Australian Government

Medical Services Advisory Committee

Public Summary Document

Application No. 1698 – Chronic Pain MedsCheck Trial

Applicant: **Pharmacy Guild of Australia**

Date of MSAC consideration: **28-29 July 2022**

Context for decision: MSAC makes its advice in accordance with its Terms of Reference, visit the MSAC website

1. Purpose of application

An application requesting funding under a future Community Pharmacy Agreement for pharmacists to provide a Chronic Pain MedsCheck service for people living with chronic pain was received from The Pharmacy Guild of Australia by the Department of Health and Aged Care.

2. MSAC's advice to the Minister

After considering the strength of the available evidence in relation to comparative safety, clinical effectiveness, cost-effectiveness and total cost, MSAC did not support public funding of the Chronic Pain MedsCheck service, under a future Community Pharmacy Agreement, for people living with chronic pain. MSAC acknowledged there is a high unmet need for coordinated multidisciplinary care for people experiencing difficulty managing chronic pain. However, MSAC had significant concerns with the trial design and conduct and as a consequence considered the evidence to be of low quality with a high risk of bias. MSAC considered the evidence presented did not demonstrate the comparative effectiveness and cost-effectiveness of Chronic Pain MedsCheck. MSAC also considered the estimated financial impact (net cost-savings) to be highly uncertain as utilisation may be underestimated and the reduction in use of other health services to manage chronic pain may be overestimated.

Consumer summary
This application from The Pharmacy Guild of Australia requested funding for community pharmacists to provide a Chronic Pain MedsCheck service for people living with chronic pain under a future Community Pharmacy Agreement. Medication review services are intended to support the quality use of medicines and reduce medication misadventure, by assisting patients to better manage and understand their medicines. There are different types of medication review services that are publicly funded through the Seventh Community Pharmacy Agreement between the Commonwealth Government, The Pharmacy Guild of Australia and the Pharmaceutical Society of Australia. This

Consumer summary

includes the Home Medicines Review, Residential Medication Management Review, MedsCheck and Diabetes MedsCheck.

The Chronic Pain MedsCheck is an in-pharmacy, patient-centred medication review service that focused on reviewing participant's medications and providing education and information to improve participant's self-management of chronic pain. A trial of the Chronic Pain MedsCheck was performed to see how well (effective) the service would be in:

- preventing incorrect use and/or overuse of pain medication
- increasing participants' pain medication health literacy
- improving participants' ability to self-manage their chronic pain
- improving participants' overall quality of life.

MSAC noted that chronic pain is a serious issue that affects many people in the community and, for various reasons, not everyone affected by chronic pain can regularly see their usual doctor (general practitioner [GP]). MSAC also noted that pharmacists play a vital role in the healthcare system. However, MSAC noted that managing chronic pain should happen in a coordinated approach involving a patient's GP and a variety of healthcare providers. MSAC was concerned that the Chronic Pain MedsCheck service does not require involvement of a GP. MSAC considered this may present safety issues because the pharmacist is not able to confirm with a doctor why a patient has been prescribed certain medications or understand if the underlying condition is worsening. MSAC considered that pharmacists could potentially provide services that help people manage their chronic pain. However, MSAC was concerned that, without GP involvement, the service may not result in the best coordinated and multidisciplinary care for people living with chronic pain.

When looking at the results of the trial, MSAC noted that the trial was not well designed. MSAC noted a large proportion of people did not complete the trial (dropped out), and that, due to problems with the trial design, there was a high risk of bias, meaning it is uncertain whether the benefits reported in the trial are accurate. Overall, MSAC considered that the trial did not provide reliable evidence to support funding this service.

MSAC's advice to the Commonwealth Minister for Health and Aged Care

MSAC acknowledged there is a high unmet need for coordinated multidisciplinary care for people experiencing difficulty managing chronic pain. However, MSAC considered the low-quality evidence had a high risk of bias and did not demonstrate the comparative effectiveness and cost-effectiveness of the Chronic Pain MedsCheck. MSAC also considered the estimated financial impact (net cost-savings) to be highly uncertain.

3. Summary of consideration and rationale for MSAC's advice

MSAC noted this application was from The Pharmacy Guild of Australia requesting funding, under a future Community Pharmacy Agreement, of Chronic Pain MedsCheck (CPMC) for people living with chronic pain. MSAC noted that the CPMC trial was funded through a grant agreement with the Department of Health and Aged Care as part of the Pharmacy Trials Program under the Sixth Community Pharmacy Agreement. MSAC noted that the CPMC Trial aimed to assess the effectiveness of a pharmacist-led, patient-centred service supporting patients taking medications to manage chronic pain and who were identified as experiencing issues with medication self-management or dependency.

MSAC noted that medication management reviews (MMR) are currently funded under the Seventh Community Pharmacy Agreement (7CPA) MMR programs: the Home Medicines Review (HMR) program, the Residential Medication Management Review (RMMR) program, and the MedsCheck and Diabetes MedsCheck programs. MSAC recalled that in 2017 it had appraised the MMR programs and at that time considered there was insufficient evidence to determine the clinical and cost-effectiveness of the MMR programs and found no clear evidence that these interventions reduce hospitalisations or mortality or improve quality of life. In general, studies examining the impact of pharmacy-based medication review services did not find clear evidence to indicate that these interventions have any impact on reducing mortality or on improving appropriateness of medication prescribing.

MSAC noted the Australian and New Zealand College of Anaesthetists Faculty of Pain Management was not supportive of the trial nor the intervention.

MSAC noted the CPMC trial was a pre-post trial with two study arms, Group A and Group B, which received face-to-face consultations with pharmacists, three months apart. Participants in Group B also received an additional telephone consultation at 6-weeks. MSAC noted that the pre-MSAC response claimed that "the trial design, consistent with the protocol, was a pragmatic pre-post trial of two versions of the CPMC intervention".

MSAC agreed with the Evaluation Sub-Committee (ESC) that the CPMC trial provided low quality evidence with a high risk of bias due to a number of issues with the trial design. MSAC agreed with ESC that the lack of collaboration with general practitioners (GP) in the CPMC trial and proposed implementation may introduce safety concerns as the pharmacist has no clinical records to confirm the diagnosis or prescribing intent, and may not be able to assess whether worsening pain is due to progression of an underlying disease process or poor medication adherence. MSAC noted that there are many people in the community who have chronic pain and who, for different reasons, do not see a GP. MSAC acknowledged that pharmacists are able to support people with chronic pain to some extent, however MSAC advised that chronic pain is a complex condition that needs coordinated multidisciplinary care. While MSAC acknowledged there is a high unmet need for coordinated multidisciplinary care for people experiencing difficulty managing chronic pain, MSAC was not convinced that implementing the proposed intervention would achieve this. MSAC considered the appropriate role for pharmacists when managing chronic back pain, a major source of chronic pain, was unclear as management should be based on non-drug interventions. MSAC also agreed with ESC that the clinical need for the Chronic Pain MedsCheck is unclear given there are existing Medicare Benefits Schedule (MBS) items that allow GPs to treat acute and chronic pain, as well as existing MedsCheck and Home Medicines Review (HMR) programs.

MSAC noted the proposed fees for the service ($98.41 for initial consultation, and $32.81 for the midpoint and follow-up consultation) are lower than those for a GP consultation of equivalent length delivering similar services (Level B $39.10 – up to 20 minutes; Level D $111.50 – over 40 minutes; Medication Management Review $161.10).

MSAC noted that the CPMC trial did not include a treatment-as-usual comparator arm, but instead used baseline data collected at the initial consultation as the comparator. MSAC noted that for such an intervention, it can be difficult to design a placebo intervention. However, MSAC agreed with ESC that using baseline data introduced bias that favoured the intervention. MSAC considered that including a treatment-as-usual comparator is especially important where attrition is likely to be large, as was the case in this trial. MSAC noted the pre-MSAC response claimed that due to the trial design and approach to analysing the data that regression to the mean was unlikely. However, MSAC was not convinced that this was correct. MSAC considered that without an appropriate treatment-as-usual comparator it is unknown how a participant's health status

would have changed overtime without the CPMC intervention and considered it would have been appropriate for the CPMC trial to include a treatment-as-usual comparator group.

MSAC was concerned that of the 1,630 pharmacies that registered for the trial, one-third of these pharmacies did not complete the training and one-third of the pharmacies did not enrol any patients. MSAC noted that pharmacies were allocated to Group A or B and to main trial or evaluation groups (where the evaluation group collected additional outcomes). MSAC noted that due to insufficient patient recruitment, the number of patients enrolled in the Group B evaluation arm of the study (n=940) did not meet the sample size required to be powered to detect the nominated differences in the primary outcomes, including the AQoL-4D (Assessment of Quality of Life), the Partners in Health (PIH) scale, and the Brief Pain Inventory-short form (BPI-sf).

MSAC noted ESC raised concerns with attrition bias due to the large loss to follow-up after baseline. The loss to follow up in Group B was higher than the expected loss to follow up (61% compared to the 40% allowed for in the sample size calculation), resulting in a small sample size and low confidence in the Group B evaluation findings. MSAC also noted the attrition rate was higher in Group B (61%) compared to Group A (34%). MSAC noted the pre-MSAC response claimed that analyses presented suggest that the CPMC trial did not have a high likelihood of attrition bias. However, MSAC agreed with ESC that the large loss to follow-up after baseline introduced serious risk of bias and raised concerns about the validity of the study outcomes.

MSAC noted the CPMC trial reported statistically significant improvement in most outcomes (e.g., self-management, pain severity, pain interference scores). However, MSAC agreed with ESC that it is unclear if improvements were clinically meaningful and that there is significant uncertainty in the magnitude of the improvements due to the trial design and risk of bias issues. MSAC noted that there was no change for the Oral Morphine Equivalence (OME) score, Emergency Department presentations or self-reported hospital admissions. MSAC was also unconvinced that the size of improvements reported in response to the relatively short-term intervention with 2-3 interactions were valid, noting the trial did not explore the impact of the telephone consultation for Group B. MSAC considered the degree of behaviour change reported does not align with established understanding on the success of behaviour interventions in other patient groups with chronic conditions.

MSAC noted the Applicant Developed Assessment Report (ADAR) presented a cost-utility analysis for the primary outcomes and a cost-effectiveness analysis for the secondary outcomes. MSAC noted that the revised base case results suggested incremental cost-effectiveness ratios (ICERs) of $14,552 and $7,897 per quality-adjusted life year (QALY) gained for Group A and B, respectively. However, MSAC noted that these are still highly uncertain, given the uncertain clinical benefit compared to usual care.

MSAC noted that the ADAR used an epidemiological approach to estimate the financial impact of funding the Group B CPMC intervention. The ADAR assumed all adults with chronic non-cancer pain would be eligible for a CPMC service, but uptake is limited by estimating that only 34% of pharmacies in Australia (n=1,920) will administer the CPMC program, based on uptake of the CPMC trial. However, MSAC agreed with ESC that the estimated number of CPMC services per year may be underestimated. MSAC noted that the estimates assume a sustained reduction in outcomes, such as prescriptions and MBS services (which should include referrals) over five years, which is unlikely given the episodic nature of chronic pain. MSAC also noted that the reduction in outcomes was calculated using un-matched cohorts, so it is unclear whether the reductions represent a real decrease or reflect a population experiencing a transient worsening of pain management. MSAC noted it was estimated that funding the Group B CPMC intervention would result in a net cost-saving of $3,373,610 at year 5 however, MSAC considered the estimated financial impact to be highly uncertain.

MSAC acknowledged there is a high unmet need for coordinated multidisciplinary care for people experiencing difficulty managing chronic pain and that there are patients who are unable or unwilling to access GP care for their condition. However, overall MSAC did not support funding of CPMC on the basis that the evidence was of a low quality with a high risk of bias and did not demonstrate the comparative effectiveness and cost-effectiveness of CPMC. MSAC also had significant concerns that funding and implementing the CPMC nationally would not lead to the successful implementation of a coordinated and integrated multidisciplinary medication review service for people living with chronic pain. MSAC also considered the estimated financial impact (net cost-savings) to be highly uncertain as utilisation may be underestimated and the reduction in use of other health services to manage chronic pain may be overestimated.

Other discussion

MSAC noted that the Department may wish to consider the points it has raised regarding trial design and methodology to ensure any future trials are appropriately designed to provide high quality evidence that can support decision making on comparative safety, effectiveness and cost-effectiveness of an intervention.

4. Background

The Chronic Pain MedsCheck (CPMC) trial was funded as part of the Pharmacy Trials Program, under the Sixth Community Pharmacy Agreement. The Pharmacy Trials Program was established to trial new and expanded community pharmacy programs that seek to improve clinical outcomes for participants by progressing the role of community pharmacies in the delivery of primary healthcare services. All trials conducted as part of the Pharmacy Trials Program will undergo a full HTA evaluation through ESC and MSAC. An expert panel, established by The Pharmacy Guild of Australia, oversaw the trial design, evaluation plan and implementation.

At its July 2021 teleconference, the MSAC Executive noted the Department had received the final report for the CPMC trial, which assessed the effectiveness of a pharmacist-led, patient-centred service supporting patients taking medications to manage chronic pain and who were identified as experiencing issues with medication self-management or dependency. The trial had two arms, Group A and Group B, which received face-to-face consultations with accredited pharmacists, three months apart, and an additional telephone consultation for Group B at the 6-week midpoint. The MSAC Executive noted that significant improvements in outcomes were seen in both trial arms compared with the baseline. The MSAC Executive noted that participants in Group B experienced a larger benefit. The MSAC Executive queried the plausibility that the additional telephone consultation provided to patients in Group B contributed to better outcomes. The MSAC Executive noted there was a high likelihood of attrition bias in the trial and so advised that analyses exploring patients who discontinued the trial and the potential impact of attrition bias would be informative for consideration by ESC and MSAC. The MSAC Executive noted there is a strong national interest in addressing chronic pain and that there is a lack of clinical services to adequately support patients with inadequately managed chronic pain.

MSAC has previously appraised three Medication Management Review Programs in April 2017: Home Medicines Review (HMR), Residential Medication Management Review (RMMR) and MedsCheck/Diabetes MedsCheck Programs (refer to MSAC Minutes). The evaluation report did not find any primary studies examining the MedsCheck or Diabetes MedsCheck services specifically, nor were any primary studies examining pharmacy-based medication review services conducted in Australia found. MSAC advised that there is no clear evidence to indicate that such services have any impact on reducing mortality or on improving appropriateness of medication prescribing, although MSAC observed a positive effect of the medication review on patient

satisfaction. MSAC advised that there is conflicting evidence on the effect of the pharmacy-based medication review on reducing hospitalisations, improving patient adherence and quality of life, and reducing drug burden and falls. Evidence demonstrating any impact of such services on reducing adverse events and health care resource use is inconclusive. MSAC was concerned about the dated nature of presented evidence as well as the sparseness of Australian studies available (particularly for RMMR and MedsCheck services), and hence the applicability of the study findings to the contemporary Australian context.

MSAC considered that the design and value of these pharmacy service programs could be improved by including formal collaboration with GPs and other healthcare networks, by being targeted to more appropriate patient populations, and by a reduction in the unit cost of providing each type of pharmacy service coupled with an incentive to increase this unit cost if adequate new evidence can be furnished to justify an increase. Further enhancement of these programs might better justify the provision of continued funding of these services. MSAC reiterated its previous advice regarding the need to collect robust comparative evidence focusing on improved health outcomes, and, at the very least, data collection by pharmacists providing these services about what services were rendered to what type of patient and at what cost.

A summary of the key matters raised by the MSAC Executive and related issues is presented in Table 1.

Table 1 Summary of key matters of concern

Component	Matter of concern	How the current assessment report addresses it
Efficacy of the Group B mid-point telephone consultation	MSAC Executive queried the plausibility that the additional telephone consultation provided to patients in Group B contributed to better outcomes.	Not addressed. The applicant advised that the literature and expert advice which suggested the need for additional support was not written up and the applicant could not provide it.
Attrition bias	MSAC Executive noted there was high likelihood of attrition bias in the trial and so advised that analyses exploring patients who discontinued the trial and the potential impact of attrition bias would be informative for consideration by ESC and MSAC.	Not adequately addressed. The applicant noted that Tables 29-32 in the ADAR included a comparative analysis of those lost to follow-up compared to those that completed the trial. A calculation of the effect size of age between those lost to follow-up and those that completed the trial was also provided. There were no sensitivity analyses presented to support the claim that using unmatched data was unlikely to impact results.
Comparison with usual care	The CMPC Trial and economic evaluation do not have an adequate usual care group. There are no comparisons of the CPMC with current services or alternative pain management options.	Not adequately addressed – baseline measurements have been used as the likely usual care outcomes at future follow-up points.
Time horizon of the economic evaluation	The economic evaluation did not have full data for the six-month time horizon of the model.	Not addressed.
Derivation of reduction in PBS and MBS services and hospital costs data	The ADAR compares the means of a complete baseline cohort and an incomplete follow--up cohort. It is uncertain if this represents a true reduction or a difference in the cohorts.	Not addressed. While the ADAR does adjust PBS data, it is unclear if this was to account for attrition.
Utilities applied in the economic evaluation	The QALY calculation did not include time spent in the health state.	Not addressed. The commentary includes a corrected calculation.

Source: compiled during the evaluation
Abbreviations: ADAR, Applicant Developed Assessment Report; CPMC, Chronic Pain MedsCheck; ESC, Evaluation Sub-committee; MBS, Medicare Benefits Schedule; MSAC, Medical Services Advisory Committee; PBS, Pharmaceutical Benefits Scheme; QALY, Quality adjusted life years.

5. Prerequisites to implementation of any funding advice

The ADAR seeks funding for this intervention under future Community Pharmacy Agreements, which have yet to be negotiated.

The ADAR does not mention any prerequisites to implementation of any funding advice. Pharmacists delivering consultations in the CPMC trial were required to complete specific continuing professional development (CPD) accredited online training. It is unclear whether the ADAR considers this prerequisite would apply to those who could deliver a CPMC if the program were funded.

6. Proposal for public funding

The ADAR proposed that the Group B intervention (comprising an initial and a 3-month follow-up consultation taking place in-pharmacy, with a 6-week midpoint telephone consultation) be considered for funding under future Community Pharmacy Agreements.

The requested fee is summarised in Table 2. The ADAR presented a derived representative cost from an activity-based costing study, which found that the representative cost and duration were higher than the trial fee and indicative duration. However, the requested fee is same as the trial payment schedule and has been used in the economic analysis and financial impact analysis.

Table 2 Summary of Chronic Pain MedsCheck consultations and requested fees

Consultation	Description of service	Mode	Trial payment schedule		Representative cost	
			Minutes	Fee	Minutes	Fee
Initial	Review and assessment of the consumer's chronic pain experience and medication usage, collection of data using mini-ePPOC, provision of information, education and/or referrals, development of a written action plan.	Face-to-face	45	$98.41	109.3	$105.17
Midpoint	Review of progress against the written action plan and amendments in needed, collection of data using mini-ePPOC, referral to additional health professional support if needed.	Telephone	15	$32.81	45	$42.32
3-month follow up	Review and assessment of progress against the written action plan, updating the plan if needed, collection of data using mini-ePPOC, provision of follow-up support, advice and/or referral as needed.	Face-to-face	15	$32.81	41.3	$38.50

Source: Applicant provided during the evaluation, Trial protocol, Tables 61-63 of ADAR
Abbreviations: mini-ePPOC, mini-electronic Persistent Pain Outcomes Collaboration

The CPMC service can be initiated by the pharmacist without referral from another health professional. There is also no requirement for formal collaboration with GPs and other healthcare networks (a record of the service, including the associated Action Plan, should be uploaded to the patient's My Health Record), but the Pharmaceutical Society of Australia's Guidelines for pharmacists providing MedsCheck and Diabetes MedsCheck services do encourage communication with prescribers or other healthcare providers, including sharing a copy of the Action Plan. Although many analgesics can be purchased without a prescription, the Department of Health and Aged Care's National Strategic Action Plan for Pain Management 2021 recommends a coordinated interdisciplinary management strategy to address pain. The trial Protocol included compulsory referral to another health professional for pre-defined mini ePPOC outputs to help standardise service provision, but it is unclear if this would be included if the service was funded. Previously, in the context of pharmacy diabetes screening, MSAC considered the service should form part of a comprehensive, coordinated and integrated system of primary care (p8, Public Summary Document [PSD] Application 1677).

Fees for existing medication management services funded under the current Seventh Community Pharmacy Agreement (7CPA) are listed in Table 3. The proposed CPMC fee schedule differs to the similar MedsCheck and Diabetes MedsCheck, which consist of a single consultation service. MedsChecks and Diabetes MedsChecks can also be delivered by any registered pharmacist without any additional training. Home Medicines Reviews must be delivered by an accredited

pharmacist and are initiated by a referring physician. The follow-up Home Medicines Review services are not automatically provided, but are available if they are deemed necessary. In general, patients are eligible for one medication management service in 12 months. An extra Home Medicines Review may be claimed if a referring physician deems there is a clinical need.

Table 3 Summary of existing Medication management services and fees

Consultation	Mode*	Fee (in 2022)
Initial MedsCheck	Face-to-face	$66.53
Initial Diabetes MedsCheck	Face-to-face	$99.79
Initial Home Medicines Review	Face-to-face	$222.77
First follow-up Home Medicines Review	Face-to-face	$111.39
Second follow-up Home Medicines Review	Face-to-face	$55.70

Source: compiled during the evaluation using information from Pharmacy Programs Administrator
*Since April 2020, temporary arrangements for COVID-19 allow eligible patients to access these services via telehealth.

The current medication management programs (Table 3) do not have an indicative duration. Table 4 presents relevant MBS fees for general practitioner consultation for similar chronic pain management.

Table 4 MBS fees for relevant consultation items (general practitioners)

MBS item	Consultation	Mode	Duration (mins)	Fee (in 2022)
23	Professional attendance by a general practitioner at consulting rooms including any of the following that are clinically relevant: (a) taking a patient history; (b) performing a clinical examination; (c) arranging any necessary investigation; (d) implementing a management plan; (e) providing appropriate preventive health care; for one or more health-related issues, with appropriate documentation-each attendance	Face-to-face	<20	$39.10
36	Professional attendance by a general practitioner at consulting rooms including any of the following that are clinically relevant: (a) taking a detailed patient history; (b) performing a clinical examination; (c) arranging any necessary investigation; (d) implementing a management plan; (e) providing appropriate preventive health care; for one or more health-related issues, with appropriate documentation-each attendance	Face-to-face	At least 20	$75.75
44	Professional attendance by a general practitioner at consulting rooms including any of the following that are clinically relevant: (a) taking an extensive patient history; (b) performing a clinical examination; (c) arranging any necessary investigation; (d) implementing a management plan; (e) providing appropriate preventive health care; for one or more health-related issues, with appropriate documentation-each attendance	Face-to-face	At least 40	$111.50
721	Attendance by a general practitioner for preparation of a GP management plan for a patient.	Face-to-face	NA	$150.10
723	Attendance by a general practitioner to coordinate the development of team care arrangements for a patient.	Face-to-face	NA	$118.95
729	Contribution by a general practitioner to a multidisciplinary care plan prepared by another provider or a review of a multidisciplinary care plan prepared by another provider	Face-to-face	NA	$73.25

MBS item	Consultation	Mode	Duration (mins)	Fee (in 2022)
731	Contribution by a general practitioner to: (a) a multidisciplinary care plan for a patient in a residential aged care facility, prepared by that facility, or to a review of such a plan prepared by such a facility; or (b) a multidisciplinary care plan prepared for a patient by another provider before the patient is discharged from a hospital, or to a review of such a plan prepared by another provider	Face-to-face	NA	$73.25
91891*	Phone attendance by a general practitioner if the attendance includes any of the following that are clinically relevant: (a) taking a short patient history; (b) arranging any necessary investigation; (c) implementing a management plan; (d) providing appropriate preventative health care	Telephone	At least 6	$39.10
91894*	Phone attendance by a general practitioner, if: (a) the attendance is performed from a practice location in Modified Monash areas 6 or 7; and (b) the attendance includes any of the following that are clinically relevant: (i) taking a detailed patient history; (ii) arranging any necessary investigation; (iii) implementing a management plan; (iv) providing appropriate preventative health care	Telephone	At least 20	$75.75

Source: compiled during the evaluation using information from MBS Online

* In most cases, telehealth items are only available to patients who have an existing relationship with the practitioner performing the service (defined as having at least one face-to-face service in the preceding 12 months).

7. Population

The ADAR did not explicitly nominate a population for the proposed service but implicitly suggested this would be the same as the trial population.

The population included in the CPMC trial were people who:

- attended a community pharmacy
- were over the age of 18
- hold a valid Medicare and/or DVA card
- were living at home in a community setting
- experienced chronic pain (pain for three months or longer)
- had not had a Home Medicines Review, MedsCheck, Diabetes MedsCheck, or Chronic Pain MedsCheck within the previous 12 months
- had been taking prescription or over-the-counter medication for their pain
- were identified by a community pharmacist as either experiencing self-management or dependency issues
- were not a current client of a recognised pain management service.

The ADAR considered that there is often a lack of access to appropriate advice and support for chronic pain in the community, and it is difficult for participants to access effective treatment that is timely and affordable. Community pharmacists see participants on a regular basis without the need for an appointment. As such, the ADAR considered pharmacists are ideally placed to

provide patient-based solutions to support people who are suffering from chronic pain. The CPMC service was expected to fill a gap in pain management services.

For medication management support, this population may not necessarily be eligible for the existing MedsCheck service (which is available to patients taking five or more medications), but may be eligible for a Home Medicines Review if their medical practitioner deems it clinically necessary. Under the 7CPA funding rules, people are eligible for one medication management service (MedsCheck, Diabetes MedsCheck, or Home Medicines Review) in 12 months.

To meet the other objectives of the CPMC – to increase health literacy, ability to self-manage their chronic pain, and overall quality of life – this population currently has access to general practitioner consultations. It should be noted that referrals to allied health services made by the pharmacists as a result of the CPMC were not subsidised by Medicare. Patients who wanted to access subsidised allied health services needed to be referred first to a general practitioner. This presents barriers to access for patients.

8. Comparator

The ADAR nominated baseline data collected at the initial consultation as the comparator within each arm, and also compares the two arms to each other (Table 5).

Table 5 Summary of comparators to the CPMC intervention(s)

Intervention (data collection timepoint)	Comparator (Group and data collection timepoint)
Group A (three months post initial consultation)	Group A (baseline data collected at initial consultation)
Group B (three months post initial consultation)	Group B (baseline data collected at initial consultation)
Group A (change at three months post initial consultation)	Group B (change at three months post initial consultation)

Source: Table 14 of ADAR

The comparator in practice should be the absence of the new service or usual care. This might involve usual pharmacist advice, provision of prescription and/or over the counter medication, a GP consultation and management plan, referral to other health professionals, a Home Medicines Review, or a standard MedsCheck delivered by pharmacists who had not undergone the study training (although it is possible that not all CMPC participants would have been eligible for a MedsCheck under the current eligibility criteria. For example, it is unclear if all participants took five or more prescription medications). Self-management or dependency may or may not have been addressed at a later date by another healthcare professional. There was no usual care group followed for three months in the trial. Baseline measurements were used to estimate the likely costs and outcomes for the 'treatment as usual' case but it is unknown how well these capture how participants' health status would have changed over time, without the CPMC intervention. The course of pain is typically episodic for people living with chronic pain, where regression to the mean often occurs over time.

For such an intervention, it can be difficult to design a placebo intervention, but a treatment as usual group would have been appropriate to capture the likely outcomes for the comparator. This is especially important where the rate of attrition is likely to be high.

9. Summary of public consultation input

Consultation feedback was received from ten organisations and one individual:

- North Western Melbourne Primary Health Network (NWMPHN),
- Australian Pain Society (APS),
- Musculoskeletal Australia,
- the Australian Pain Management Association (APMA),
- the Royal Australian College of General Practitioners (RACGP),
- the Australian Medical Association (AMA); and
- the National Rural Health Alliance (NRHA)
- the Australian Society of Anaesthetists (ASA)
- the Faculty of Pain Medicine (FPM)
- the Pharmaceutical Society of Australia (PSA).

The advantages of the proposed service were stated to be:

- Improved access to high-quality pain services in the community. Intervention likely to contribute to addressing the greater need for reduced access to services in rural areas.
- Improvements in health outcomes such as pain severity, pain interference, psychological distress, pain self-efficacy and self-management. Statistically significant changes in general activities and sleep. Improvements in nutritional measures. Improved health literacy and patient education by early intervention for the person experiencing pain who may be using medications in an unsafe manner.
- Earlier intervention for patients at risk of developing sub-acute or chronic pain or therapeutic opioid problems and preventing their occurrence.
- Decreased utilisation of primary healthcare e.g., General Practitioner services and decreased presentations to Emergency Departments for chronic pain management and pain medication related adverse effects.
- Additional skills training for pharmacists.
- The CPMC service is helpful for those who also buy their vitamins, supplements, medicinal cannabis, NSAIDs etc from chemists.

The disadvantages of the proposed service were stated to be:

- Lack of involvement of patient GP. Potential to reduce coordination of care. May dilute an important health service interaction with a patient's GP that can reduce the burden of chronic pain medication usage.
- Chronic Pain Management is best managed by multidisciplinary teams. This is where a pharmacist should work collaboratively within this arrangement. This work cannot be performed in silos where the other factors driving chronic pain are not addressed. Patients with chronic pain require multidisciplinary care rather than that provided by a single practitioner (regardless of specialty). Others considered chronic pain is best managed through a medical specialist-led multidisciplinary approach. Isolated measures can fragment and duplicate care.
- No benefit of this service for patients, their families and carers.
- The studied population were not receiving pain medicine or interventions at the start of the study.
- Inequitable access to service as patient participation is dependent on an existing relationship with the pharmacist.
- People with chronic Pain are a vulnerable group of patients, that require close monitoring and the development of a sustained therapeutic relationship.

- Scheduling conflicts between the person, their carers and pharmacists
- Frequent interruptions to pain management sessions if staffing levels within participating
- pharmacists is not sufficient. The time required for each consultation was underestimated by pharmacists involved in the trial.
- There is a significant amount of scrutiny and monitoring in Australia around opioid prescription practices. Our community tells us that they feel disadvantaged and are often subject to tapering without their own voice being heard or considered. The CPMC service needs to be managed sensitively for a community already struggling with pain management.
- RACGP has serious concerns with the proposed CPMC model and its potential to shift chronic pain diagnosis and management away from medically trained professionals, leading to isolation and fragmentation of patient care. RACGP also has issues with the trial findings.
- Lack of reference to Aboriginal and Torres Strait Islander participants in the trial.

The following other points were raised:

- The ultimate area of increased funding should lie within the remit of their GP, given the centrality of their relationship to their patient.
- Pharmacists conducting pain management reviews would benefit from access to hospital discharge Summaries for persons who have had an inpatient or Emergency Department presentation and any relevant pain history including previous treatments, imaging and referrals.
- There needs to be good communication from the pharmacist and the general practitioner to ensure a continued therapeutic relationship and appropriate care delivery.
- Other services such as psychological services and physiotherapy need to be involved. Consideration needs to be given to the ability of pharmacists to refer to allied health practitioners e.g. physiotherapists, psychologists, social workers.
- A review of MBS codes for chronic care provided by allied health professionals needs to be conducted.
- A better approach - Pharmacists in general practice - The RACGP notes many of the trials funded under the Community Pharmacy Agreements, including the CPMC Trial, are implemented largely in isolation from general practice and other important primary care services. These trials represent a missed opportunity to support pharmacists to provide high-quality medication services in close alignment and collaboration with their local general practice, which has the potential to significantly improve patient outcomes.
- Comprehensive training in evidence-based pain science and the biopsychosocial management of chronic pain, including the role of other health professionals and when to refer on, is essential to this intervention. Such training must be contemporary, regularly updated and accessible to pharmacists living throughout the country.

10. Characteristics of the evidence base

The ADAR included a single study, the Chronic Pain MedsCheck (CPMC) trial.

As confirmed by the applicant, the ADAR is the final trial report. There was no other final report or publication produced on numbers. Perhaps due to the prescribed ADAR format, the trial was not reported consistently with standards outlined in the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) and Consolidating Standards of Reporting Trials (CONSORT) statements, as stated in the trial protocol. The trial does not appear to be registered in the Australian New Zealand Clinical Trials Registry or ClinicalTrials.gov. Prospective trial registration,

in a publicly accessible database, is a requirement set out in the Declaration of Helsinki, which is the cornerstone document guiding the ethical conduct of research in humans by physicians.

The CPMC trial was a pre-post trial with random assignment of clusters (individual pharmacies) to a study arm:

- An initial and 3-month in-pharmacy face-to-face consultation between the pharmacist and the trial participant (Group A).
- An initial and 3-month in-pharmacy face-to-face consultation between the pharmacist and the trial participant, with an additional telephone consultation 6 weeks after the initial consultation (Group B).

Additionally, pharmacies in each arm were randomly allocated into 'main trial' and 'evaluation' groups. There was no difference in the intervention delivered in 'main trial' and 'evaluation' groups, but there were additional outcomes collected in the 'evaluation' group: quality of life, self-management, health literacy, and service satisfaction. The 'evaluation' groups were intended to compare Group A and Group B, and the power of the trial is based on this 'evaluation' group sub-study (the 'evaluation trial'). Due to insufficient participant recruitment numbers at the evaluation sites and some of these sites withdrawing from the trial, additional 'main trial' sites were selected at random to become 'evaluation' trial sites in June 2019. The sample size calculation was based on detecting a difference in the study primary outcomes of the AQoL-4D, the PIH scale, and the BPI-sf in 'evaluation' sites, and assumed a 40% loss to follow up. However, the 'evaluation trial' still did not meet the pre-specified required sample size calculated for Group B.

There was no 'usual care' group in the trial. The baseline measurements used as a proxy for usual care are unlikely to represent 'treatment as usual' outcomes and may not represent how participants' health status would have changed over time, without the intervention. The course of pain is typically episodic for many people living with chronic pain, where regression to the mean often occurs over time. Baseline measurements may be capturing people seeking treatment during a pain flare up. Comparing these measurements to outcomes after a period of time when the pain flare may have resolved for a number of reasons) unrelated to the current intervention (such as regression to the mean) may not be appropriate.

Participants, investigators and assessors were not blinded to the treatment allocation.

The ADAR did not conduct a risk of bias assessment of the CPMC trial using an appropriate tool. During the evaluation, a risk of bias assessment using the National Institutes of Health (NIH) Quality Assessment Tool for Before-After (Pre-Post) Studies With No Control Group was conducted.

The study is considered to be at a high risk of bias for the following reasons:

- The ADAR did not include a participant flow diagram, and did not report the number of participants approached, screened, and deemed eligible and ineligible. Reasons for non-participation were not reported, despite the trial protocol stating that they were collected. It seems unlikely that all eligible participants were enrolled, as there were pharmacies who registered for the trial, completed the training, and commenced patient recruitment, but did not have a patient commence the trial.
- The number enrolled in the Group B evaluation arm of the study (n=940) did not meet the sample size required to be powered to detect the nominated differences in the primary outcomes including the AQoL-4D, the PIH scale, and the BPI-sf (n=1201). There was also higher than expected loss to follow-up (61% compared to the 40% allowed for in the sample size calculation), resulting in a small sample size and low confidence in the

Group B evaluation findings. No statistical adjustments for multiple comparisons appeared to have been made outside of the primary outcomes.

- A large loss to follow-up after baseline (47% overall), well above a generally accepted guideline of 20%[1,2], raises serious concerns about the validity of the study outcomes. Attrition was of particular concern for the favoured Group B intervention. There were 61% of participants lost to follow-up in Group B, compared to 34% of participants in Group A. The ADAR has acknowledged that this may be attributed to volunteer bias, whereby healthier trial participants were followed up (for example, provided responses to the AQoL-4D questionnaire). It is difficult to know the extent of this volunteer bias as analyses exploring differences in the characteristics of patients who discontinued the trial were not presented for Group A vs Group B.
- The ADAR's main clinical analysis compared the average outcomes for two very different populations at baseline (the whole cohort) and follow-up (only those who came back for their final follow-up visit). The analyses for the outcomes did not make any attempt to account for the attrition. This was inconsistent with the statistical plan in the trial Protocol which stated, "If the assumptions of missing at random appear reasonable, multiple imputation of missing data will be attempted". The change in outcome measurements between baseline and follow-up presented in the ADAR is a comparison between a full baseline cohort and a smaller follow-up cohort which may be biased. These comparisons assume that the baseline scores of those lost to follow-up are the same as those followed up and that the change in outcomes for those lost to follow-up will be the same as those followed up.
- Outcomes assessors were not blinded to participants' exposures/interventions.

It was unclear in the ADAR which outcomes were the primary outcomes of the trial. The outcomes presented in Table 6 were identified in the trial protocol's statistical plan as study primary endpoints used to calculate the study sample size. The trial protocol indicated that the analysis for the evaluation trial (comparing Group A and B evaluation sites) would be on an Intention to Treat (ITT) basis. While all participants who received the intervention were included in the analyses, the ADAR did not use any method, such as imputing missing data or using the last observation carried forward, to explore the possible impact of the attrition. It is likely that attrition was not random (due to differences in baseline characteristics). The ADAR reported informal feedback received from pharmacies suggested participants' lack of time and competing priorities were key reasons for non-completion. The most frequently-reported reason for not conducting follow-up services was individuals declining to participate in the trial after the initial consultation, which suggests that withdrawal could have been related to the outcomes of interest such as worsening health or not experiencing a benefit from the intervention.

Additionally, as the CPMC trial did not have a concurrent control group, the attribution of any differences to the intervention alone is uncertain (there may have been temporal changes, other changes in treatment, etc). Examples of previous medication review studies reporting pain-related outcomes are summarised in Table 6 (Ocampo et al. 2015 did not specifically recruit a population with chronic pain). The results do not show much difference between the intervention and control groups. In the randomised controlled trials (RCTs) (Barker et al. 2012, Bruhn et al. 2013, and Neilson et al. 2015), both intervention and control groups experienced the same trend

[1] NIH Quality Assessment Tool for Before-After (Pre-Post) Studies With No Control Group, https://www.nhlbi.nih.gov/health-topics/study-quality-assessment-tools

[2] Schulz KF and Grimes DA. (2002). Sample size slippages in randomised trials: exclusions and the lost and wayward. The Lancet. 359(9308): 781-785. 10.1016/S0140-6736(02)07882-0

in health utilities over time. MSAC previously considered Barker (2012) and Ocampo (2015) in consideration of Sixth Community Pharmacy Agreement (6CPA) Medication Management Review (MMR) Programs.

Table 6 Key features of other evidence for pharmacist interventions for pain

Reference	N	Design/ duration	Intervention/ control	Patient population (Country)	Outcome(s)	Risk of bias
Barker et al. 2012[a]	120	RCT/ 6 months	Pharmacist post-discharge home medicine review/ Standard care	Patients hospitalized for chronic heart failure (USA)	No significant difference in AQoL or the bodily pain dimension of SF-36 between intervention and control groups at baseline, 1 or 6 months. Significant improvement in the physical functioning (p=0.024) and mental health (p=0.018) dimensions at 6 months in the intervention group.	*Low*
Bruhn et al. 2013[b]	193	RCT/ 6 months	Pharmacist review with prescribing/ Pharmacist review/ Treatment as usual	Patients prescribed acute analgesia (UK)	Statistically significant improvement in SF-12 physical component score within the treatment as usual arm, no significant difference within other arms or between arms. Statistically significant deterioration in SF-12 mental component score within the treatment as usual arm, no significant difference within other arms.	*Low*
Neilson et al. 2015[c]	125	RCT/ 6 months	Pharmacist review with prescribing/ Pharmacist review/ Treatment as usual	Patients receiving regular prescribed analgesia (UK)	QALYs in intervention groups relative to the treatment as usual group were largely unchanged after adjusting for baseline characteristics.	*Low*
Ocampo et al. 2015[d]	140	Pre-post/ 18 months	Monthly medication reviews with follow-up in a community pharmacy/ Baseline measurements	Patients attending a community pharmacy (Spain)	Improvement in the bodily pain, physical functioning and mental health dimension of SF-36 (p<0.001)	*Moderate*

Source: Compiled during the evaluation.

[a] Barker A, Barlis P, Berlowitz D, Page K, Jackson B, Lim WK. (2012). Pharmacist directed home medication reviews in patients with chronic heart failure: A randomised clinical trial. International Journal of Cardiology. 159(2): 139-43. doi: 10.1016/j.ijcard.2011.02.034

[b] Bruhn H, Bond CM, Elliott AM, et al. (2013). Pharmacist-led management of chronic pain in primary care: results from a randomised controlled exploratory trial. BMJ open, 3(4), e002361. doi: 10.1136/bmjopen-2012-002361

[c] Neilson AR, Bruhn H, Bond CM, et al. (2015). Pharmacist-led management of chronic pain in primary care: costs and benefits in a pilot randomised controlled trial. BMJ open, 5(4), e006874. doi: 10.1136/bmjopen-2014-006874

[d] Ocampo CC, Garcia-Cardenas V, Martinez-Martinez F, Benrimoj SI, Amariles P, Gastelurrutia MA. (2015). Implementation of medication review with follow-up in a Spanish community pharmacy and its achieved outcomes. International Journal of Clinical Pharmacy. 37(5): 931-10. doi: 10.1007/s11096-015-0145-9.

11. Comparative safety

Safety was not explicitly measured as part of the trial. The ADAR reported that there were no known deaths occurring during the trial period. There were no statistically significant changes in the average number of ED presentations or hospital admissions after the intervention compared to the period before baseline, although these data were based on participant recall, only "pain related" ED presentations and hospital admissions, and there was a large loss to follow up. Also, it is unknown in the absence of the new service how ED presentations and hospital admissions

would have evolved. However, given the training required and that the nature of the intervention is within pharmacists' usual scope of practice, the commentary considered that it is unlikely the intervention would produce significant safety concerns. However, ESC considered that there is a risk of inferior safety when the intervention is applied but the underlying diagnosis and rationale for prescribing is unknown, raising the potential for misdiagnosis or inappropriate treatment.

12. Comparative effectiveness

The clinical results of the CPMC trial are presented in Table 7 and Table 8. The results were divided into primary and secondary outcomes based on the trial protocol.

Table 7 Summary of the change in the primary outcome from initial to follow-up in Groups A and B

	Initial measure			Follow-up measure			Change from initial to follow-up	
	n (% of total)	Mean (SD)	Median	n (% of initial)	Mean (SD)	Median	Mean (95% CI)	P value[a]
AQoL utility score (AQoL-4D questionnaire)[b] *-0.04-1.00 scale, where -0.04 = worst health state and 1.00 = best health state*								
Group A	1,443 (86.98)	0.58 (0.26)	0.61	725 (50.24)	0.63 (0.25)	0.68	**0.05 (0.03, 0.07)**	**0.00**
Group B	562 (59.79)	0.53 (0.28)	0.54	234 (41.64)	0.70 (0.24)	0.75	**0.17 (0.13, 0.21)**	**0.00**
Self-management total score (Partners in Health [PIH] scale)[b] *0-96 scale, higher scores indicate higher self-management capacity*								
Group A	1,452 (87.52)	71.08 (14.35)	72	725 (49.93)	76.69 (13.41)	78	**5.61 (4.36, 6.86)**	**0.00**
Group B	565 (60.11)	72.82 (15.71)	76	239 (42.30)	73.98 (15.00)	76	**1.16 (1.18, 3.51)**	**0.00**
Pain severity (a BPI-sf item included in the mini-ePPOC)[c] *0-10 scale, where 0-4 = mild pain, 5-6 = moderate pain, 7-10 = severe pain (10 represents the worst possible scenario)*								
Group A	4,316 (100.00)	6.09 (2.08)	6	2,853 (66.10)	5.20 (2.24)	5	**-0.89 (-0.99, -0.79)**	**0.00**
Group B	3,923 (100.00)	6.15 (2.20)	6	1,521 (38.77)	4.60 (2.54)	5	**-1.55 (-1.69, -1.41)**	**0.00**
Pain interference (general activities) (a BPI-sf item included in the mini-ePPOC)[c] *Higher scores indicate more interference*								
Group A	4,316 (100.00)	5.72 (2.62)	6	2,853 (66.10)	4.81 (2.58)	5	**-0.91 (-1.03, -0.78)**	**0.00**
Group B	3,923 (100.00)	5.80 (2.73)	6	1,521 (38.77)	4.15 (2.79)	4	**-1.65 (-1.82, -1.49)**	**0.00**
Pain interference (sleep) (a BPI-sf item included in the mini-ePPOC)[c] *Higher scores indicate more interference*								
Group A	4,316 (100.00)	5.27 (3.04)	6	2,853 (66.10)	4.38 (2.86)	5	**-0.88 (-1.03, -0.74)**	**0.00**
Group B	3,923 (100.00)	5.25 (3.15)	5	1,521 (38.77)	3.56 (2.91)	3	**-1.69 (-1.88, -1.51)**	**0.00**

Source: Table 58 of ADAR

Abbreviations: AQOL, The Assessment of quality of life instrument; BPI-sf, Brief Pain Inventory short form; CI, Confidence interval; ePPOC, mini-electronic Persistent Pain Outcomes Collaboration; SD, Standard deviation

Note: Bolded values signify a statistically significant change (p<0.05)

[a] Multilevel mixed-effects linear regression with time as the fixed effect and pharmacy and individual as the random effects

[b] Collected at evaluation sites only

[c] The BPI-sf is a 9-item questionnaire used to evaluate the severity of a participant's pain and the impact of this pain on the participant's daily functioning. The mini-ePPOC includes two of the nine BPI-sf items. Pain interference appears to be one item, with two subcategories included in the mini-ePPOC (general activities and sleep).

Table 8 Summary of the changes in secondary outcomes from initial to follow-up in Groups A and B

	Initial measure			Follow-up measure			Change from initial to follow-up	
	n (% of total)	Mean (SD)	Median	N (% of initial)	Mean (SD)	Median	Mean (95% CI)	P value
Psychological distress (Patient Health Questionnaire-4 [PHQ-4]) *Higher scores indicate more experience of psychological distress*								
Group A	4,316 (100.00)	3.35 (3.38)	2	2,853 (66.10)	2.62 (2.96)	2	**-0.73 (-0.88, -0.58)**	**0.00[a]**
Group B	3,923 (100.00)	3.47 (3.60)	2	1,521 (38.77)	2.33 (3.20)	1	**-1.13 (-1.34, -0.93)**	**0.00[a]**
Pain self-efficacy (Pain self-efficacy 2-item short form [PSEQ-2]) *Higher scores indicate less severe impairment*								
Group A	4,316 (100.00)	7.37 (3.08)	8	2,853 (66.10)	8.14 (2.80)	8	**0.77 (0.63, 0.91)**	**0.00[b]**
Group B	3,923 (100.00)	7.22 (3.31)	7	1,521 (38.77)	8.60 (3.19)	9	**1.38 (1.18, 1.57)**	**0.00[b]**
Average morphine equivalent dose[c]								
Group A	2,161 (50.07)	50.84 (63.90)	30	1,359 (62.89)	49.87 (62.35)	30	-0.97 (-5.26, 3.33)	0.07[a]
Group B	1,809 (46.11)	47.74 (54.30)	30	700 (38.70)	47.82 (54.52)	30	0.08 (-4.67, 4.82)	0.60[a]
Healthy literacy total score[d] *6-60 scale, higher scores indicate better understanding of chronic pain and medications*								
Group A	1,450 (87.40)	39.05 (11.3)	39	725 (50.00)	45.71 (9.52)	46	**6.66 (5.71, 7.63)**	**0.00[a]**
Group B	565 (60.11)	44.11 (12.27)	46	238 (42.12)	44.60 (12.01)	47	0.49 (1.36, 2.34)	0.60[a]
ED presentations								
Group A	4,316 (100.00)	0.16 (0.65)	0	2,853 (66.10)	0.15 (0.62)	0	-0.01 (-0.04, 0.01)	0.67[a]
Group B	3,923 (100.00)	0.16 (0.69)	0	1,521 (38.77)	0.14 (0.65)	0	-0.02 (-0.03, 0.01)	0.40[a]
Hospital admissions								
Group A	4,316 (100.00)	0.10 (0.47)	0	2,853 (66.10)	0.09 (0.48)	0	-0.00 (-0.01, 0.00)	0.26[a]
Group B	3,923 (100.00)	0.10 (0.43)	0	1,521 (38.77)	0.09 (0.46)	0	-0.00 (-0.01, 0.00)	0.50[a]

Source: Table 58 of ADAR

Abbreviations: CI, Confidence interval; ED, Emergency Department; SD, Standard deviation

Note: Bolded values signify a statistically significant change (p<0.05)

[a] Multilevel mixed-effects linear regression with time as the fixed effect and pharmacy and individual as the random effects, adjusted for pain severity and pain interference

[b] Multilevel mixed-effects linear regression with time as the fixed effect and pharmacy and individual as the random effects

[c] It is unclear how many participants used opioid medication; this may or may not represent all of the eligible population for this outcome

[d] Collected at evaluation sites only

The ADAR reported statistically significant improvements in most outcomes in both intervention groups when compared to baseline. Average morphine equivalence dose, health literacy, decreases in ED presentations (Grade 1 and 2) and hospitalisations which would be indicative of a Grade 3 and above adverse events (using Common Terminology Criteria for Adverse Events [CTCAE v5.0]), were not statistically significant.

The use of the word 'improvements' here is slightly misleading as the sample for the baseline and follow-up measurements is different due to loss to follow up. These comparisons assume that the baseline scores of those loss to follow-up are the same as those followed up and that the change in outcomes for those lost to follow-up will be the same as those followed up. It should be noted that Group B was underpowered for AQoL utility score, self-management total

score, average morphine equivalent dose, and health literacy total score partly due to the large loss to follow up. There were no statistical adjustments for multiple comparisons outside of the primary outcomes. Given the large number of comparisons, the likelihood of spurious differences cannot be excluded.

Also, while there are differences in outcomes at baseline and follow-up of those included at each measurement point, the expected changes in outcomes in the comparator (usual care) are not known. Like with other chronic pain studies, regression to the mean is highly likely whereby some recruited individuals improve over time unrelated to the current intervention.[3] Overall, given the large attrition and possible regression to the mean, there is low confidence that these results reflect improvements solely due to the CPMC intervention.

The difference in secondary outcomes between baseline and follow-up were also statistically significant but again they suffer from the same issues as the primary outcomes. Also, these outcomes were not necessarily considered clinically significant. A 1-point decrease in pain interference (measured using the Brief Pain Inventory) is the threshold for minimally important change.[4] Group B met this minimally important change in pain interference, while Group A did not. For both pain severity (measured using the Brief Pain Inventory short form), and the Partners in Health scale (measuring self-management), a 10% change is considered to be of clinical interest[5,6]. In both Groups A and B, pain severity reached this 10% threshold, and self-management did not. The minimal clinically important differences for the other outcomes were not defined.

Randomisation occurred at the pharmacy level, with no matching of pharmacies (for example, on characteristics such as size or socioeconomic status). Despite more pharmacies being randomly allocated to Group B (n=283 vs n=267 in Group A), the overall number of participants recruited in Group B was lower, particularly in the evaluation sites. The lower recruitment may have reflected the higher time commitment required by the additional service and outcomes collected. Reasons for participants declining to participate in the trial were not reported in the ADAR. This information may be useful to assess if there is a difference that suggests patients have a preference for one of the interventions and whether differences in outcomes may at least partly be due to difference in the participants recruited into each group. The difference in attrition suggests some underlying difference between Group A and Group B.

Pharmacies were randomly allocated to a study arm, and then randomly allocated into the 'evaluation' or 'main trial' groups for the 'evaluation trial' sub-study. The ADAR did not state how randomisation occurred. The evaluation trial Group A and Group B appear to have similar gender balance compared to the overall Group A and B, but are more metropolitan and experience more socioeconomic disadvantage. In Group A, 52% of participants were living in areas with decile numbers 1-5, compared with 59% in Group A evaluation. In Group B, 55% of participants were living in areas with decile numbers 1-5, compared with 63% in Group B evaluation. The

[3] Whitney CW, Von Korff M. (1992). Regression to the mean in treated versus untreated chronic pain. Pain. 50(3): 281-285. 10.1016/0304-3959(92)90032-7

[4] Dworkin RH et al. (2008). Interpreting the Clinical Importance of Treatment Outcomes in Chronic Pain Clinical Trials: IMMPACT Recommendations. The Journal of Pain. 9(2): 105-121. 10.1016/j.jpain.2007.09.005

[5] Dworkin RH et al. (2008). Interpreting the Clinical Importance of Treatment Outcomes in Chronic Pain Clinical Trials: IMMPACT Recommendations. The Journal of Pain. 9(2): 105-121. 10.1016/j.jpain.2007.09.005

[6] Battersby M, Harris M, Smith D, Reed R, Woodman R. (2015). A pragmatic randomized controlled trial of the Flinders Program of chronic condition management in community health care services. Patient Education and Counseling. 98(11): 1367-75. 10.1016/j.pec.2015.06.003

commentary considered that it is difficult to understand how the baseline health status compares between the main trial and evaluation trial sub-study.

Clinical claim

The ADAR's clinical claim was that relative to treatment as usual (which it considered to have the same outcomes as the baseline measurements), the interventions had non-inferior safety and superior effectiveness. The ADAR also claimed that the Group B intervention with the additional midpoint consultation (i.e. three consultations) showed greater improvements in most of the participant health outcomes from initial to follow-up compared to Group A (i.e. two consultations).

Based on the evidence presented, it is difficult to have confidence that these claims are well supported. The use of baseline measurements to estimate the likely future outcome for 'treatment as usual' is also likely to be problematic in this setting and does not show how participants' health status would have changed over time, without the CPMC intervention. There was large attrition in the trial and the analysis did not explore the potential bias that this introduces, or present an intention to treat (ITT) analysis imputing missing data. Safety was not measured as part of the trial and with no usual care arm, evaluating the level of adverse events expected in usual care is difficult. Overall, the impact of the service itself compared to usual care is highly uncertain.

The evidence supporting the claim that the Group B intervention was superior is similarly uncertain. Due to low recruitment and high attrition, Group B was not powered to detect differences in quality of life, self-management, pain severity and pain interference. The ADAR did not present the literature review or details of expert advice supporting the inclusion of the extra telephone consultation. The ADAR cited one study (Gammaitoni et al. 2000) on the use of telephone-based prescription and medication counselling services delivered by palliative-care specialists, for treating chronic pain, which found significantly increased patient satisfaction and increased in relief from medication, but no significant change in quality of life. Gammaitoni's intervention was completely via telephone, rather than the mixed delivery of the Group B CPMC intervention, and many of the patient satisfaction benefits may not apply. It is difficult to assess whether Group B's greater difference in mean health outcomes between baseline and follow-up can be attributed to the extra 15-minute telephone consultation.

13. Economic evaluation

The ADAR economic evaluation comprises a cost-utility analysis (CUA) for the primary outcome (QALYs) and a cost effectiveness analysis (CEA) for secondary outcomes (Table 9). The primary outcome analysis is the focus of the commentary and most useful to consider for the funding decision.

The ADAR presented a modelled economic evaluation based on baseline versus follow-up results from the CPMC trial (i.e. pre vs post). Costs and outcomes at baseline were assumed to be Treatment-As-Usual (TAU). Results of the 3-month follow-up were used to determine whether the intervention was effective in providing benefits to trial participants.

Table 9 Summary of the economic evaluation

Component	Description
Perspective	Healthcare system
Population	Adults with chronic pain (>=3 months), taking medication for their pain, experiencing self-management or dependency issues, and living at home in a community setting
Comparator	Treatment-As-Usual (TAU), baseline measurements
Type(s) of analysis	Cost utility analysis and cost effectiveness analysis
Outcomes	**Primary outcome:** Cost per QALY **Secondary Outcomes:** Cost per unit reduction in pain interference measured using the BPI as part of the mini-ePPOC Cost per unit reduction in pain severity measured using the BPI as part of the mini-ePPOC Cost per unit reduction in pain self-efficacy measured using the PSEQ-2 as part of the mini-ePPOC Cost per unit increase in self-management measured using the PIH Cost per unit reduction in morphine equivalent units Cost per PBS script reduction Cost per MBS service reduction
Time horizon	Six months
Computational method	Trial based. A quasi-experiment of pre vs post intervention
Generation of the base case	Trial based
Discount rate	Not applicable as the model duration is less than one year
Software	Microsoft Excel 2016

Source: Table 85 of ADAR
Abbreviations: BPI: Brief pain inventory; MBS, Medicare Benefits Schedule; mini-ePPOC, The miniature electronic persistent pain outcomes collaboration questionnaire; QALY, Quality adjusted life years; PBS, Pharmaceutical Benefits Scheme; PIH, The Partners in Health Scale; PSEQ-2, Pain self-efficacy questionnaire; TAU, treatment as usual

The inputs to the economic evaluation are the difference in costs and outcomes for each group compared to treatment as usual. Usage pre-baseline was assumed to be TAU, while usage in the three months after was expected to have changed solely due to the pharmacist-led intervention (Table 10).

There is a high degree of uncertainty around both of these assumptions. For example, there was low confidence in the estimated clinical benefits in the economic model due to the study design (lack of usual care group) and attrition reasons outlined in the assessment of clinical evidence.

There is also a large degree of uncertainty around the costs and outcomes due to the following reasons:

- Quality of life was measured using AQoL-4D, and only included as an outcome in the evaluation groups. The economic evaluation has generalised the results of the evaluation groups to the entire cohort. Both Group A evaluation and Group B evaluation appear to have similar gender balance compared to the overall Group A and B, but are more likely to live in a metropolitan location and experience more socioeconomic disadvantage.
- Consistent with other outcomes, there was large attrition in follow-up for quality of life (50% in Group A and 58% in Group B). The participants who returned the AQoL-4D questionnaire had different characteristics to the participants who provided the baseline AQoL-4D. For example, participants who provided responses were generally older than

the baseline participants (72.7% vs 44.6% for Group A and 65.8% vs 40.18% for Group B were aged 65 years or older).

- The utility gain (quality of life) appears to be calculated using the change in mean score from baseline to follow-up, without any adjustment for the time spent in different health states or accounting for the large loss in follow up. In the quality adjusted life year (QALY) calculation, the ADAR implicitly assumes that the utility change from baseline to 3-month follow-up would last from day 1 post baseline for a whole year (even past their six-month time horizon).

- The cost of the interventions assumes that all individuals attend all follow-up visits. This overestimates the cost per patient recruited but it also needs to be balanced with whether those who do not complete follow-up would actually receive the same benefits as those followed up. Based on the trial results this is highly unlikely.

- The hospitalisation and ED presentation costs were inflated from 2017-18 from the Independent Hospital Pricing Authority. The derived cost per acute hospitalisation was $4,864.14. This was an underestimate; in the most recent update from the Independent Hospital Pricing Authority, for 2019-20, the average cost per acute hospitalisation was $5,335. The derived cost per ED presentation, $732, was also a slight underestimate, compared to the 2019-20 average cost of $775.

- The population providing the PBS costs data is small and not well characterised. In Group A, there was PBS utilisation data for 12% (n=497/4316) of participants at baseline and 6% (n=171/2853) of participants who completed follow up. In Group B, it was 7% (n=275/3923) of participants at baseline and 6% (n=90/1521) of participants who completed follow up. It is unclear which medication classes are included and excluded. There were several inconsistencies in the data presented. It is unclear why an 'average cost per script at baseline' was used to adjust the PBS usage post the CPMC intervention when the real data were available, and no other costs or outcomes were similarly adjusted.

- The MBS usage data had similar limitations to the PBS usage data: some inconsistencies in the reporting, large attrition, and small sample sizes that were not well characterised. In Group A, there was MBS utilisation data for 12% of participants at baseline and 5% of participants who completed follow up. In Group B, it was 12% of participants at baseline and 10% of participants who completed follow up. The MBS costs were used without any adjustment. The process of extracting these data from Services Australia was unclear; the attrition seen here may be due to low consent rates from participants.

- The change in hospitalisation and ED usage had similar limitations and was also based on self-reported data from participants. Participants were asked how many times in the last three months they visited an ED because of their pain and/or been admitted to hospital because of their pain. This method has several limitations. The reliability of these outcomes is decreased, as participants may forget, or misremember episodes. Participants may also have different understandings of what 'because of their pain' means within the context of the trial.

- The estimated cost savings are derived by comparing the mean value of the complete baseline cohort with the mean value of an incomplete follow-up cohort. The ADAR did not report full characteristics for participants who completed and were lost to follow-up in Group A and B, but the difference in the raw PBS usage pre- and post-intervention suggests that the characteristics of those who completed follow-up and those lost to follow-up were not balanced.

- While the MBS usage should have included any referrals generated within 6 months as a result of the intervention, referrals to allied health services made by the pharmacists as a result of the CPMC were not subsidised by Medicare. Patients who wanted to access subsidised allied health services needed to be referred first to a general practitioner. Any additional flow-on costs here are not estimated.

Table 10 Cost of the intervention produced in the economic evaluation presented in the ADAR.

	Group A			Group B		
Costs per person	**Pre-baseline* ($)**	**Post CPMC ($)**	***Cost differences (CPMC – pre baseline)***	**Pre-baseline [a] ($)**	**Post CPMC ($)**	***Cost differences (CPMC – pre baseline)***
Intervention costs						
Pharmacy intervention	NA	131.22	*131.22*	NA	164.03	*164.03*
Estimated future cost implications						
PBS costs	310.94	250.91[b]	*-60.03*	216.92	145.94[b]	*-70.98*
MBS costs	590.07	449.01	*-141.06*	560.16	311.07	*-249.09*
Hospitalisation costs	498.13[c]	438.16[c]	*-59.97*	494.85[c]	457.31[c]	*-37.54*
ED presentation costs	114.43[c]	109.15[c]	*-5.28*	114.34[c]	101.65[c]	*-12.69*
Total	$1,513.57	$1,378.46	*-135.11*	$1,386.27	$1,180.00	*-206.27*

Source: Tables 70, 71, 72, 73, 89, 90, 91, 92 of the ADAR.
Italics indicates results generated during the evaluation.
Abbreviations: CPMC: Chronic Pain MedsCheck; ED: Emergency Department; MBS, Medicare Benefits Schedule; NA, not applicable; PBS, Pharmaceutical Benefits Scheme
Note: The significance of the cost differences were not reported in the ADAR, and in some cases how the cost implications were calculated made estimating the uncertainty difficult.
[a] *Used to proxy for potential TAU costs*
[b] *Adjusted cost based on average script price at baseline; The script price in PBS data is the price for the quantity dispensed.*
[c] *3 months of data*

The results of the economic evaluation are presented in tables below. The commentary has included a revised stepped economic analysis for Group A in Table 11 and Group B in Table 12 which addresses some of the key issues identified.

- Step 1 is the base case economic evaluation presented in the ADAR.
- Step 2 revises the cost of the intervention, and assumes there is no change in PBS and MBS usage, hospitalisations or emergency department presentations, due to the large uncertainty in the impact of the intervention on these outcomes. The intervention fee has been included as the only cost of the intervention with usual care having no incremental cost (given the large uncertainty in the cost implications of PBS and MBS usage, hospitalisations and emergency department presentations, no cost differences have been assumed).
- Step 3 revises the QALYs to include time spent in the health state, and assumes all participants achieved the improved AQoL-4D score immediately following the intervention and spend three months at the improved health state. This also assumes that those lost to follow-up would have received this same benefit which is highly uncertain.
- Step 4 applies the study attrition rates (34% in Group A and 61% in Group B) to the cost of the intervention and the QALYs, and assumes that participants lost to follow-up did not experience any change in AQoL-4D score while participants who completed follow-up

experienced the full improvement in AQoL-4D score immediately following the intervention. Regression to the mean is still not considered.

The revised base case results (Step 4) indicated Incremental Cost-Effectiveness Ratios (ICERs) of $14,552 and $7,897 per QALY gained for Group A and B, respectively, However, these are still highly uncertain given the uncertain clinical benefit compared to usual care. The likelihood that both Group A and Group B are less cost effective than usual care cannot be excluded.

Table 11 Results of the economic evaluation and stepped economic analysis for Group A

Step	CMPC Intervention	Baseline	Increment	ICER
Step 1 – Base case presented in Table 103 of ADAR				
Costs	$1,378.46	$1,513.57	-$135.11	
QALYs	0.63	0.58	0.05	DOMINANT
Step 2 – Revised cost of the intervention due to the large uncertainty in the cost implications				
Costs	*$1,644.54*	*$1,513.57*	*$131.22*	
QALYs	*0.63*	*0.58*	*0.05*	*$2,624.40*
Step 3 – Revised cost of the intervention due to the large uncertainty in the cost implications and study QALYs transformed to the appropriate time horizon				
Costs	*$1,644.54*	*$1,513.57*	*$131.22*	
QALYs	*0.1575*	*0.145*	*0.0125*	*$10,497.60*
Step 4 – Revised cost of the intervention due to the large uncertainty in the cost implications, study QALYs transformed to the appropriate time horizon, and the study attrition rate of 34% in Group A				
Costs	*$1,633.63*	*$1,513.57*	*$120.06*	
QALYs	*0.15325*	*0.145*	*0.00825*	*$14,552.73*

Source: Tables 94, 103, 104 of ADAR.
Italics indicates results generated during the evaluation.
Abbreviations: CMPC: Chronic Pain MedsCheck; QALY: quality-adjusted life year.

Table 12 Results of the economic evaluation and stepped economic analysis for Group B

Step – Group B	CMPC Intervention	Baseline	Increment	ICER
Step 1 – Base case presented in Table 104 of ADAR				
Costs	$1,180.00	$1,386.27	-$206.27	
QALYs	0.70	0.53	0.17	DOMINANT
Step 2 – Revised cost of the intervention due to the large uncertainty in the cost implications				
Costs	*$1,550.30*	*$1,386.27*	*$164.03*	
QALYs	*0.70*	*0.53*	*0.17*	*$964.88*
Step 3 - Revised cost of the intervention due to the large uncertainty in the cost implications and study QALYs transformed to the appropriate time horizon				
Costs	*$1,550.30*	*$1,386.27*	*$164.03*	
QALYs	*0.175*	*0.1325*	*0.0425*	*$3,859.53*
Step 4 –Revised cost of the intervention due to the large uncertainty in the cost implications, study QALYs transformed to the appropriate time horizon, and the study attrition rate of 61% in Group B				
Costs	*$1,517.17*	*$1,386.27*	*$130.90*	
QALYs	*0.149075*	*0.1325*	*0.016575*	*$7,897.44*

Source: Tables 94, 103, 104 of ADAR.
Italics indicates results generated during the evaluation.
Abbreviations: CMPC: Chronic Pain MedsCheck; QALY: quality-adjusted life year.

The ADAR presents sensitivity analyses for primary and secondary outcomes, using 95% upper and lower bound confidence intervals (CIs). When unavailable, an arbitrary 20% was used for upper and lower bounds. This was applied to costs and QALYs.

Hospitalisation costs and MBS service usage were the main drivers in the Group A and B analyses. For Group B vs A, the same variables in addition to QALYs were key drivers. Since the sensitivity analyses just presents the case for percentage higher or lower costs in each of the inputs (hospitalisations, ED presentations, trial costs, PBS/MBS costs, QALYs), this simply shows which inputs made up a higher proportion of total cost implications.

The sensitivity analyses did not explore the uncertainty introduced by the high attrition, for example by modelling potential scenarios such as if participants lost to follow-up received no health gain, or the usual care arm had some level of regression to the mean seen in previous chronic pain trials. It would also have been useful to present sensitivity analyses exploring some of the assumptions made in the economic model, including the arbitrary choice of using 6 months' PBS and MBS data and the method used to adjust the post-intervention PBS costs.

14. Financial/budgetary impacts

The ADAR uses an epidemiological approach to estimating financial impact using the proportion of the population who would be eligible for a CPMC service. The ADAR presents a financial impact analysis for both Group A and Group B.

Table 13 presents the population parameters used in the financial impact analysis. The ADAR has applied the estimated prevalence of chronic pain and chronic cancer pain to a population aged 18 years and older. There are a number of assumptions:

- The chronic pain prevalence rate of 15.4% obtained from Miller (2017) was for people aged 15 or older, while the ADAR is applying the prevalence rate to a population aged 18

or older. However, the prevalence rate in people aged 16-19 was less than 10%; it is unlikely to have a large impact on the estimates.

- The chronic cancer pain prevalence rate of 7.1% obtained from the AIHW uses results from the Survey of Health Care 2016. The Survey of Health Care participants were aged 45 and over. Applying this rate to a population aged 18 years and over likely overestimates the prevalence.

Table 13 Population data sources applied in financial estimates

Data	Source and value	Justification
Population of Australia	ABS	-
Population of Australia aged under 16	ABS – 18.7%	Average of proportions projected over 5 years
Population of Australia aged 15 -17	ABS – 3.6%	-
Prevalence of chronic pain, aged 15 and over	Miller et al (2017) – 15.4%	-
Prevalence of chronic cancer pain, aged 45 and over	AIHW – 7.1%	-

Source: Section E1 of ADAR
Abbreviations: ABS, Australian Bureau of Statistics; AIHW, Australian Institute of Health and Welfare

The uptake of the eligible population is the key parameter that influences the overall financial impact.

The ADAR assumes all adults with chronic non-cancer pain would be eligible for a CPMC service, but uptake is limited by estimating that only 34% of pharmacies in Australia (n=1,920) will administer the CPMC program, based on uptake of the trial. If rolled out in practice and longer-term income was possible, more pharmacies may be willing to administer the program. Also based on trial recruitment, the ADAR assumes that pharmacies will deliver an average of 15 CPMC services per year. Recent MedsCheck and Diabetes MedsCheck claims data suggest this is an underestimate. For example, there were 142,418 Diabetes MedsCheck services paid in 2021. The estimated prevalence of adults with diabetes in Australia is 5.4%, much lower than the chronic pain estimate of 15.4%. It should be noted that the uptake of Diabetes MedsCheck services in 2021 may have been restricted by a claiming limit of 20 MedsChecks and/or Diabetes MedsChecks per pharmacy per month. The ADAR did not mention any claiming limit in the proposal for public funding, or considered a claiming limit in the financial implications. The uptake of a funded program is likely to differ from participation in a research trial due to patient expectations and different financial incentives.

The financial implications over 5 years presented in Table 14 for Group A and Table 15 for Group B are based on:

- For Group A, an average cost of the CMPC program per patient per year of $131.11 based on an average frequency of use of the CPMC of two services (an initial and a follow-up consultations) per year. For Group B, an average cost of the CMPC program per patient per year of $164.03 based on an average frequency of use of the CPMC of three services (an initial and two follow-up consultations) per year. This is likely an over estimate as it is likely that many who attend their first visit will not attend their mid-point visit or follow-up visit. The large attrition in the trial is likely to translate into real-world practice.
- There are no out-of-pocket costs to the patient for the CPMC service in the trial and it is assumed this would also be the case if funded in practice. The ADAR reported 54% of trial

participants were referred to another medical or health service as a result of the initial consultation (although it was also noted that a quirk in some trial software may have resulted in some unnecessary referrals). As referrals from a pharmacist to allied health services are not subsidised by Medicare, participants may have borne these costs out-of-pocket. The impact of these referrals on patient costs were not recorded in the trial.

- The trial outcomes were reported at 3 months for hospitalisation and ED presentations as these were applied in the financial estimates without adjustment. The application implicitly assumes that there will be no further changes in hospitalisations or ED presentations from 3 months to 12 months.
- A sustained reduction in outcomes, such as scripts and MBS services over five years, which is unlikely given the episodic nature of chronic pain. The reduction in outcomes was calculated using un-matched cohorts, so it is unclear whether the reductions represent a real decrease or reflected a different follow-up population.
- A stable cost for total provider benefits paid and total out of pocket cost (for Group A this was $60.03 and $49.05, respectively; for Group B this was $70.98 and $46.14, respectively) over five years to estimate savings to the PBS. These costs were derived by subtracting the adjusted PBS price at follow-up from the baseline PBS price. There is large uncertainty over the calculation of the adjusted price at follow-up and therefore how representative the savings to the PBS are of the true impact of the intervention on PBS usage. Functionally, this results in a total cost to the PBS of $10.98 per script in Group A and $24.84 per script in Group B.

The calculation of the total costs to the MBS and PBS seems to have accounted for a decrease in services twice, by using a per person cost decrease and then multiplying that by decrease in number of MBS and PBS services. A revised financial impact has been presented correcting this, but still maintaining the PBS price for total provider benefits paid and total out of pocket cost calculated in the ADAR (for Group A this was $60.03 and $49.05, respectively; for Group B this was $70.98 and $46.14, respectively) due to the uncertainty in the outcome presented.

Table 14 Net financial implications of Chronic Pain MedsCheck (Group A intervention) to government

Parameter	2021	2022	2023	2024	2025
Estimated use and cost of the proposed health technology					
Number of people eligible for a CPMC	2,901,074	2,949,041	2,996,778	3,043,891	3,090,422
Number of people who receive a CPMC	28,814	29,290	29,765	30,232	30,695
Number of services of CPMC (two services per person, as in Group A)	*57,628*	*58,580*	*59,530*	*60,464*	*61,390*
Cost to the [Community Pharmacy Agreement*] (with appropriate copayments excluded)	$3,780,972	$3,843,487	$3,905,703	$3,967,104	$4,027,749
Financial impact					
Change in use of hospital inpatient services costs	-$1,681,864	-$1,709,672	-$1,764,660	-$1,764,660	-$1,791,636
Change in use and costs of ED visits	-$190,018	-$193,160	-$196,287	-$199,373	-$202,420
Net financial impact to state and territory government budgets	**-$1,871,883**	**-$1,902,832**	**-$1,933,634**	**-$1,964,033**	**-$1,994,057**
Change in use and costs of PBS medications	-$4,428,089	-$4,501,304	-$4,574,169	-$4,646,079	-$4,717,103
Change in use and costs of MBS services	-$10,730,475	-$10,907,894	-$11,084,465	-$11,258,723	-$11,430,834
Net financial impact to government budgets	**-$7,759,530**	**-$7,887,827**	**-$8,015,511**	**-$8,141,522**	**-$8,265,981**
Revised financial impact					
Revised change in use and costs of PBS medications	*-$316,417*	*-$321,648*	*-$326,855*	*-$331,994*	*-$337,069*
Revised change in use and costs of MBS services	*-$4,064,449*	*-$4,131,651*	*-$4,198,532*	*-$4,264,536*	*-$4,329,728*
Revised net financial impact to government budgets	***-$599,894***	***-$609,813***	***-$619,684***	***-$629,426***	***-$639,048***

Source: Tables 67-69, 129-130 of ADAR.
Italics indicates results generated during the evaluation.
Abbreviations: CPMC, Chronic Pain MedsCheck; ED, Emergency Department; MBS, Medicare Benefits Schedule; PBS, Pharmaceutical Benefits Scheme.

Table 15 Net financial implications of Chronic Pain MedsCheck (Group B intervention) to government

Parameter	2021	2022	2023	2024	2025
Estimated use and cost of the proposed health technology					
Number of people eligible for a CPMC	2,901,074	2,949,041	2,996,778	3,043,891	3,090,422
Number of people who receive a CPMC	28,814	29,290	29,765	30,232	30,695
Number of services of CPMC (three services per person, as in Group B)	*86,442*	*87,870*	*89,295*	*90,696*	*92,085*
Cost to the [Community Pharmacy Agreement*] (with appropriate copayments excluded)	$4,726,359	$4,804,505	$4,882,277	$4,959,031	$5,034,839
Financial impact					
Change in use of hospital inpatient services costs	-$1,121,243	-$1,139,782	-$1,158,232	-$1,176,440	-$1,194,424
Change in use and costs of ED visits	-$358,923	-$364,858	-$370,764	-$376,593	-$382,350
Net financial impact to state and territory government budgets	**-$1,480,166**	**-$1,504,639**	**-$1,528,996**	**-$1,553,033**	**-$1,576,774**
Change in use and costs of PBS medications	-$2,433,895	-$2,474,137	-$2,514,187	-$2,553,713	-$2,592,751
Change in use and costs of MBS services	-$31,894,760	-$32,422,110	-$32,946,942	-$33,464,899	-$33,976,473
Net financial impact to government budgets	**-$29,602,296**	**-$30,091,743**	**-$30,578,852**	**-$31,059,580**	**-$31,534,384**
Revised financial impact					
Revised change in use and costs of PBS medications	*-$715,852*	*-$727,687*	*-$739,467*	*-$751,092*	*-$762,574*
Revised change in use and costs of MBS services	*-$7,177,418*	*-$7,296,090*	*-$7,414,196*	*-$7,530,754*	*-$7,645,876*
Revised net financial impact to government budgets	***-$3,166,911***	***-$3,219,273***	***-$3,271,385***	***-$3,322,814***	***-$3,373,610***

Source: Tables 67-69, 129-130 of ADAR.
Italics indicates results generated during the evaluation.
Abbreviations: CPMC, Chronic Pain MedsCheck; ED, Emergency Department; MBS, Medicare Benefits Schedule; PBS, Pharmaceutical Benefits Scheme.

15. Other relevant information

The ADAR also presented a large number for qualitative results exploring pharmacists' experience of providing the CPMC, and the potential changes in a pharmacist's role as a result of providing the CPMC. These discussions are general in nature and do not allow better quantification of costs and benefits of the program but may offer some relevant points to assist roll out should MSAC decide to recommend the program for funding. These include:

- Increasing accessibility for culturally and linguistically diverse populations by providing education resources in more languages.
- Increasing accessibility for rural and regional populations.
- Reviewing the consultation schedule. Qualitative feedback suggested the consultations were time consuming and the number of follow-up services were insufficient. Some

pharmacists and patients may prefer a larger number of shorter consultations to fit into workflow and/or lifestyle.

- Mechanisms for quality assurance. Approximately one third of respondents to the pharmacist survey rated 'developing an action plan' at least somewhat difficult to perform, and there were various suggestions to improve the trial software. The proposal is not clear on whether the aspects of the trial that help to standardise service delivery, such as mandatory referral algorithms, would be included if funded.

16. Key issues from ESC to MSAC

Main issues for MSAC consideration

Clinical issues:

- The eligibility criteria for the key trial were not well defined nor indicative of the participant experiencing poorly managed chronic pain – a diagnosis that should be made by a medical practitioner.
- The intervention provided by the pharmacists was not well described.
- Very low confidence in the estimate of effect – multiple biases in study design, results and statistical analysis mean the reported data are unlikely to provide a reliable estimate of the effect of the intervention.
- The lack of a concurrent comparator arm meant regression to the mean cannot be excluded as an explanation for the results.
- Lack of care coordination – the Chronic Pain MedsCheck study design and proposed implementation do not include liaison with the patient's GP which is integral for ensuring coordinated multidisciplinary care for the management of chronic pain. It would be more appropriate for GPs to refer patients to ensure the service is targeted to those who need it.
- Safety concerns – there is a risk of inferior safety when the intervention is applied but the underlying diagnosis and rationale for prescribing is unknown.

Economic issues:

- Miscalculation of QALYs – the revised QALYs in the commentary are more appropriate. The clinical inputs and estimated QALYs remain susceptible to bias (and are likely unreliable) due to problems in the trial which favour the intervention.
- Costs and adjustments – costs are affected by attrition rates. The cost of the intervention may be overestimated because it does not account for attrition.

Financial issues:

- Varying time periods for costs – extrapolation of 3-month follow-up data and 6-month linked data to 12-month financial estimates is not likely to be realistic of resource use for a chronic condition after a short-term intervention.
- Uptake may be underestimated – the proposed number of Chronic Pain MedsChecks performed per year is low compared with other MedsChecks. If uptake is higher, this will increase costs.

Other relevant information:

- There may be potential duplication of services with existing pharmacy programs and MBS items.

- ESC considered that the points raised regarding the limitations in the trial design and methodology could be useful to inform future trials and evaluations of chronic pain interventions.

ESC discussion

ESC noted that this application requested funding for Chronic Pain MedsChecks under a future Community Pharmacy Agreement. The Pharmacy Guild of Australia entered into a grant agreement with the Department of Health and Aged Care to undertake the Chronic Pain MedsCheck trial as part of the Sixth Community Pharmacy Agreement. The trial used a pharmacist-based intervention with aims of improving health literacy regarding patients' pain medications, preventing incorrect use and overuse of pain medications, and improving overall quality of life.

ESC noted that, in 2017, MSAC had assessed the cost-effectiveness of the MedsCheck and Diabetes MedsCheck programs and found no clear evidence that these interventions reduce hospitalisations or mortality or improve quality of life. In general, studies examining the impact of pharmacy-based medication review services did not find clear evidence to indicate that these interventions have any impact on reducing mortality or on improving appropriateness of medication prescribing.

ESC noted the consultation feedback. Several submissions noted the need for a coordinated multidisciplinary approach to chronic pain care, which is not reflected in the Chronic Pain MedsCheck design. The lack of detail about the required training for Chronic Pain MedsCheck delivery was also noted, including how the training was designed or evaluated and its content, including sensitivities for patients taking opioid medications. ESC noted the Faculty of Pain Medicine of the Australian and New Zealand College of Anaesthetists were not supportive of the trial nor the intervention.

ESC noted the population in the trial included adults who had chronic pain (as determined by the pharmacist) and were experiencing issues with self-management or pain medication dependency. Trial participants had not had a Home Medicines Review, MedsCheck, Diabetes MedsCheck or Chronic Pain MedsCheck within the previous 12 months; and were not a current client of a recognised pain management service. ESC considered that the reasons for referring patients into the trial were not well defined nor representative of an individual experiencing poorly managed chronic pain.

ESC noted the intervention and design of the trial. Group A had two face-to-face consultations with pharmacists 3 months apart. Group B had the same two face-to-face consultations, plus an additional telephone consultation at 6 weeks. Pharmacists undertook online continuing professional development (CPD) training before taking part in the trial. ESC considered that only pharmacists with the appropriate training should provide the service. The initial consultation comprised a review and assessment of the participant's chronic pain experience and medication use; provision of education and/or referrals; development of an action plan; and self-management strategies. ESC noted that no details were provided of what the medicines check, or action plan involved.

ESC noted the trial and proposed implementation did not involve collaboration with general practitioners (GPs). ESC considered that this proposed model of care may introduce safety concerns as the pharmacist has no clinical records to confirm the diagnosis or prescribing intent, and may not be able to assess whether worsening pain is due to worsening of an underlying disease process or poor medication adherence. ESC considered patients may be recommended over-the-counter medications by the pharmacist that are inappropriate for their clinical situation

due to the lack of coordinated care. ESC considered that it would be more appropriate for GPs to refer patients to ensure the service is better targeted. ESC also noted existing MBS items that allow GPs to treat acute and chronic pain, as well as existing MedsCheck and Home Medicines Review programs (which have a limit on services). ESC considered that other programs such as MedsCheck and Home Medicines Reviews already exist, so the clinical need for a Chronic Pain MedsCheck was unclear. ESC considered that it was unclear how the intervention would manage patients on higher doses of opioids (≥ 60 mg/day Oral Morphine Equivalent [OME]) where the underlying risk of harm to patients is greater.

ESC noted several sources of bias in the trial design, which were all judged to be at a high level. Outcomes were not reported consistently with standards outlined in the STROBE and CONSORT statements, as stated in the Trial Protocol. There were no data on the number of patients who were approached but not enrolled, who were randomised but dropped out, or who were excluded. No treatment-as-usual group was included as a comparison, and the randomisation of patients into groups was not described. Participants were not matched for socioeconomic status.

ESC noted the substantial dropout rates in the trial. A total of 1630 pharmacies registered for training, but only 550 pharmacies enrolled patients (267 pharmacies in Group A and 283 in Group B): in other words, 66% of enrolled pharmacies did not continue or did not enrol patients. Patient dropout rate and loss to follow-up were also high. A total of 8239 patients were enrolled, but a considerable proportion of patients dropped out or were lost to follow-up, and these rates differed by trial arm: 34% in Group A; 61% in Group B. ESC considered that this high and inconsistent attrition of patients introduced a serious risk of bias.

ESC raised concerns with the statistical analysis of the trial results. There was no adjustment for multiple comparisons, and no imputation or other methods to adjust for the large loss to follow-up. The statistical analysis compared baseline scores for the entire cohort with 3-month scores for the participants who were not lost to follow-up. Outcomes such as quality of life, which were only measured in a subgroup of participants, were combined for both groups then applied to the entire cohort. ESC considered that this would likely overestimate the benefit and bias in favour of the intervention as it was unlikely that participant data were missing at random and participants who did not benefit from the intervention would be less likely to continue. Overall, ESC considered that the although the study was presented as a randomised trial by the applicant, the study is more appropriately described as a before-and-after study as the primary outcome was not a comparison between randomised groups.

ESC noted the primary outcomes measured in the trial. ESC noted that no minimum clinically important difference (MCID) was defined for the utility score using the AQoL-4D (Assessment of Quality of Life) questionnaire. ESC noted that for the self-management total score using the Partners in Health scale and the pain severity score using a Brief Pain Inventory (short form [BPI-sf]) item included in the mini-ePPOC[7], the MCID was defined as a 10% difference in the score. For the pain interference in general activities or sleep, ESC noted that the MCID was defined as a 1-point difference.

ESC noted the secondary outcomes were health literacy total score, average morphine equivalent dose, emergency department admissions and hospital admissions. A patient satisfaction survey was also administered at the end of the 3-month visit. ESC noted the lack of blinding in measurement of subjective outcomes, including the patient satisfaction survey (which may have been administered by the pharmacist). ESC considered this introduced a further high risk of bias. In addition, quality-of-life outcomes were only measured in a subset of patients and extrapolated

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to all patients, including those lost to follow up. ESC considered that this method was inappropriate.

ESC noted that the results for some outcomes were statistically significantly different; however, it was not clear whether these differences were clinically meaningful. It was also unclear whether the results reflected the natural history of chronic pain, where patients seek further treatment during a period of worsening pain, as there was no usual care group in the trial for comparison. ESC considered that it was not possible to exclude regression to the mean as a contributor to results of the before-and-after analysis. ESC noted there was no change in secondary outcomes of morphine equivalence dose, hospital admissions or emergency department presentations, although some of these were based on patient recall and hence may be subject to further bias.

ESC noted the advice from the MSAC Executive that analysis exploring patients who discontinued the trial and the potential impact of attrition bias would be informative. The applicant provided a comparison of age, sex and postcode between participants, which did not show large differences. ESC considered that the applicant's additional information did not resolve the issues regarding loss to follow-up and that this remained a substantial source of bias. ESC considered that an analysis appropriately accounting for attrition would not provide a more reliable or informative estimate of effect due to the other limitations in the trial. ESC also noted that the MSAC Executive had queried the plausibility that the additional telephone consultation provided to patients in Group B contributed to better outcomes. This was not addressed in the application.

ESC noted that the clinical issues from the trial (particularly the high attrition rate and missing data) flowed through to the economic evaluation. The economic evaluation assumed that the baseline measurements were equivalent to treatment-as-usual; however ESC noted that flare-ups of chronic pain can often lead patients to seeking treatment. Consequently, baseline data should not be considered reflective of a steady state. This could also lead to reduced costs for services and medication as patients improve over time, which was not accounted for in the economic evaluation. The economic evaluation also assumed there would be no improvement from baseline without the service. Again, this may not be valid assumption as demonstrated in other trials in chronic pain that include a treatment-as-usual group. ESC noted that the cost per prescription was adjusted as the cost per prescription decreased over time. ESC considered that the approach was conservative but assumed the reduction in cost was due to the PBS safety net rather than other causes. ESC considered the true difference between groups in the trial for both costs and outcomes could also be narrower, given the high loss to follow-up and the likelihood that those lost to follow-up were not benefiting from the intervention. The applicant did not adequately address these issues in their pre-ESC response.

ESC accepted the adjustment of quality-adjusted life years (QALYs) in the commentary to account for only 3 months of data rather than 12 months. This reduced the QALY gain from 0.05 for Group A (as presented in the ADAR) to 0.0125. The economic evaluation by the applicant assumed an immediate impact on QALYs; however, if a more reasonable assumption of a linear onset of response over time is applied, the QALY gain reduces to 0.00625.

ESC considered the costs in the economic evaluation, noting that the Pharmaceutical Benefits Scheme (PBS) costs were substantially different between groups at baseline, and the intervention costs did not account for attrition. ESC noted the missing data on Medicare Benefits Schedule (MBS) and PBS costs and queried whether this could also be due to patients refusing consent for data linkage.

ESC noted the revised incremental cost-effectiveness ratios (ICERs) in the commentary, which changed the outcome from being dominant to an ICER of $14,552.73 for Group A and $7,897.44 for Group B. ESC noted that the secondary outcomes were subject to the same

issues as the primary outcomes, and it was uncertain at what level these secondary outcomes would be considered cost-effective. ESC also noted that patients who are referred by a pharmacist to allied health services may experience out-of-pocket costs that were not accounted for in the economic evaluation.

ESC noted a number of issues with the financial impact analysis, including double counting in the reduction of MBS and PBS costs, and that the financial analysis was subject to the same sources of bias as the ICER. Revised estimates that removed double counting were still cost saving, but substantially less so than the ADAR. ESC considered that the extrapolation of 3-month follow-up data and 6-month linked data to 12-month financial estimates was not likely to be realistic. ESC also noted that the number of Chronic Pain MedsChecks per year proposed in the ADAR (around 28,000–30,000) was substantially lower than the number of Diabetes MedsChecks performed per year (142,418), although the prevalence of diabetes is 5.4% compared with 15.4% for chronic pain. If uptake of Chronic Pain MedsChecks is higher than in the ADAR, this will also affect the financial estimates.

ESC considered that the points raised regarding trial design and methodology could be useful to inform future trials and evaluations of medication management review interventions/programs and chronic pain interventions.

17. Applicant comments on MSAC's Public Summary Document

The Pharmacy Guild of Australia (the Guild) is disappointed with MSAC's appraisal of the CPMC trial. The Guild considers that the CPMC intervention was shown to be effective in improving a number of participant health outcomes, including pain severity, pain interference and overall level of psychological distress. Community pharmacists provide a range of services, many without the barrier of an appointment, which extend well beyond the provision of prescription medicines and, as such, pharmacies are often the first contact point of the primary health care system for many people. These services include and are not limited to referral to and collaboration with a General Practitioner or Hospital Emergency Services; and other appropriate health professionals where required. The PSD notes concerns of the lack of collaboration with GPs as part of the CPMC intervention, however with just over half of the trial participants (53.9%) being referred to another medical or health service as a result of their initial consultation, pharmacists did most commonly refer participants to GPs, making up 75% of referral across all CPMC trial sites.

The Guild does not agree with MSAC's view that the CPMC trial provided low quality evidence with a high risk of bias due to a number of issues with the trial design. The trial Protocol allowed for *a "40% lost-to-follow up/dropout rate"* and acknowledged that "*it is likely that a reasonably high proportion of patients will drop out of the trial and not attend for their subsequent visits".* This is typical for a trial of a community-based intervention such as this one. The CPMC trial used the Intention-to-treat (ITT) principle in analysing the data, as specified in the Protocol, to minimise the risk of any bias that may have resulted from participants dropping out of the trial.

The Guild also does not agree with MSAC's concerns regarding the validity of the study outcomes. The trial design, consistent with the Protocol, was a pragmatic pre-post trial of two versions of the CPMC intervention (Group A – two contact points and Group B – three contact points) with community pharmacies allocated randomly into one of the two groups. Outcomes of the two versions of the CPMC intervention were compared to provide an indication of which version was more effective and cost-effective at improving participants' self-management of chronic pain. It was not a randomised controlled trial (RCT) conducted under tightly controlled conditions; it was a proof of concept to see if community pharmacists delivering an intervention to chronic pain patients in the community delivered benefits.

18. Further information on MSAC

MSAC Terms of Reference and other information are available on the MSAC Website: visit the MSAC website