)	51.3 (115.9)	47.2 (131.1)	-4.1 (22.8)	382 (139, 181-661)	-3.5 (22.8)	
Sex	Mean (SD)	Mean (SD)	Mean (SD)	Mean (SD), range	Mean (SD)	0.76 <sup>^^</sup>
Female (n=437)	47.6 (108.7)	46.0 (112.9)	-1.6 (33.5)	338 (234, 180-661)	-0.4 (35.5)	
Male (n=283)	52.8 (92.5)	51.4 (95.9)	-1.4 (18.5)	343 (214, 181-650)	0.3 (28.6)	
Number of adherent days (baseline score)	Mean (SD)	Mean (SD)	Mean (SD)	Mean (SD), range	Mean (SD)	0.96 <sup>^^</sup>
0-5 days (n=106)	44.3 (74.1)	42.5 (81.3)	-1.8 (36.0)	347 (189, 180-661)	-0.6 (46.3)	
6-7 days (n=489)	51.8 (106.1)	49.8 (110.6)	-2.0 (33.17)	346 (257, 180-650)	-0.9 (31.0)	
Median number of medications =7	Mean (SD)	Mean (SD)	Mean (SD)	Mean (SD), range	Mean (SD)	0.33 <sup>^^</sup>
<Median (n=236)	47.0 (93.7)	46.0 (95.3)	-1.0 (30.7)	347 (258, 180-661)	0.8 (35.3)	
≥Median (n=359)	52.8 (92.8)	50.1 (94.7)	-2.7 (26.5)	346 (182, 180-650)	-1.9 (28.4)	
Self -assessed health status at baseline (SF1)	Mean (SD)	Mean (SD)	Mean (SD)	Mean (SD), range	Mean (SD)	0.22 <sup>^^</sup>
'Good, Fair, Poor, Very Poor' (n=409)	49.8 (111.2)	49.0 (107.2)	-0.8 (30.3)	335 (229, 180-650)	0.3 (34.0)	
'Excellent' or 'very good' (n=103)	49.8 (45.7)	45.5 (49.7)	-4.3 (15.2)	335 (130, 183-609)	-2.8 (19.1)	
Health service-related characteristics						
Patient attended a health service with a median IRSEO score (=55)	Mean (SD)	Mean (SD)	Mean (SD)	Mean (SD), range	Mean (SD)	0.15 <sup>^^</sup>
< 55 (n=346)	55.0 (160.0)	52.2 (176.7)	-2.8 (20.5)	354 (245, 181-661)	-2.0 (16.7)	
>= 55 (n=374)	44.7 (112.2)	44.4 (108.3)	-0.3 (34.8)	327 (232, 180-650)	1.5 (40.6)	
Intervention-related characteristics						
Patient who had a HMR compared to patient who had a non-HMR	Mean (SD)	Mean (SD)	Mean (SD)	Mean (SD), range	Mean (SD)	0.035 <sup>^^</sup>
Non-HMR (n=314)	48.6 (108.1)	49.2 (95.7)	0.6 (24.8)	336 (253, 180-613)	2.2 (30.1)	
HMR (n=258)	50.7 (101.2)	46.5 (112.4)	-4.2 (22.5)	345 (180, 182-650)	-2.9 (19.3)	
Patients who received an MBS service for item 10987 or 10997 during the follow-up period**	Mean (SD)	Mean (SD)	Mean (SD)	Mean (SD), range	Mean (SD)	0.32 <sup>^^</sup>
No (n=334)	58.8 (118.8)	57.9 (113.3)	-0.9 (21.9)	337 (292, 180-622)	0.7 (29.2)	
Yes (n=386)	41.7 (55.0)	39.7 (60.9)	-2.0 (27.5)	342 (248, 180-661)	-0.9 (29.5)	

Bold p-values imply statistically significant change at the 0.05 level.

^P-values (paired data) were derived from the cluster-adjusted (ACCHS cluster) comparison of annualised differences in eGFR against -3 and were determined using the `svy linearized : regress Stata` command. The value of -3 was the theoretically expected mean annual eGFR (ml/min/1.73m<sup>2</sup>) linear decline.

^^Cluster adjusted p-values (ACCHS cluster) were determined using the `svy linearized : regress Stata` command with differences of annualised eGFR as the outcome measure.

\* Follow-up time is the number of days between two measurements. It was defined as the time between the most recent baseline eGFR value and the follow-up eGFR value closest to the end-of study date (31/10/2019).

\*\*MBS items 10987 and 10997 provide a rebate for a service by a practice nurse or an Aboriginal and Torres Strait Islander Health Practitioner (e.g. staff within ACCHSs) that includes a follow-up the assessment of the medication adherence of an Indigenous patient.

SD= cluster adjusted standard deviation (ACCHS cluster).

Health service= Aboriginal community-controlled health service (ACCHS)

HMR= Home Medicines Review. A completed HMR represents a comprehensive medication management review that fulfils the criteria for a Medicare Benefits Scheme (MBS) claim for item 900, as sourced from the integrated pharmacist's logbook.

IRSEO= Indigenous Relative Socioeconomic Outcomes index. The IRSEO reflects relative advantage or disadvantage at the Indigenous Area level, where a score of one (1) represents the most advantaged area and a score of 100 represents the most disadvantaged area.<sup>199</sup>

MBS= Medicare Benefits Schedule

Non-HMR= a comprehensive medication management review that was not an HMR, as sourced from the integrated pharmacist's logbook.

SF1= 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?'*



**Table 15: Mean difference in *absolute cardiovascular disease risk (CVD risk)\** in IPAC study participants (n=38) using paired pre and post-intervention measures, stratified by selected participant, health service, and intervention characteristics, and adjusted for health service cluster and the length of follow-up time.**

IPAC participants with paired data for CVD risk (n=38)	CVD risk (% unit)*			P-value
	Mean value pre-enrolment	Mean value during follow-up	Difference	
	Mean (SD)	Mean (SD)	Mean (SD, 95% CI)	
	11.9 (7.2)	10.9 (5.4)	-1.0 (2.6, -1.8 to -0.12)	0.027^
Participant-related characteristics				
Median age at baseline =58 years	Mean (SD)	Mean (SD)	Mean (SD)	0.78^^
<Median (n=18)	9.5 (9.8)	8.3 (8.9)	-1.2 (1.4)	
≥Median (n=20)	14.0 (5.8)	13.2 (4.9)	-0.8 (2.7)	
Median length of stay in the study =255 days (IQR: 203-316)	Mean (SD)	Mean (SD)	Mean (SD)	0.30^^
<Median (n=19)	12.2 (9.5)	11.6 (7.8)	-0.6 (2.2)	
≥Median (n=19)	11.5 (5.1)	10.2 (3.6)	-1.3 (2.1)	
Sex	Mean (SD)	Mean (SD)	Mean (SD)	0.17^^
Female (n=29)	10.2 (2.9)	9.5 (1.9)	-0.7 (2.2)	
Male (n=9)	17.2 (8.1)	15.4 (6.6)	-1.8 (2.0)	
Number of adherent days (baseline score)	Mean (SD)	Mean (SD)	Mean (SD)	0.28^^
0-5 days (n=6)	13.0 (5.2)	10.7 (3.3)	-2.3 (3.3)	
6-7 days (n=26)	10.5 (3.6)	9.8 (2.4)	-0.7 (2.1)	
Median number of medications =5	Mean (SD)	Mean (SD)	Mean (SD)	0.28^^
<Median (n=14)	11.4 (2.7)	10.8 (3.8)	-0.6 (2.7)	
≥Median (n=18)	10.7 (7.4)	9.3 (6.5)	-1.3 (1.8)	
Self-assessed health status at baseline (SF1)	Mean (SD)	Mean (SD)	Mean (SD)	0.10^^
'Good, Fair, Poor, Very Poor' (n=26)	10.8 (4.7)	10.0 (3.7)	-0.8 (2.6)	
'Excellent' or 'very good' (n=5)	10.6 (5.6)	8.4 (4.3)	-2.2 (1.8)	
Health service-related characteristics				
Patient attended a health service with a median IRSEO score (=61)	Mean (SD)	Mean (SD)	Mean (SD)	0.64^^
< 61 (n=13)	10.5 (5.1)	9.4 (2.9)	-1.1 (2.4)	
>= 61 (n=25)	12.6 (7.5)	11.7 (5.4)	-0.9 (2.7)	
Intervention-related characteristics				
Patient who had a HMR compared to patient who had a non-HMR	Mean (SD)	Mean (SD)	Mean (SD)	0.039^^
Non-HMR (n=22)	11.4 (6.9)	10.9 (5.4)	-0.5 (1.9)	
HMR (n=8)	15.8 (2.4)	13.4 (1.2)	-2.4 (1.1)	
Patients who received an MBS service for item 10987 or 10997 during the follow-up period**	Mean (SD)	Mean (SD)	Mean (SD)	0.16^^
No (n=19)	14.0 (4.1)	12.4 (1.9)	-1.6 (3.2)	
Yes (n=19)	9.8 (8.3)	9.4 (8.0)	-0.4 (1.1)	

Bold p-values imply statistically significant change at the 0.05 level.

^P-value (paired data) was derived from the cluster-adjusted (ACCHS cluster) comparison of CVD risk differences against zero and was determined using the svy linearized : regress Stata command.

^^Cluster adjusted p-values (ACCHS cluster) were determined using the svy linearized : regress Stata command with differences in CVD risk as the outcome measure. The follow-up time in days between the enrolment date and the end of study date was added to all cluster-adjusted linear regression models.

\* Estimated 5-year risk of a primary cardiovascular event according to the Framingham risk equation (1991) for those not at high risk according to clinical criteria (<http://www.cvdcheck.org.au/>)<sup>200</sup>

\*\*MBS items 10987 and 10997 provide a rebate for a service by a practice nurse or an Aboriginal and Torres Strait Islander Health Practitioner (e.g. staff within ACCHSs) that includes a follow-up the assessment of the medication adherence of an Indigenous patient.

SD= cluster adjusted standard deviation (ACCHS cluster).

CVD= cardiovascular disease

Health service= Aboriginal community-controlled health service (ACCHS)

HMR= Home Medicines Review. A completed HMR represents a comprehensive medication management review that fulfils the criteria for a Medicare Benefits Scheme (MBS) claim for item 900, as sourced from the integrated pharmacist's logbook.

IRSEO= Indigenous Relative Socioeconomic Outcomes index. The IRSEO reflects relative advantage or disadvantage at the Indigenous Area level, where a score of one (1) represents the most advantaged area and a score of 100 represents the most disadvantaged area.<sup>201</sup>

MBS= Medicare Benefits Schedule

Non-HMR= a comprehensive medication management review that was not an HMR, as sourced from the integrated pharmacist's logbook.

SF1= 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?'

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