

Commonwealth Department of Health

Sixth Community Pharmacy Agreement Pharmacy Practice Incentive Program:

Dose Administration Aids

Initial Evaluation - Final Report

17th November 2016

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Abbreviations

| **Abbreviation** | **Expanded Text** |
| --- | --- |
| **3CPA** | Third Community Pharmacy Agreement |
| **4CPA** | Fourth Community Pharmacy Agreement |
| **5CPA** | Fifth Community Pharmacy Agreement |
| **6CPA** | Sixth Community Pharmacy Agreement |
| **ABS** | Australian Bureau of Statistics |
| **ADR** | Adverse Drug Reaction |
| **ATSI** | Aboriginal and Torres Strait Islander |
| **BP** | Blood Pressure |
| **CALD** | Culturally and Linguistically Diverse |
| **CBA** | Cost-Benefit Analysis |
| **CBP** | Calendar Blister Pack |
| **CEA** | Cost-Effectiveness Analysis |
| **CI** | Confidence Interval |
| **CIs** | Clinical Interventions |
| **DAA** | Dose Administration Aid |
| **DVA** | Department of Veterans Affairs |
| **EQ5D** | EuroQoL 5-dimension |
| **HBA1c** | Glycated Haemoglobin |
| **HIC** | Health Insurance Commission |
| **HMR** | Home Medicines Review |
| **HTA** | Health Technology Assessment |
| **ICER** | Incremental Cost-Effectiveness Ratio |
| **INR** | International Normalised Ratio |
| **MBS** | Medical Benefits Schedule |
| **MPR** | Medication Possession Ratio |
| **MSAC** | Medical Services Advisory Committee |
| **NHMRC** | National Health and Medical Research Council |
| **NIDDM** | Non-Insulin Dependent Diabetes Mellitus |
| **OARS-IADL** | Older Americans Resource and Services Instrumental Activities of Daily Living |
| **OP** | Original Pack |
| **PBS** | Pharmaceutical Benefits Scheme |
| **PHA** | Population Health Area |
| **PhARIA** | Pharmacy Access/Remoteness Index of Australia |
| **PICO** | Population, Intervention, Comparator, Outcome |
| **PMP** | Patient Medication Profiling |
| **PPI** | Pharmacy Practice Incentives |
| **PSA** | Pharmaceutical Society of Australia |
| **PwC** | PricewaterhouseCoopers |
| **QCPP** | Quality Care Pharmacy Program |
| **QUM** | Quality Use of Medicines |
| **QUMAX** | Quality Use of Medicines Maximised (for Aboriginal and Torres Strait Islander People) |
| **RACF** | Residential Aged Care Facility |
| **RCF** | Residential Care Facility |
| **RMMR** | Residential Medication Management Reviews |
| **RP** | Reminder Packaging |
| **SD** | Standard Deviation |
| **SEIFA** | Socio-Economic Indexes for Areas |
| **SS** | Staged Supply |
| **TGA** | Therapeutic Goods Administration |
| **TTR** | Time in Therapeutic Range  |

Executive summary

On the 28th June 2016, the Department of Health engaged HealthConsult to evaluate three Pharmacy Practice Incentives (PPI) Program initiatives: Dose Administration Aids (DAAs), Staged Supply (SS), Clinical Interventions (CIs). This report presents the initial evaluation of the DAA initiative, which has involved:

* a literature review to identify data to inform the comparative clinical and cost-effectiveness of the DAA initiative and ‘like’ programs internationally; and
* an examination of the available Australian utilisation data from the DAA initiative going back to its start under earlier Community Pharmacy Agreements (CPAs).

Background

The DAA priority area was established under the Better Community Health Initiative of the Fourth Community Pharmacy Agreement (4CPA) and Fifth Community Pharmacy Agreement (5CPA) between the Pharmacy Guild of Australia and the Commonwealth Government. The DAA initiative was continued under the Sixth Community Pharmacy Agreement (6CPA), as part of the PPI Program directed at improving medication compliance through community pharmacies in Australia. The Guild and the Commonwealth Government jointly assess the payment amount the eligible community pharmacy is entitled to receive for the provision of DAAs. This amount is based on the number of services and pharmacy size (prescription volume).

Under 6CPA, all funded programs and services need to be reviewed by the Medical Services Advisory Committee (MSAC) for clinical and cost-effectiveness and the health benefits they offer to the community.

The current Pharmaceutical Society of Australia (PSA) *Dose Administration Aids Service* – *Guidelines and Standards for Pharmacists* (2007) defines a DAA to be a ‘well-sealed, tamper-evident device that allows individual medicine doses to be organised according to the prescribed dose schedule’. Patient selection is based on the pharmacist’s assessment (collaboratively with the patient’s general practitioner, community nurse and carer) of each consumer for his/her likelihood to benefit from, and ability to use, a DAA.

According to the PSA Guidelines (2007), the consumers most likely to benefit from DAAs include those living in the community and taking five or more medicines daily (including non-prescription medicines); or with a medical history suggesting problems managing medicines (e.g. prior hospitalisation due to poor adherence); or with a complex regimen of medicines; or with signs of cognitive or physical impairment that may affect their ability to effectively manage medicines. Thus, patient groups that commonly access this service may include the elderly, who are often on multiple medications, and patients with cognitive disabilities who may have trouble understanding or remembering their dosage regimes.

It is important to note that the DAA incentive payment calculation is based on a formula that takes into account the number of DAAs provided as well as the number of PBS scripts. Therefore, there is only an indirect relationship between the amount of the incentive payment and the volume of DAA services provided by a given pharmacy.

Methodology

Literature search

A systematic literature review was undertaken in August 2016 to identify studies that provide evidence relating to the safety, effectiveness, costs and cost-effectiveness of DAAs or similar medicine compliance aids provided by pharmacists to individuals living in the community. The grey literature was also searched, as were the reference lists of included studies.

Table ES.1 presents the evidence selection criteria. Studies that assessed the use of DAAs that are packed by the patient were excluded, as were studies that examined the use of DAAs as part of a more comprehensive pharmacy care program or as part of a multifaceted pharmacy intervention that included pharmacist’s medication follow-up, education, counselling, home visits, or refill reminders.

Table ES.1 Selection criteria for evidence relating to DAA services provided by community pharmacies

|  |  |
| --- | --- |
| Criteria | Description |
| Population | Community patients taking one or more self-administered medications (prescribed or over-the-counter). ‘Self-administered’ refers to the administration of a medication without the active assistance of a health care professional. It allows for medication administered by a family member or carer.Note: Patients living in a residential aged care facility or a correctional facility are excluded.Subpopulations:* geriatric population
* cognitive or physical impairment
* chronic mental illness
* chronic disease (e.g. asthma, diabetes, cardiovascular disease)
* concurrent use of multiple medications (polypharmacy)
 |
| Intervention | Any tamper-evident, adherence devices (e.g. compartmentalised boxes, blister or bubble packs, sachet systems) provided by community pharmacies to assist medication management for a consumer by having medicines divided into individual doses and arranged according to the dose schedule throughout the day. The adherence device (or dose administration aid) may be packed by the community pharmacist or a third party. Note: Injected, topical or inhaled medicines, and co-packaged or fixed-dose combinations are not excluded, as long as the packaging includes a reminder system. |
| Comparator | Community patients in the absence of the intervention. |
| Outcomes | * adherence/compliance/concordance with prescribed dose schedule (e.g. pill count, self-report)
* clinical outcomes (e.g. BP in patients with hypertension, HbA1c in patients with diabetes, seizure frequency in patients with epilepsy, psychological symptoms in patients with mental illness)
* adverse drug events/reactions and medication-related problems
* safety outcomes (harms or errors associated with packaging devices)
* mortality
* health care resource use (ED attendance, hospitalisation, GP visits, specialist visits)
* patient acceptance/satisfaction
* health-related quality of life
* costs and cost-effectiveness
 |
| Study design | Comparative studies (randomised or non-randomised controlled trials, cohort studies, case control studies) or systematic reviews of comparative studies.Applicability to the Australian context will be considered. |
| Publication type | Full English-language publications or reports. Conference abstracts are excluded. |
| Search period | No year restrictions |

Abbreviations: BP, blood pressure; DAA, dose administration aid; ED, emergency department; GP, general practitioner; HBA1c, glycated haemoglobin.

The search identified two publications relating to an Australian DAA project funded under the Third Community Pharmacy Agreement (3CPA), and two previous evaluations of the DAA initiative funded under the 4CPA and 5CPA. The findings of these reports are summarised in the main body of this evaluation report. The intention of these summaries is to provide MSAC with an understanding of the approaches taken to evaluate the DAA initiative in Australia, as well as a high level overview of the findings of previous evaluations in relation to effectiveness and cost-effectiveness of the service. The publications under 3CPA concluded that “the preliminary best practice models for the provision of DAA services to RCFs and patients living in the community developed in the study addresses the key barriers to the provision of safe, effective and efficient DAA services. An evaluation of these models has found that, they are likely to be beneficial in achieving improvements in practice and generally feasible.” The evaluations of 4CPA and 5CPA concluded that, due to a lack of data, the impact of the 4CPA and 5CPA DAA service on patient health outcomes could not be evaluated.

Three relevant systematic reviews (including a Cochrane Review) were identified that evaluated the use of medication reminder packaging for improving adherence to self-administered medication regimens. All three systematic reviews evaluated a combination of adherence-aimed interventions, which confounds the findings for DAAs. For this reason, only those studies that examined DAAs independently of other adherence enhancing programs were selected for inclusion in the current Review.

A total of nine primary studies were identified that examined the use of a DAA or a similar medication compliance aid independently from additional reminder systems or other pharmacy care interventions. No studies were identified that assessed the impact of an incentive payment to pharmacists for the provision of DAAs to community patients.

The nine included studies were mixed in design and included seven randomised controlled trials (RCTs) (one good quality, two fair quality and four poor quality), one prospective cohort study (poor quality) and one retrospective matched cohort study (poor quality). One included study was conducted in New Zealand, one in Canada, and the remaining seven studies were conducted in North America.

Five studies assessed DAAs or similar compliance aids in people taking medications for hypertension (Dupclay et al, 2012; Schneider et al, 2008; Simmons et al, 2000; Skaer et al, 1993a; Becker et al, 1986), two studies were in people taking medications for diabetes (Simmons et al, 2000; Skaer et al, 1993b), one study was in elderly patients with multiple medical conditions (Winland-Brown et al, 2000), one study was in patients taking warfarin to prevent thromboembolic events (Dumas et al, 2016), and one study was in healthy elderly patients taking vitamin supplements (Huang et al, 2000).

There were no studies that were specifically conducted in patients with cognitive or physical impairment or with chronic mental illness. None of the included studies reported results for patients taking only one medication compared with those concurrently using multiple medications (polypharmacy).

Utilisation analysis

The only data available for inclusion in the utilisation analysis were claims payment data held by the Department of Health. These data have been analysed in the context of geographical factors that have been inferred from the postcode of each pharmacy. Those factors included remoteness; overall population, chronic disease prevalence and proportion of population aged over 65 years by Primary Health Network (PHN) geographic areas. These factors were used to assess whether the growth in DAA services has occurred in line with the populations that the program is intended to target. Key metrics in the analysis are limited to the amount of claims paid and the number of patient DAA services provided.

Results of the literature review

The key research questions for the literature review of DAA services primarily relate to the potential advantages to consumers that are outlined in the PSA Guidelines (2007).

***Is there evidence that a DAA service provided by community pharmacies provides benefits to consumers, compared with no DAA service provided by community pharmacies, in terms of improvement in medication adherence and management; reduction in the incidence of adverse drug events; and reduction in medication-related hospitalisation?***

Adherence

The evidence on the effectiveness of DAAs on adherence to medication is mixed. Four studies (three RCTs and one retrospective matched cohort study) showed that the use of DAAs or similar medicine compliance aids significantly improved adherence to medication for diabetes and hypertension, as manifested by improvements in the medication possession ratio (MPR). However, the evidence was less convincing for adherence measured by pill counts, with two of three studies showing no effect. The effect of drug reminder packaging was more pronounced when used in combination with other interventions such as a refill reminder.

The current evidence base consists of poor to fair quality studies with significant methodological limitation, inadequate length of follow-up, and moderate-to-high risk of bias. Therefore, findings from these studies should be interpreted with caution.

There are currently no studies that assessed the effect of the Australian DAA initiative on adherence to medication. Further high-quality studies of adequate size and duration, assessing the use of DAAs or similar medicine compliance aids on adherence to self-administered long-term medication use are required to draw firm conclusions.

Clinical outcomes

Although the purpose of DAAs is to improve medication compliance, this outcome will not necessarily be accompanied by clinically meaningful improvements in clinical outcomes as modest amounts of non-adherence may still leave patients within a therapeutic window. Four of the included studies reported the effect of DAAs on clinical outcomes.

A single prospective cohort study of poor quality assessed the impact of pillbox use on clinical outcomes in warfarin users. The study found that pillbox use was not associated with time in therapeutic range (TTR) <60% or international normalised ratio (INR) instability; however, these results may be biased by unmeasured confounders such as concomitant drug use. Therefore, the effect of pillbox on INR instability among warfarin users remains inconclusive and further research is still needed in this area.

Evidence from two RCTs (one fair quality and one good quality) showed that the use of reminder packaging in patients taking antihypertensive medication significantly decreased diastolic blood pressure but not systolic blood pressure, compared with control. An older study of poor quality failed to demonstrate an effect of reminder packaging on blood pressure control (or on adherence). Evidence from a good quality RCT of small size showed that in patients with poorly controlled diabetes, reminder packaging significantly decreased glycated haemoglobin at eight months of follow up compared with original packaging.

High quality studies of adequate size and duration assessing the clinical effectiveness of reminder packaging interventions are required before firm conclusions can be drawn.

Patient satisfaction

There is insufficient evidence to assess patient acceptance or satisfaction with pharmacist-prepared DAAs or similar medicine compliance aids. Patient satisfaction was marginally reported, with only three of the included studies reflecting on this outcome. Future research into adherence aids should incorporate the opinions of study participants to identify what they would desire in a medicine compliance aid and how they evaluate current devices available, with consideration given to their ease of opening, transportability and display features.

Other outcomes

None of the included studies specifically reported outcomes relating to adverse drug events, (or adverse drug reactions or medication-related problems), mortality, or health-related quality of life. None of the included studies provided information on the safety or harms associated with DAA use, such as dispensing or packaging errors.

***Is there evidence that a DAA service provided by community pharmacies results in cost offsets or cost savings through prevention of hoarding of medicines?***

No studies were identified that specifically addressed this research question (hoarding).

But, two RCTs by Skaer et al examined the use of unit-of-use reminder packaging on health care resource costs in hypertensive (1993a) and diabetic (1993b) patients. Both studies were conducted in the context of the US Medicaid system, with patient-level claims data regarding the use of, and expenditure for, healthcare services derived from the South Carolina Medicaid computer archive. Both studies reported that the use of reminder packaging resulted in a statistically significant increase in prescription expenditure and a non-significant decrease in total costs (calculated as the sum of prescription, physician, hospital and laboratory costs) compared with the control group using standard medicine vials. However, the two studies were of poor methodological quality and their results should be interpreted with caution. Furthermore, they have limited applicability to the Australian context.

***What costs are associated with a DAA service provided by community pharmacies?***

A project undertaken by the University of Queensland and funded under the 3CPA (Phase 3 Final Report May 2006) included an analysis of workflow observations from 83 pharmacists (based on data gathered in Phase 2, Final Report 2004). The base case model presented in the report provided details of costs for 30 customers using an average of eight medicines per week. The total cost for the base case was estimated at $543.88 for customers using original packaging (which equates to $18.13 per customer) compared to $1,070.50 for customers using DAAs ($35.75 per customer).

The 2010 evaluation of the 4CPA DAA/Patient Medication Profile (PMP) programs, which was commissioned by the Department of Health, estimated the average cost for a pharmacy to deliver a DAA service per patient/per week to be $17.25, based on the average number of hours per week spent by various pharmacy staff members in providing the DAA service to all community based patients (as self-reported by pharmacies).

No other studies were found that reported the cost for a pharmacy to deliver a DAA service.

***Is there evidence that a DAA service provided by community pharmacies is cost-effective, compared with no DAA service provided by community pharmacies?***

The project undertaken by the University of Queensland and funded under the 3CPA (Phase 2 Final Report November 2004) included cost-effectiveness and cost-benefit analyses based on 30 community customers receiving DAA versus 30 community customers receiving original packaging over one year. The authors concluded “at present DAAs are not cost-effective in the community setting. This is largely because the provision of DAAs by pharmacy is a labour-intensive and costly exercise. Sensitivity analysis, however, suggests the potential for delivery of a cost-effective DAA service if the magnitude of the benefits and the efficiency of the service provision were greater”.

Post development and implementation of best practice models and tools to facilitate improvements in the way DAAs are used in the RCF and community setting (described in the subsequent publication University of Queensland, Phase 3 Final Report May 2006), a more sophisticated methodology to re-examine the cost-effectiveness of DAAs in the community setting was undertaken. Again it included cost-effectiveness and cost-benefit analyses based on 30 community customers receiving DAA versus 30 community customers receiving original packaging over one year. The incremental cost to prevent one adverse drug reaction (ADR) was estimated to be $9,163. The incremental cost to avoid one death using DAA was estimated to be $16,362.

A cost-benefit analysis comparing the cost of DAAs, and subsequent reduction in healthcare costs given the decrease in ADRs, with the benefits to consumers of using the DAAs in terms of willingness-to-pay, showed that the costs of providing DAAs outweigh the benefits of DAAs by $13,291 per year or $443.03 per DAA customer.

A cost-benefit analysis was also performed for patients living in the community, utilising a full range of health service use data extracted from the (then) Health Insurance Commission and patient data (included as part of the Phase 3 follow-up). The analysis showed that the costs of providing DAAs to 30 community customers outweighs the benefits of DAAs by $9,381 per year. However, these analyses must be interpreted in light of significant differences between the DAA and original packaging patient groups, with DAA customers in general exhibiting a greater severity of illness than original packaging customers.

There were no other studies identified that assessed the cost-effectiveness of DAAs or similar medicine compliance aids.

Results of the utilisation analysis

The available data show that the volume of the claims for patient DAAs supplied has increased substantially between 2012 and 2015 nationally, and that the number of participating pharmacies has also increased, especially in remote and very remote regions. But, the claims data do not contain any information regarding patients’ age, frailty, mental faculties or health status; or any other patient characteristic to help determine if the program is reaching the target patient population.

To address this issue the 2015 claims data were analysed against indicators of the target population (i.e. diabetes prevalence as an example of chronic disease, mental health issues prevalence as an indicator of patient who might be disturbed on confused, and proportion of population aged over 65 years, as an indicator of patients who may have medication adherence issues). This analysis identified no significant relationships, for example, it could not be shown that PHN areas with higher proportions of population aged over 65 years also had higher per capita DAA services rates or higher investment of DAA program resources.

Conclusions

The evaluation found that the identified overseas evidence is generally of poor to fair quality and has limited applicability to the Australian DAA initiative. That said, the available literature is inconclusive as to whether DAAs are effective in improving medication adherence, clinical outcomes, patient satisfaction; or whether DAAs are cost effective. Although the three phase 3CPA project undertaken by the University of Queensland included two cost-effectiveness analysis (the Phase 2 Final Report found DAAs to not be cost-effective and the Phase 3 Final Report found DAAs to be cost effective), how relevant either of the cost-effective analysis is to the current DAA model is problematic.

Further, no studies were identified that assessed the impact of an incentive payment to pharmacists for the provision of DAAs to community patients. There is a larger body of evidence for DAAs used in combination with other adherence-aimed interventions, but in these studies the findings for DAAs are confounded.

In order to make a more robust assessment of the clinical and cost effectiveness of DAAs, further research is required. Such research would best take the form of a study that included:

* a high-quality study of adequate size (number of patients) and duration that assessed the use of DAAs delivered through community pharmacies on medication adherence, clinical outcomes, health care utilisation, and patient satisfaction (through primary data collection and linkage to secondary datasets, e.g. MBS, PBS, hospital utilisation, and so on);
* a robust costing study that measured the unit cost of the delivering of a DAA service in a variety of settings across the community pharmacy sector;
* a translational study that takes the results of the unit cost and outcome measurement work and calculates cost effectiveness (no further primary data collection would be required).

# Introduction

On the 28th June 2016, the Australian Government Department of Health engaged HealthConsult to evaluate the Sixth Community Pharmacy Agreement (6CPA) Pharmacy Practice Incentives (PPI) Program: Dose Administration Aids (DAA). This initial evaluation involved:

* a literature review to identify data to inform the comparative clinical and cost-effectiveness of the DAA initiative, including a review of the international literature to determine whether results for ‘like’ programs can be extrapolated to be considered as evidence for the DAA initiative in Australia; and
* an examination of Australian utilisation data from the DAA initiative since its start under earlier CPAs, with an emphasis on elucidating the characteristics and volumes of:
	+ pharmacy services delivered via the program;
	+ pharmacists and pharmacies delivering these services; and
	+ individuals receiving these services.

## Sixth Community Pharmacy Agreement

In May 2015, the Australian Government and Pharmacy Guild of Australia entered into the 6CPA, which provides around $18.9 billion in remuneration for community pharmacy, as well as support to the pharmaceutical supply chain (with a further $372 million provided for chemotherapy compounding fees). Up to $1.26 billion in funding is available under the 6CPA for evidence-based, patient-focused professional pharmacy programs and services. This consists of:

* $613 million for the continuation of a number of programs and services from 5CPA;
* $50 million for a new pharmacy trial program; and
* up to $600 million for new and expanded community pharmacy programs.

The 6CPA includes three key funding elements:

* community pharmacy remuneration;
* ensuring that all Australians have timely access to the Pharmaceutical Benefits Scheme (PBS) medicines they require regardless of the cost of the medicine or where they live; and
* community pharmacy programs directed at improving consumer management of their medications and delivering primary healthcare services through community pharmacy.

## Pharmacy Practice Incentives Program

The 6CPA PPI Program provides a financial incentive to pharmacists to deliver compliance initiatives. As part of the 6CPA, there are several continuing PPI Programs directed at improving medication compliance through community pharmacies in Australia. The continuing programs include:

* Medication Adherence Programs
	+ Dose Administration Aids (DAAs)
	+ Clinical Interventions (CIs)
	+ Staged Supply (SS)
* Medication Management Programs
	+ Home Medicines Reviews (HMR)
	+ Residential Medication Management Reviews (RMMR)
	+ MedsCheck and Diabetes MedsCheck
* Rural Support Programs
	+ Rural Pharmacy Workforce Program
	+ Rural Pharmacy Maintenance Allowance
* Aboriginal and Torres Strait Islander (ATSI) Programs
	+ Quality Use of Medicines Maximised for ATSI People (QUMAX)
	+ S100 Pharmacy Support Allowance
	+ ATSI Workforce Program (Pharmacy Assistant Traineeship Scheme and Pharmacy Scholarships Scheme)
* eHealth:
	+ Electronic Prescription Fee

Under 6CPA, all programs and services need to be reviewed by the Medical Services Advisory Committee (MSAC) for clinical and cost-effectiveness and the health benefits they offer to the community. This process is being used to ensure pharmacy programs and services are assessed against the same standards of evidence as for other health professions. It supports a consistent approach to informing investment that delivers the greatest benefit to consumers.

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# Dose Administration Aids

This Section describes the DAA initiative, which falls under the broader Medication Adherence Program within 6CPA. DAAs are described in the literature as devices that assist patients in better managing their medicines by arranging their medicines into individual doses according to the prescribed dose schedule throughout the day. A DAA can either be a unit-dose pack or a multi-dose pack. Examples of DAAs include compartmentalised plastic boxes, blister or bubble packs; and sachet systems. The DAA devices may be filled by the patient, or by a third party such as a community pharmacy. DAAs that are filled by the patient are available; however, they are outside the scope of this evaluation.

## DAA initiative

The DAA priority area was established under the Better Community Health Initiative of the Fourth Community Pharmacy Agreement (4CPA) and Fifth Community Pharmacy Agreement (5CPA) between the Pharmacy Guild of Australia and the Commonwealth Government.[[1]](#footnote-1) The Pharmaceutical Society of Australia (PSA) *Dose Administration Aids Service* – *Guidelines and Standards for Pharmacists* (July 2007)define DAA to be a ‘well-sealed, tamper-evident device that allows individual medicine doses to be organised according to the prescribed dose schedule’. Australian pharmacists may provide DAAs for selected patients to assist in the safe and effective administration of a patient’s medicines.

Community pharmacists are part of the primary health care system, and play an important role in the management of chronic conditions within the community through their increased access to patients and the delivery of professional services, such as the DAA service. Patients can access community pharmacies without making an appointment. There are over 5,000 community pharmacies across metropolitan, regional, and remote Australia. Therefore, community pharmacists are appropriately positioned to implement programs aimed at improving medication adherence and management in the community.

## Objectives of the DAA initiative

The DAA initiative is part of an initiative to expand the role of community pharmacy, beyond medication dispensing to an increased primary healthcare contribution. According to the PSA guidelines and standards (PSA, 2007), the aim of the DAA initiative is to:

* improve medication adherence and management;
* reduce the incidence of adverse drug events due to medicines mismanagement;
* reduce medication-related hospitalisation due to medicine misuse; and
* possible cost savings through prevention of hoarding of medicines.

## Participation in the DAA initiative

To be eligible to receive incentive payments for providing DAA services, a community pharmacy must:

* be a Section 90 Pharmacy;
* be accredited by an approved Pharmacy Accreditation Program such as the Quality Care Pharmacy Program (QCPP);
* agree to publicly display and comply with the Community Pharmacy Service Charter and Customer Service Statement;
* register for the DAA priority area via the 6CPA Registration and Claiming Portal;
* continue to meet the above eligibility criteria while participating in the DAA priority area;
* deliver DAA services in accordance with the PPI Program Specific Guidelines.

Eligible community pharmacies are entitled to claim incentive payments four times a year for providing DAAs to patients living within the community, as long as the following criteria are met (PSA, 2007):

* the patient’s medicine/s in the DAA are dispensed and packed by the claiming eligible community pharmacy in accordance with the quality Standard in the pharmacy; or
* the patient’s medicine/s in the DAA are dispensed by the claiming eligible community pharmacy but are packed at another site (DAA packing warehouse, another pharmacy, etc.) that meets the pharmacy approval authority requirements in the relevant state or territory, as well as the relevant quality standard; and
* the DAA patient is not living in a Government funded Residential Aged Care Facility (RACF) or a correctional facility.

The Guild and the Australian Government jointly assess the payment amount the eligible community pharmacy is entitled to receive for the provision of DAAs. This is based on the number of services and pharmacy size (e.g. prescription volume). The eligible community pharmacy claimable prescription volume is sourced from the Department of Human Services records.

## Patient groups most likely to benefit from DAA services

A literature review performed by the Australian National Prescribing Service (Easton et al, 2009) identified that individuals at highest risk of adverse drug events or medication error in the community are older patients, those taking multiple medications, those with serious health conditions, and those taking high risk medications (e.g. cardiovascular drugs, antithrombotic drugs, analgesics, antibiotics, oral anti-diabetic drugs, antidepressants, antiepileptic drugs and chemotherapeutic agents). The review found that in Australia, 5.6% of hospital admissions in the general population to 30.4% of admissions in the elderly were associated with adverse drug events. Medication errors in the community were found to occur at all stages in the medication management process from prescribing, supply and administration to therapeutic drug monitoring, medical records documentation, referrals and hospital discharge summaries.

Eligible community pharmacies may provide DAAs for selected patients to assist in the safe and effective administration of a patient’s medicines and to enhance adherence. Patient selection is based on the pharmacist’s assessment (collaboratively with the patient’s general practitioner [GP], community nurse and carer) of each consumer for their likelihood to benefit from, and ability to use, a DAA. The assessment takes into consideration the consumer’s behaviours and attitudes to taking medicines that may impact on DAA use, and conditions that may limit the consumer’s capacity to safely and effectively use the DAA (e.g. visual impairment, diminished dexterity due to arthritis), and confirming that the consumer can effectively use the proposed DAA. A written agreement between the consumer and the pharmacist is then drafted in order to formalise the service to be delivered, and a DAA profile for the patient is created.

According to the *Guidelines and Standards for Pharmacists: Dose Administration Aids Service* (PSA, 2007), consumers that are most likely to benefit from this service include those:

* living in the community; and
* taking five or more medicines daily (including non-prescription medicines);
* with a medical history suggesting problems managing medicines (e.g. prior hospitalisation due to poor adherence);
* with a complex regimen of medicines; or
* with signs of cognitive or physical impairment that may affect their ability to effectively manage medicines.

Therefore, the most common patient groups that may access this service include the elderly, who are often on several different medications, and patients with cognitive disabilities who may have trouble understanding or remembering their dosage regimes.

It is important to note that while certain population groups have the potential to benefit from DAAs, the eligibility criteria may not always closely align with those groups most likely to benefit. Therefore, it is necessary to evaluate the evidence on the effectiveness of the DAA initiative among these patient groups or the broader population.

## Types of medicines suitable for DAAs

The PSA *Professional Practice Standards* (2010) and *Guidelines and Standards for Pharmacists: Dose Administration Aids Service* (2007) have provided general guidance on stability issues related to the repackaging of oral solid dosage forms into DAAs and are summarised as follows:

* Medicines that are generally unsuitable for packing into DAAs include cytotoxic, effervescent, dispersible, buccal, and sublingual and hygroscopic medicines.
* Medicines administered on an ‘as required’ basis are generally unsuitable for packing into DAAs since they may be taken unnecessarily on a regular basis or removed from the blister for use at an earlier or later stage, thus exposing the remaining contents to the environment.
* Only devices that are well sealed and tamper-evident should be used.
* The length of time taken for the end-to-end packing process should be kept to a minimum; tablets and capsules should be removed from the manufacturer’s foil or blister pack immediately before the DAA is packed, and the DAA sealed immediately after it is packed.
* Any heat sealing methods should be used quickly and efficiently to minimise exposure of medicines to heat, especially medicines that might be affected when the backing of a DAA is heat-sealed, for example, soft gel capsules.
* The packed DAAs should be stored in an area that is cool, dry and protected from light, and the time between packing and dispensing should be kept to a minimum.
* When a DAA needs to be transported by independent couriers or other means, consideration should be given to the likely storage conditions (e.g. exposure to heat, humidity, and moisture) and the length of time the DAA will be in transit.
* It is useful to maintain a list of medicines/medicine types that should not be removed from their original pack for packing in a DAA.

# Review methodology

This Section describes the methodology used to identify and assess the evidence relating to DAAs. The evaluation encompasses a systematic literature review of Australian and international evidence for the safety, effectiveness and cost-effectiveness of DAA services provided by pharmacists to individuals living in the community, and an analysis of available data on the utilisation of the service provided under the PPI Program.

## Systematic literature review

### Research questions and PICO criteria

The key research questions for the evaluation of DAA services relate to the potential advantages to consumers that are outlined in the PSA *Dose Administration Aids Service – Guidelines and Standards for Pharmacists* (July 2007).[[2]](#footnote-2)

* Is there evidence that a DAA service provided by community pharmacies provides benefits to consumers, compared with no DAA service provided by community pharmacies, in terms of:
	+ improvement in medication adherence and management;
	+ reduction in the incidence of adverse drug events; and
	+ reduction in medication-related hospitalisation?
* Is there evidence that a DAA service provided by community pharmacies results in cost offsets or cost savings through prevention of hoarding of medicines?

Additional research questions of relevance to the evaluation relate to the costs and cost-effectiveness of the service:

* What costs are associated with a DAA service provided by community pharmacies?
* Is there evidence that a DAA service provided by community pharmacies is cost-effective, compared with no DAA service provided by community pharmacies?

Table 3.1 presents the selection criteria for evidence assessing the safety, effectiveness and cost-effectiveness of DAA services.

Table 3.1 Selection criteria for evidence relating to DAA services provided by community pharmacies

|  |  |
| --- | --- |
| Criteria | Description |
| Population | Community patients taking one or more self-administered medications (prescribed or over-the-counter). ‘Self-administered’ refers to the administration of a medication without the active assistance of a health care professional. It allows for medication administered by a family member or carer.Note: Patients living in a residential aged care facility or a correctional facility are excluded.Subpopulations:* geriatric population
* cognitive or physical impairment
* chronic mental illness
* chronic disease (e.g. asthma, diabetes, cardiovascular disease)
* concurrent use of multiple medications (polypharmacy)
 |
| Intervention | Any tamper-evident, adherence devices (e.g. compartmentalised boxes, blister or bubble packs, sachet systems) provided by community pharmacies to assist medication management for a consumer by having medicines divided into individual doses and arranged according to the dose schedule throughout the day. The adherence device (or dose administration aid) may be packed by the community pharmacist or a third party. Note: Injected, topical or inhaled medicines, and co-packaged or fixed-dose combinations are not excluded, as long as the packaging includes a reminder system. |
| Comparator | Community patients in the absence of the intervention. |
| Outcomes | * adherence/compliance/concordance with prescribed dose schedule (e.g. pill count, self-report)a
* clinical outcomes (e.g. BP in patients with hypertension, HbA1c in patients with diabetes, seizure frequency in patients with epilepsy, psychological symptoms in patients with mental illness)
* adverse drug events/reactions and medication-related problems
* safety outcomes (harms or errors associated with packaging devices)
* mortality
* health care resource use (ED attendance, hospitalisation, GP visits, specialist visits)
* patient acceptance/satisfaction
* health-related quality of life
* costs and cost-effectiveness
 |
| Study design | Comparative studies (randomised or non-randomised controlled trials, cohort studies, case control studies) or systematic reviews of comparative studies.Applicability to the Australian context will be considered. |
| Publication type | Full English-language publications or reports. Conference abstracts are excluded. |
| Search period | No year restrictions |

Abbreviations: BP, blood pressure; DAA, dose administration aid; ED, emergency department; GP, general practitioner; HBA1c, glycated haemoglobin.

**a** See Appendix 5 for a summary of medication adherence measures.

### Search strategy

A comprehensive search of peer-reviewed scientific literature was conducted in August 2016 to identify studies that provide evidence relating to the safety, effectiveness and cost-effectiveness of DAAs or similar medicine compliance aids provided by pharmacists to individuals living in the community. Four electronic databases were searched for original research papers describing systematic reviews, meta-analyses, or comparative studies, as shown in Table 3.2. The search of Medline, Embase, International Pharmaceutical Abstracts, and the Cochrane Library was unrestricted by date and was searched up to 23rd August 2016. The specific search terms used to identify relevant literature are outlined in Appendix 3.

The Health Systems Evidence database (McMaster Health Forum) and databases maintained by Health Technology Assessment (HTA) agencies[[3]](#footnote-3) were also searched to identify relevant literature. In addition, the reference lists of relevant systematic reviews, selected narrative reviews, and primary articles were examined to identify studies not otherwise found in the literature searches.

A search of pharmacy organisations[[4]](#footnote-4) and the grey literature was also performed to identify previous evaluations of the DAA initiative in Australia, and similar community pharmacist-led programs from other jurisdictions.

Table 3.2 Data bases searched

|  |  |
| --- | --- |
| Database | Search period |
| Embase via Ovid | Up to 23 August 2016 |
| Medline via Ovid | Up to 23 August 2016 |
| International Pharmaceutical Abstracts via Ovid | Up to 23 August 2016 |
| The Cochrane Library (includes Cochrane Database of Systematic Reviews, Database of Abstracts of Reviews of Effects, Cochrane Central Register of Controlled Trials, NHS Economic Evaluation Database, Health Technology Assessment, Cochrane Methodology Register) | Up to 17 August 2016 |
| Health Systems Evidence | Up to 14 September 2016 |
| HTA websites and databases | Up to 14 September 2016 |

### Selection of relevant evidence

The literature search outlined above identified 1976 unique citations. The following exclusion criteria were applied:

* Wrong publication type– excludes narrative reviews.
* Wrong intervention – excludes studies that examined the use of DAAs or similar compliance aids as part of a more comprehensive pharmacy care program or were part of a multifaceted pharmacy intervention that included pharmacist’s medication follow-up, education, counselling, home visits, or refill reminders. Studies that evaluated the use of DAAs that are packed by the patient (or self-packed) were excluded. Studies that assessed the use of automated medication dispensing devices were excluded.[[5]](#footnote-5)
* Wrong comparator – excludes studies that compared DAAs with other compliance aids.
* Wrong population – excludes RACF patients, hospital inpatients, recently discharged patients, or patients with infectious disease requiring short treatment duration.
* Wrong outcomes – excludes studies that do not assess one of the outcomes outlined in Section 3.1.1.
* Not in English – excludes studies not published in English language or those that do not include at least some information (e.g. a summary) in English.
* Superseded – excludes systematic reviews that have been updated.

The exclusion of citations from the searches is presented in Table 3.3.

Table 3.3 Summary of the process used to identify relevant studies and reports

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
| Description | Embase, Medline, International Pharmaceutical Abstracts, Cochrane Library | Hand searched references | Health System Evidence | Grey literature |
| **Total number of citations**  | 2836 | 16 | 10 | 4 |
| Duplicates within and across sets removed |  | 861 |  |  |
| Total number of citations screened | 1955 | 16 | 1 | 4 |
| Excluded at title/abstract review: |  |  |  |  |
| * Wrong population
 | 31 | 2 | *0* | *0* |
| * Wrong intervention
 | 1773 | 9 |  |  |
| * Wrong outcome
 | 20 |  |  |  |
| * Wrong publication type
 | 39 | 3 |  |  |
| *Total citations excluded at title/abstract review*: | *1863* | *14* |  |  |
| Citations screened at full text review | 92 | 2 | 1 | 4 |
| Excluded at full text review: |  |  |  |  |
| * Wrong population
 | 9 |  |  |  |
| * Wrong intervention
 | 65 |  | 1 |  |
| * Wrong outcome
 | 2 |  |  |  |
| * Wrong publication type
 | 6 |  |  |  |
| *Total citations excluded at full text review:* | *82* | *0* | *1* | *0* |
| Included citations from database searches | 10 | 2 | 0 | 4 |
| **Total included studies** |  | **12** |  |  |
| **Total included CPA reports** |  | **4** |  |  |

Abbreviations: CPA, Community Pharmacy Agreement

A total of 12 relevant studies of DAAs or similar compliance aids (three systematic reviews and nine primary studies) were identified from the literature search. The quality of the included systematic reviews was assessed using the AMSTAR measurement tool. The quality of the included primary studies was assessed using questions the National Health and Medical Research Council (NHMRC). These instruments and the quality assessment shown in Appendix 6).

In addition, the targeted search of the websites of relevant pharmacy organisations identified a CPA-funded DAA project and two previous evaluations of the CPA DAA initiative.

### List of included studies

#### Previous evaluations of the PPI Program DAA initiative

The search identified two publications relating to an Australian DAA project funded under the Third Community Pharmacy Agreement (3CPA), and two previous evaluations of the DAA initiative funded under the 4CPA and 5CPA. The citations are provided in Table 3.4. Section 0 provides a summary of the findings of the DAA project and the two program evaluations.

Table 3.4 Citation details for projects and evaluations funded under a CPA

|  |  |
| --- | --- |
| Study ID | Citation |
| University of Queensland (2004) | Effectiveness and cost-effectiveness of Dose Administration Aids (DAAs). Phase 2. Final Report. Retrieved from http://6cpa.com.au/wp-content/uploads/Effectiveness-and-cost-effectiveness-of-Dose-Administration-Aids-executive-summary.pdf |
| University of Queensland (2006) | Effectiveness and cost-effectiveness of Dose Administration Aids (DAAs). Phase 3. Final Report. Retrieved from http://6cpa.com.au/wp-content/uploads/Effectiveness-and-cost-effectiveness-of-Dose-Administration-Aids-phase-3-DAA-phase-3-Final-Report.pdf |
| PwC (2010) | Australian Department of Health and Ageing. Evaluation of the DAA/PMP Programs. Retrieved from https://www.health.gov.au/internet/main/publishing.nsf/Content/F520A0D5EDEA0172CA257BF0001D7B4D/$File/DAA%20PMP%20Report.pdf |
| PwC (2015) | PricewaterhouseCoopers (2015). Combined Review of Fifth Community Pharmacy Agreement Medication Management Programmes (Final Report). Retrieved from https://www.health.gov.au/internet/main/publishing.nsf/Content/6EF022DE87761986CA257EC80013198B/$File/combined-review-5cpa-medication-management-programmes-final-report-and-appendices.pdf |

Abbreviations: CPA, Community Pharmacy Agreement; DAA, Dose Administration Aid; PMP, Patient Medication Profile; PwC, PricewaterhouseCoopers

#### Systematic reviews

The literature search for systematic reviews of DAAs identified three eligible publications, which are listed in Table 3.5. The three included systematic reviews evaluated the use of medication reminder packaging for improving adherence to self-administered short or long-term medications. However, all of the systematic reviews included studies of reminder packaging aids combined with adherence enhancing programs. These additional reminder systems are not part of the DAA service under review. Therefore, only those individual studies that examined the effect of DAA use on adherence and other outcomes in the PICO, and independently of other reminder systems or pharmacy interventions, were selected for inclusion in the current evaluation.

Table 3.5 Citation details for included systematic reviews

|  |  |
| --- | --- |
| Study ID | Citation |
| Boeni (2014) | Boeni F, Hersberger KE, Arnet I (2014). Multidrug punch cards in primary care: A mixed methods study on patients' preferences and impact on adherence. Frontiers in Pharmacology, Systematic Reviews, (3):29 |
| Mahtani (2011) | Mahtani KR, Heneghan CJ, Glasziou PP, Perera R (2011). Reminder packaging for improving adherence to self-administered long-term medications. Cochrane Database of Systematic Reviews, (9):CD005025. |
| Zedler (2011) | Zedler BK, Kakad P, Colilla S, Murrelle L, Shah NR (2011). Does packaging with a calendar feature improve adherence to self-administered medication for long-term use? A systematic review. Clinical Therapeutics, 33(1):62-73. |

The literature search identified a number of other systematic reviews and narrative reviews that did not focus on DAAs but on any pharmacy-based intervention aimed at improving medication adherence. Systematic reviews that presented analysis (or meta-analysis) from pharmacy interventions that included services other than the DAA on its own (such as refill reminders, home visits, medication review, telephone calls, education, and continuous monitoring, pharmacist follow-ups) were excluded. A list of these reviews and the reasons for their exclusion are presented in Appendix 4. The reference lists of each of the excluded systematic reviews were hand-searched to identify any relevant studies not identified elsewhere.

#### Primary studies

The systematic literature search for primary studies of DAAs identified nine eligible publications that assessed DAAs where medicines were packaged either manually by the pharmacist, a specialised company, or an automated system. Table 3.6 presents the list of included studies and the type of DAA used. All included studied examined the use of a DAA or a similar medication compliance aid independently from additional reminder systems or other pharmacy care interventions. None of the included studies assessed the impact of an incentive payment to pharmacists for the provision of DAAs to community patients.

Table 3.6 Citation details for included studies of DAAs

|  |  |  |
| --- | --- | --- |
| Study ID | Citation | Type of DAA used in the intervention |
| Dumas (2016) | Dumas S, Rouleau-Mailloux E, Bouchama N, Lahcene H, Talajic M, Tardif JC, et al. (2016). Pillbox use and INR stability in a prospective cohort of new warfarin users. Journal of Managed Care and Specialty Pharmacy, 22(6):676-84. | Pre-packed pillbox by pharmacist. Intervention also included pillboxes packed by the patients, the results of which are excluded from this Report. |
| Dupclay (2012) | Dupclay L, Eaddy M, Jackson J, Raju A, Shim A (2012). Real-world impact of reminder packaging on antihypertensive treatment adherence and persistence. Patient Preference and Adherence, 6:499-507. | Use of a monthly reminder blister pack with clear labelling information (days supplied, brand/generic name, storage information, instructions for use) found on the front of the pack. A reminder to reorder was found inside the blister card. |
| Schneider (2008) | Schneider PJ, Murphy JE, Pedersen CA. (2008) Impact of medication packaging on adherence and treatment outcomes in older ambulatory patients. Journal of theAmerican Pharmacists Association, 48: 58–63. | Use of a daily-dose blister packaging. |
| Huang (2000)VITAL | Huang HA, Maguire MG, Miller ER, Appel LJ. (2000) Impact of pill organizers and blister packs on adherence to pill taking in two vitamin supplement trials (VITAL). American Journal of Epidemiology; 152: 780–7. | Use of a pre-packed blister pack. |
| Simmons (2000) | Simmons D, Upjohn M, Gamble GD. (2000) Can medication packaging improve glycemic control and blood pressure in Type 2 diabetes? Diabetes Care; 23(2):153–6. | Calendar blister package prepared at one pharmacy marked with the days of the week and the time of dosage. |
| Winland-Brown (2000) | Winland-Brown JE, Valiante J. (2000) Effectiveness of different medication management on elders’ medication adherence. Outcomes Management for Nursing Practice; 4: 172–6. | The intervention group received a pillbox that was prefilled on a weekly basis. |
| Skaer (Hypertension) (1993a) | Skaer TL, Sclar DA, Markoski DJ, Won J. (1993). Effect of value-added utilities on prescription refill compliance and health care expenditures for hypertension. Journal of Human Hypertension; 7: 515–8. | The intervention group received standard pharmaceutical care and were provided unit-of-use packaging with each prescription refill request. |
| Skaer (NIDDM 1993b) | Skaer TL, Sclar DA, Markoski DJ, Won J. (1993) Effect of value-added utilities on prescription refill compliance and medicaid health care expenditures: a study of patients with non-insulin dependent diabetes mellitus. Journal of Clinical Pharmacy and Therapeutics; 18: 295–9. | The intervention group received standard pharmaceutical care and were provided unit-of-use packaging with each prescription refill request. |
| Becker (1986) | Becker LA, Glanz K, Sobel E,Mossey J, Zinn SL, Knott KA. (1986) A randomized trial of special packaging antihypertensive medications. Journal of Family Practice; 22(4):357–61. | Pillbox, foil-sealed. |

Appendix 4 presents a list of other primary studies of DAAs that were identified through the literature search and the reasons for their exclusion. Studies that examined the use of DAAs as part of a more comprehensive pharmacy care program or were part of a multifaceted pharmacy intervention were excluded. Studies that assessed self-packed multi-compartment aids or pill boxes and automated medication dispensing devices were also excluded. Other exclusions were applied to studies that assessed DAAs in a hospital setting or compliance aids used for patients with infectious diseases with a short duration of therapy.

## DAA utilisation analysis

Utilisation was calculated from the DAA claims payment data made by individual pharmacy, covering claims paid on dates between 5th January, 2012 and 26th May, 2016.

DAA claims payment data for 2015 have been analysed in the context of geographical factors that have been inferred from the postcode of each pharmacy. Those factors included are remoteness[[6]](#footnote-6) (see Table 7.2); overall population, chronic disease prevalence and proportion of population aged over 65 years by Primary Health Network (PHN) geographic areas. These factors were used to assess whether the growth in DAA services has occurred in line with the populations that the program is intended to target.

The claims payments administration system changed in March 2014. Before the change, payments to pharmacies were annotated with the ‘Pharmacy ASN’ identifier. After the change claims payments were annotated using the ‘Organisation Number’ identifier. Both identifying codes are used in Section 90 registers to identify individual pharmacies. These codes were used to assist in locating each pharmacy within its postcode.

Postcodes were mapped to remoteness using the Australian Bureau of Statistics (ABS) mapping table and to PHAs and PHN areas via Statistical Areas Level 2 (SA2), ABS Australian Statistical Geography Standard (ABS ASGS) 2011.

Key metrics in the analysis are limited to claims paid and the number of patients supplied with DAAs in the claim period (these metrics are recorded in the claims payment administration systems pre and post the system change). Claims paid and the volumes of patients supplied with DAAs are not closely related since the payment formula relates to volume at the level of individual pharmacies, as well as overall.

# Previous evaluations of the PPI Program

This Section summarises the findings of the 3CPA project that recommended subsidised funding of DAA services by community pharmacies, as well as two evaluations of the DAA initiative funded by the Commonwealth under the 4CPA and 5CPA. The intention of these summaries is to provide MSAC with an understanding of the approaches taken to evaluate the DAA initiative in Australia, as well as a high level overview of the findings of previous evaluations in relation to effectiveness and cost-effectiveness of the service.

## 3CPA DAA Project by University of Queensland 2006

Quality Medication Care Pty Ltd, in conjunction with the University of Queensland, evaluated the effectiveness and cost-effectiveness of DAAs in the community and residential care facility (RCF) settings. The project, which developed preliminary best practice models for both settings, was funded as part of the 3CPA between the Commonwealth and the Pharmacy Guild of Australia. The Phase 3 Final Report (May 2006) recommended that the preliminary best practice model for the community setting, and the findings of the evaluation, should be used to inform the development of, and implementation plan for a subsidised DAA service for community patients. Further, the 2006 Final Report recommended that the government supports the use of DAA services in the community where patients meet the appropriate access criteria and the service provided reflects best practice.

The project was composed of three phases:

* **Phase 1** (Final Report November 2004) involved a synthesis of the literature that expanded and updated an earlier review of the literature on DAAs (conducted by the University of South Australia in 1997), taking into account national and international literature published from 1997 to December 2002. Focus groups and structured interviews were also conducted with stakeholders in Phase 1 to identify key issues.
* **Phase 2** (Final Report November 2004) involved recruitment of pharmacies, residential care facilities and consumers, and the development of data collection instruments. Observation studies were conducted in the community and RCF settings. The goal of observation in the community setting was to examine what impact using a DAA has on the consumers’ lifestyle, and to observe the procedures (time and cost) involved for community pharmacy in supplying DAAs to domiciliary consumers.
* **Phase 3** (Final Report May 2006) involved the development of best practice models and tools to facilitate improvements in the way DAAs are used in the RCF and community settings. This was based on the DAA literature review (Phase 1); current practice and standards of DAA provision (Phase 2); views of stakeholders obtained through focus groups and structured interviews; consensus development panel techniques; consultation with the Therapeutic Goods Administration (TGA); and evaluation of the feasibility and impact of best practice models. The cost-effectiveness of DAAs was then again examined in the community setting by measuring and valuing the benefits to the health care system from a societal perspective.

Additional data on health service use subsidised by the Australian government were extracted from the (then) Health Insurance Commission (HIC) and the Department of Veterans Affairs (DVA) (although the latter was not received in time for analysis). Information on other health service use and benefits of using DAAs was collected by conducting a follow-up survey of Phase 2 community patient participants. To adjust for the inherent differences between DAA users and users of medication in their original packs (OP) arising from the non-random sampling, multivariate modelling of baseline characteristics was used.

### Conclusions relating to DAA use, patient satisfaction, and safety

The 2006 Final Report concluded that DAAs are effective in the community setting. DAA users in general exhibited a greater severity of illness, and:

* were more likely to live alone, more likely to have a carer, and more likely to make greater use of community health workers than non-DAA users;
* have lower scores for functionality on the Older Americans Resource and Services Instrumental Activities of Daily Living (OARS-IADL) scale;
* have more hospitalisations per year and fewer illnesses but the same number and type of medicines as non-DAA users.

DAAs appeared to have a positive impact on the satisfaction, medication management practices and the clinical status of the users. This conclusion was based upon the following findings:

* DAA users maintained a better continuity of medication supply (i.e. were less likely to run out of medication) and were less likely to hoard medications compared with non-DAA users.
* DAA users reported fewer adverse drug reactions compared with non-DAA users.
* DAA users were more likely to rate their medication management system as useful, easy and convenient.

### Cost of supplying DAAs

Table 4.1 presents a summary of the costs of OP and DAA provision for the various resource use categories. The measurement of these costs was based on a detailed content analysis of workflow observations from 83 pharmacists performed in Phase 2. The base case model presented in the report provided details of costs for 30 customers using an average of eight medicines per week. The total cost for the base case was estimated at $543.88 for customers using OPs, compared to $1,070.50 for customers using DAAs. This equates to $18.13 per customer for OPs and $35.75 per customer using DAAs, or an additional $17.62 per customer.

With the exception of the costs of dispensing, the costs incurred in all cost categories were greater for DAA customers than for OP customers. As expected, the cost of packing and checking DAAs was the key cost in providing DAAs to community customers, accounting for 67% of the total weekly cost difference in providing DAAs or OPs. For OP customers, the key cost driver was the actual cost of dispensing.

Table 4.1 Summary of DAA and OP costs

|  |  |  |  |
| --- | --- | --- | --- |
| **Resource use category** | **OP****Cost/week** | **DAA****Cost/week** | **Cost differencea** |
| Prescription management by pharmacy | $12.07 | $23.01 | $10.94 |
| Dispensing medication | $415.39 | $415.39 | $0.00 |
| Packing and checking costs | $0.00 | $354.86 | $354.86 |
| Delivery of medication | $15.42 | $86.93 | $71.51 |
| Counselling | $4.73 | $4.89 | $0.15 |
| Account management | $7.14 | $19.32 | $12.19 |
| Additional costs | $89.13 | $168.10 | $78.97 |
| **Total for 30 customers** | **$543.88** | **$1,072.50** | **$528.61** |
| **Total cost per customer** | **$18.13** | **$35.75** | **$17.62** |

Source: Phase 1 and 2 Final Report (2004), Table 9.14, p. 184; Phase 3 Final Report (2006), Table 9.1, p. 209

Abbreviations: DAA, Dose Administration Aid; OP, original pack

**a** Cost per week for DAA minus cost per week for OP.

Sensitivity analyses showed that the incremental cost of a DAA (the cost per DAA customer minus the cost per OP customer) ranged between $12.57 and $29.27 depending on variations in packing time, the type of pack used, who packs, and the level of additional services provided. For example, Dosetts were more expensive to prepare per customer per week ($29.27) than blister packs ($16.93) and automated packing ($17.48), due to longer packing times and the greater likelihood of the pharmacist doing the packing. Automated were more expensive than blister due to increased equipment costs that is likely to be offset with larger volume DAA supply. The cost difference between DAAs and OPs also varied depending on whether a packing and checking DAA service is provided ($12.57) or a full DAA service that includes prescription and account management, and delivery ($20.05).

The model was also sensitive to variations in the number of customers and/or number of medicines. When compared with the base model of 30 customers per week, and keeping the number of medicines constant (at eight medicines), providing DAAs to 10 customers costs $4.68 more per customer per week ($22.30 vs $17.62). The cost per DAA is minimised when a greater number of customers are using a smaller number of medicines (e.g. 120 customers using four medicines costs $13.57 per customer per week); conversely, higher costs per customer are likely when a pharmacy supplies a small number of customers using a large number of medicines (e.g. 10 customers using 12 medicines costs $25.40 per customer per week).

### Cost-effectiveness of DAA services

The Phase 2 Final Report (2004) concluded that “at present DAAs are not cost-effective in the community setting. This is largely because the provision of DAAs by pharmacy is a labour-intensive and costly exercise. Sensitivity analysis, however, suggests the potential for delivery of a cost-effective DAA service if the magnitude of the benefits and the efficiency of the service provision were greater. The collection of additional outcome and service use data, including follow-up of community patients who participated in the study may provide an alternative view on cost-effectiveness.” In the RCF setting the authors concluded that “the use of DAAs in the RCF setting is cost-effective. When the costs of providing medicines to residents using DAAs from the pharmacist and the RCF perspective are summed and compared with the costs for providing OPs, DAA are the lower cost alternative.” Subsequent to the 2004 Report, the Phase 3 work involved not only developing but implementing best practice models and tools to facilitate improvements in the way DAAs are used in the RCF and community settings and then undertaking a more sophisticated methodology to re-examine the cost-effectiveness of DAAs in the community setting.

Table 4.2 shows the results of the cost-effectiveness analysis (CEA) presented in the Phase 3 report, interpreted as the additional cost to prevent one adverse drug reaction (ADR) and to avoid one death using DAA, based on 30 community customers receiving DAA versus those receiving OPs over one year. The incremental cost effectiveness ratio (ICER) using the first outcome measure was estimated to be $9,163. The ICER/life year gained was estimated to be $16,362.

Of note, the rate of ADRs was lower in both Phase 2 and Phase 3 for the DAA sample compared to the OP group. In Phase 2, 48% and 33% of OP and DAA patients, respectively, suffered from an ADR (P =0.007). In Phase 3, the corresponding proportions were 32% and 22% (P =0.147). This apparent improvement is due in part to the greater proportion of ADR experienced by people who had exited the study by Phase 3.

Table 4.2 Results of cost-effectiveness analysis comparing 30 DAAs customers to 30 OP customers based on the frequency of ADRs and deaths avoided

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
| **Outcome measure** | **Percent of customers****achieving outcome** | **Number of customers achieving outcome** | **Total cost of alternatives** | **Cost/event avoided** |
| No ADR for OP | 68.2% | 20.5 | $28,281.93 | $9,162.65 |
| No ADR for DAA | 78.2% | 23.5 | $55,769.87 |  |
| **Difference** | -10% | 4.56 | $27,487.94 |  |
| Deaths/year OPs | 4.6% | 1.4 | $28,281.93 | $16,361.87 |
| Deaths/year DAAs | 10.2% | 3.1 | $55,769.87 |  |
| **Difference** | -5.6% | -1.7 | $27,487.94 |  |

Source: Phase 3 Final Report (2006), Table 9.6, p. 215

Abbreviations: ADR, adverse drug reaction; DAA, Dose Administration Aid; OP, original pack

### Cost-benefit analysis of DAAs based on decrease in ADRs

A cost-benefit analysis (CBA) was also undertaken to compare the cost of DAAs, and subsequent reduction in healthcare costs given the decrease in ADRs, with the benefits to consumers of using the DAAs (in terms of willingness-to-pay [WTP]).

Table 4.3 shows the costs to pharmacy of providing medicines in OPs and DAAs, the potential costs and consequences of OPs and DAAs, and the benefits of DAAs to consumers (WTP). Based on these values, the costs of providing DAAs to 30 community customers outweigh the benefits of DAAs by $13,291 per year or $443.03 per DAA customer. The model was most sensitive to variations in the cost of DAAs.

Table 4.3 Costs and benefits of DAAs and OPs, based on 30 customers

|  |  |  |
| --- | --- | --- |
|  | **Total cost of alternatives** | **Cost per customer** |
| **Cost to pharmacy (C)** |  |  |
| Total cost OP per yearTotal cost DAA per yearTotal cost OP-DAA | $28,281.93$55,769.87-$27,487.94 | $942.73$1,859.00-$916.26 |
| **Cost savings to healthcare system (B1)** |  |  |
| Cost ADR + consequence OPCost ADR + consequence DAACost ADR + consequence OP-DAA | $6,024.70$984.96$5,039.74 | $167.99 |
| **WTP (benefits to customer) (B2)** |  |  |
| WTP per week for DAA per personWTP per year for DAAN \* WTP/year | $5.87$305.24$9,157.20 | $305.24 |
| Costs (C) + costs savings (B1) + benefits (B2) | -$13,291.00 | -$443.03 |

Source: Phase 3 Final Report (2006), Table 9.7, p. 216

Abbreviations: ADR, adverse drug reaction; DAA, Dose Administration Aid; OP, original packaging; WTP, willingness-to-pay

### Financial impact of DAA services

A financial impact model was constructed based on patient data on resource use and outcomes collected in Phases 2 and 3, and health service use, Medical Benefits Schedule (MBS) and PBS data, as well as additional residential care and community care costs. This analysis must be interpreted in light of DAA customers in general exhibiting a greater severity of illness than OP customers.

Table 4.4 presents the results of the financial model. The cost per patient per year in the OP arm was $5,156 compared with $7,966 per patient using a DAA. Over a 12-month period, the DAA use strategy resulted in 0.7 fewer deaths but cost an additional $45,040 in health service and support costs. In this model, the cost of PBS drugs was the highest service cost for the OP arm of the model but residential care was the highest service cost for the DAA arm. The biggest difference between the two arms in costs for a single resource was also in residential care use, with the DAA arm estimated to cost 1.9 times more than the OP arm, reflecting the fact that 7.4% of DAA patients were admitted to a RCF compared with 3.8% of OP patients. Overall, 83% of the total difference in costs between the groups was accounted for by non-medical support (RCF care and community care).

Table 4.4 Financial impact of DAA use to OP with 30 patients in each arm

|  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- |
| **Arm** | **Event** | **Probability** | **No. of patients** | **Cost per patient** | **Total cost** |
| OP | PBS drugs | 100.0% | 30.0 | $2,089.54 | $62,686.20 |
|  | GP services | 100.0% | 30.0 | $504.51 | $15,135.30 |
|  | Pathology | 87.9% | 26.4 | $145.17 | $3,828.13 |
|  | Other MBS | 22.4% | 6.7 | $978.79 | $6,577.47 |
|  | MBS hospital | 24.1% | 7.2 | $1,117.19 | $8,077.28 |
|  | Community care | 47.1% | 14.1 | $2,098.95 | $29,658.19 |
|  | RCF admission | 3.8% | 1.1 | $25,178.35 | $28,703.32 |
|  | Death | 7.6% | 2.3 | - | - |
| **Total cost** |  |  |  |  | **$154,665.90** |
| DAA | PBS drugs | 100.0% | 30.0 | $2,423.46 | $72,703.80 |
|  | GP services | 98.5% | 29.6 | $510.10 | $15,073.46 |
|  | Pathology | 85.3% | 25.6 | $189.93 | $4,860.31 |
|  | Other MBS | 20.6% | 6.2 | $577.16 | $5,218.89 |
|  | MBS hospital | 23.5% | 7.1 | $844.48 | $5,953.58 |
|  | Community care | 58.9% | 17.7 | $2,263.74 | $40,000.22 |
|  | RCF admission | 7.4% | 2.2 | $25,178.35 | $55,895.94 |
|  | Death | 5.3% | 1.6 | - | - |
| **Total cost** |  |  |  |  | **$199,706.19** |

Source: Phase 3 Final Report (2006), Table 9.13, p. 222

Abbreviations: DAA, Dose Administration Aid; GP, general practitioner; OP, original pack; MBS, Medical Benefits Schedule; PBS, Pharmaceutical Benefits Scheme; RCF, residential care facility.

### Cost-benefit analysis of DAAs using health system data

A CBA was performed for patients living in the community, utilising a full range of health service use data extracted from HIC and patient data (collected in Phase 3 follow-up). This analysis must be interpreted in light of DAA customers in general exhibiting a greater severity of illness than OP customers. Table 4.5 shows the results of the analysis, with the costs of providing DAAs to 30 community customers outweighing the benefits of DAAs by $9,381 per year.

Table 4.5 Results of cost-benefit analysis utilising HIC data and patient outcomes

|  |  |  |
| --- | --- | --- |
| **Formula** | **Value** | **Perspective** |
| Total cost OP | $28,281.93 | to pharmacist |
| Total cost DAA | $55,769.87 | to pharmacist |
| Net cost of DAA | -$27,487.94 | to pharmacist |
| Total HIC and support costs OP | $103,839.96 | to healthcare system |
| Total HIC and support costs DAA | $94,890.33 | to healthcare system |
| Net HIC and support costs | $8,949.62 | to healthcare system |
| Willingness-to-pay for DAA | $9,157.20 | to patient |
| Net social benefit (or cost) | -$9,381.12 |  |

Source: Phase 3 Final Report (2006), Table 9.17, p. 225

Abbreviations: DAA, Dose Administration Aid; HIC, Health insurance commission; OP, original pack.

### Summary of main findings of the economic evaluation

The provision of DAAs by pharmacists is expected to cost $27,488 extra to supply DAAs to 30 community customers for one year, compared with supplying 30 community customers with OPs. The cost of DAA provision may be offset by some savings to the healthcare system due to the prevention of ADRs. A difference in the rate of ADRs and consequences in terms of service use translates to a potential saving for the DAA group of $5,040 in one year. However, consideration of a full range of service use (HIC and patient support services) failed to result in cost savings to offset the cost of DAA supply. The DAA group costs exceeded the OP group costs by over $45,040 in one year. DAAs were considered to have direct benefits to the customers using them that were measured through WTP. Community customers using DAAs were willing to pay a mean of $5.61 per DAA/per week in Phase 3 of the evaluation. This equates to a total of $8,752 per 30 customers per year. A closer investigation of costs and benefits to patients living in the community suggest a considerable reduction in additional costs of DAAs, a net social cost of $9,381 for 30 patients over 12 months.

Sensitivity analyses confirmed that costs associated with DAAs were considerably higher than benefits to the health care system where benefits are measured by patient WTP for a service for which they have been traditionally undercharged (pharmacies charged an average of $3.50/week in Phase 2 despite average costs to the pharmacy of $17.62/week).

The authors acknowledged a range of study limitation, including significant differences between the OP and DAA patient groups, patients lost to follow-up, lack of randomisation, and lack of baseline data to monitor improvements in health associated with using a DAA. DAA patients in this study were sicker, had higher health service utilisation rates and higher costs. From a quality use of medicine perspective, the fact that DAA patients were utilising health services more frequently than OP patients could suggest that DAA patients were more proactive in maintaining their health and were therefore more likely to frequent a health professional, or that better monitoring with appropriate action is taken. Other limitations included not using a health-related utility instrument (such as the EQ5D) at intermittent data collection intervals to enable change in health to be monitored.

## 4CPA DAA/PMP Evaluation by PricewaterhouseCoopers 2010

PricewaterhouseCoopers (PwC) was commissioned by the Department of Health to conduct an evaluation of the DAA/Patient Medication Profile (PMP) programs implemented by the Pharmacy Guild of Australia as part of the Research and Development program undertaken within the 3CPA (PwC 2010). The DAA program was implemented in two phases and was available to all Section 90 pharmacies in Australia:

* Phase 1: September 2007 to June 2009.
* Phase 2: July 2009 to June 2010.

The aim of the DAA program was to provide an opportunity for eligible patients to remain living effectively and confidently within their own homes, through better medication management from accessing a DAA service through their local community pharmacy. The DAA program aimed to reduce medication-related hospitalisation and adverse events through improving medication management and adherence for people in the community.

The PMP program, which also aimed to reduce the risk of medication-related adverse events, was also implemented in two phases: Phase 1 – April 2008 to June 2009; Phase 2 – July 2009 to June 2010. As such, many pharmacies offered both programs and many patients received multiple services, making it difficult to estimate the unique impact of DAAs or PMPs on costs and health outcomes.

The purpose of the 2010 evaluation was to review existing data and evidence for the DAA and PMP programs, to inform the potential patient and pharmacy benefits in providing these services to the Australian community, as well as inform any potential value of future government investment. The overall approach to the evaluation was one of program effectiveness evaluation, rather than an intervention efficacy approach. Due to the limitations of the DAA program data (including missing data, lack of comparable data across phases, limited data on health outcomes of patients, and lack of data to undertake a robust CBA), corroborative data from existing research, the PBS (for the purpose of describing medication use and the associated costs), and the admitted patient care National Minimum Data Set (NMDS) were used, with information on core subgroups extrapolated from one data set to another.

The admitted patient care NMDS was obtained for the purpose of providing an overview of medication-related incidents in the Australian hospital setting. The cohort of patients participating in the DAA program were referenced to the trends and outcomes on similar subgroups in the national data sets describing acute patient care and medications usage. However, a major limitation is that data on hospitalisations from the NMDS may not provide accurate measures of the incidence or prevalence of conditions because not all people with a type or degree of illness are treated in hospital and there are multiple admissions for some chronic conditions.

### Medication-related incidents in Australia

The evaluation found that in 2007/2008, there were 133,369 separations due to medication-related incidents. Approximately 45.0% of all medication-related admissions were for patients aged 65 or over, approximately 58.0% were female and the majority were assigned as emergency. The average length of stay (LOS) (including same-day separations) in hospitals for medication-related admissions was 8.3 days, which was substantially higher than LOS for all patient admissions (3.3 days). The contribution of medication-related adverse events to hospitalisations in Australia over the period 2009-2010 was estimated at $660 million. Australians aged 85 years and over were taking approximately 5.7 medications in March 2009, compared to 5.1 medications for those aged between 75 and 84 years.

The evaluation outlined a number of risk factors for non-adherence with medication, based on multiple sources of data (existing literature, DAA and PMP service data, admitted patient care data and PBS data). These included:

* individuals on five or more medicines;
* individuals aged 65 years and over;
* individuals who do not have access to social support or live alone;
* nature of the condition and complex medication regimens.

Patients bearing signs of cognitive/physical impairment (with the exception of psychiatric patients) are also more likely to display poor adherence with their medication regimen.

### Key findings relating to the DAA program

The evaluation found that in the absence of any specific patient eligibility criteria for participation, pharmacists were successful in targeting populations that are thought to be at risk of non-adherence with medication. Only 10% of patients who were recruited to these services were found to have no risk factors.

Table 4.6 summarises the main findings of the evaluation in relation to the DAA initiative.

Table 4.6 Main findings of the PwC 2010 evaluation-DAAs

|  |  |
| --- | --- |
| Domain | Key findings |
| Pharmacy results |  |
| Rates of completion of pharmacies in Phase 1 and Phase 2 of the DAA program | Retention of both pharmacies and patients was high in both Phase 1 and Phase 2 of the DAA program, with retention slightly higher in Phase 2 – approximately 82.0% of pharmacies and 79.0% of patients remained in the program at the end of April 2010.  |
| Characteristics of the pharmacies who participated in Phase 1 of the DAA program | A broad range of pharmacies participated in the DAA program. The distribution of participating pharmacies across State, PhARIA and SEIFA was representative of community pharmacies nationally, suggesting that there may be no ‘type’ of pharmacy which is more likely to opt-in to providing the DAA service. These results also suggest that the results from the DAA program are likely to be generalisable to pharmacies nationally. |
| Length of time pharmacies had been providing the DAA service | In Phase 1, very few pharmacies were new to providing the DAA service on entry to the program; approximately 99% reported that they had been providing the service for at least three months, with the vast majority having provided it for more than 24 months. Note: these data were not collected for Phase 2. |
| Provision frequency of DAAs | In Phase 1, the majority of pharmacies (75.5%) reported that they provide DAAs to their patients on a weekly basis, 18.6% on a fortnightly basis and 3.4% on a monthly basis. Note: these data were not collected for Phase 2. |
| Packaging brands used for DAAs | In both Phase 1 and Phase 2, Manrex Webstercare was the most commonly used brand and was used by nearly 60.0% of pharmacies, which was followed by QuickPAK for WiniFRED (approximately 13.0%). |
| Type of medicines packed in the DAA | In Phase 1, approximately 31.0% of pharmacies reported that they packed non-prescribed medications in the DAA, while the remaining 69.0% did not. |
| Other 4CPA services provided by the pharmacy | The majority of participating pharmacies in Phase 2 reported providing other 4CPA funded pharmacy services, with the most common being HMRs and PMPs. Note: these data were not collected in Phase 1. |
| Patient results |  |
| Rates of completion of patients in Phase 1 and Phase 2 of the DAA program | Approximately 75% and 79% of patients completed Phase 1 and Phase 2, respectively, of the DAA program. |
| Age and gender of participating DAA patients | In both phases, most participating patients were aged 55 years or older. For both phases, the largest proportion of participants were aged 75 to 84 years, and the 85 to 94 age category was the second most common. These older groups accounted for approximately half of the participants. Approximately 59.0% of patients were females. |
| Geographic characteristics of DAA patients | In both Phases, the majority of participating patients were from NSW, VIC and QLD. |
| Type of concession/entitlement card | The vast majority of participating patients had concession cards, with by far the most common being a pension card. |
| Availability of support for DAA patients with managing their medications | The majority of patients in the program received assistance with managing their medications and almost half of patients live alone. |
| Medical conditions prevalent in DAA patients | In Phase 2, the majority of patients had a cardiovascular (90%), nervous system (61%) or alimentary system (58%) condition. |
| Number and types of medications taken by DAA patients | For patients in both phases, multiple medications were common. In Phase 1, the majority were taking more than four medications, and in Phase 2, the majority were taking between three to six medications (76.0%). The most common medications amongst patients in the DAA program were blood pressure medication and lipid modifying agents. |
| Proportion of patients with risk factors | In Phase 2, approximately 64% of recruited patients had two or more risk factors (i.e. aged 65 and over, had 5 or more medications, and/or lived alone). Approximately 9% of patients had no risk factors. |
| Source of referral to the DAA service | In Phase 2, nearly 40.0% of referrals were from the GPs, and approximately 50.0% of referrals were from a pharmacist. |
| Medication-related events | Very few patients in Phase 1 reported any medication-related events (3.6%). Note: these data were not collected in Phase 2. |
| Period that patients was receiving the DAA service | In Phase 2, nearly 42% of the cohort had been receiving DAAs for more than 24 months, with <5% were new to the DAA service.  |
| Other 4CPA services received by patients | Just over half of patients were receiving one or more additional 4CPA services, with the majority receiving PMPs (42.8% in Phase 1 and 48.9% in Phase 2). |
| Reasons patients exit the DAA program | The patterns of exit and their reasons were similar in both Phase 1 and Phase 2.Approximately 9,044 patients exited the program across both phases. The most common reason for exit for both Phase 1 and Phase 2 was most commonly death (N=3,789 across both phases), or the patient moving. Exit to another care facility was relatively rare. |

Source: PwC (2010), p.42

Abbreviations: 4CPA, Fourth Community Pharmacy Agreement; DAA, Dose Administration Aid; HMR, Home Medicines Review; PhARIA, Pharmacy Access/Remoteness Index of Australia; PMP, Patient Medication Profiling; PwC, PricewaterhouseCoopers; SEIFA, Socio-Economic Indexes for Areas.

### Cost of the DAA service

In Phase 1, pharmacies reported on whether there was a charge for the DAA service in their pharmacy and how much that charge was. Approximately 93.0% of pharmacies reported that they charge for the DAA service. The majority of pharmacies (63.0%) charged less than $5.00 per DAA, while approximately 30.0% charged between $5.00 and $10.00. Very few pharmacies charged nothing (0.1%) or more than $10.00 (0.1%).

The cost of delivering DAA services was estimated using data collected in Phase 2. The average cost for a pharmacy to deliver a DAA service per patient/per week was estimated to be $17.25, based on the average number of hours per week spent by various pharmacy staff members in providing the DAA service to all community based patients (as self-reported by pharmacies).

The evaluation report noted that pharmacies with a low prescription volume had a tendency to provide DAAs to fewer patients whereas pharmacies with higher prescription volume had a tendency to provide DAAs to more patients. A test for independence showed that prescription volume and number of patients receiving the DAA service was significantly related to the amount charged to patients for the DAA service. Pharmacies that provided more DAA services (in a one week period) were consistently more likely to charge their patients less than pharmacies that provide fewer DAA services (in a one week period). There were no meaningful differences in the amount charged to patients for a DAA based on pharmacy location (remoteness).

### Impact on health outcomes

Data from the DAA program were insufficient to evaluate the impact of the service on health outcomes. The evaluation report claims that previous studies investigating the cost-effectiveness and cost-benefits of adherence strategies, such as DAAs and PMPs, have consistently found significant health improvements and cost savings that are attributable to relatively low-cost interventions delivered by health professionals. Two ‘case studies’ from the published literature are provided in the report as a framework for extrapolating the impact of improved adherence as a result of DAAs and PMPs, on hospitalisations, health care costs and mortality. The evaluation report also claims that increasing the adherence of medication regimens in the elderly population, through the DAA and PMP services, may contribute to the reduction of premature admission to RACFs; however, it is acknowledged that no known studies have been conducted that would allow for this extrapolation.

## 5CPA Program Combined Review by PricewaterhouseCoopers 2015

The DAA program was evaluated as part of the Review of the PPI Program performed by PwC in 2015. The overall aim of the Review was to better inform how the 5CPA Medication Management programs and services (including PPI Program and Medication Management Program) contribute to improving consumer health outcomes, in order to better inform future investment by the Australian Government in pharmacy programs and services. PwC evaluated the three priority areas in the PPI Program: CIs, DAAs and SS. The Review methodology involved an analysis of full program data in order to assess the uptake and volume of services delivered over the duration of the 5CPA (between 2011 and 2014), stakeholder consultations, consumer focus groups, practitioner focus groups, a practitioner survey and a consumer survey.

Table 4.7 summarises the main findings of the evaluation in relation to the DAA initiative. A total of 767 primary health care practitioners, with the majority being pharmacists (94%), responded to the practitioner survey. More than half (57%) were involved in the DAA program. Results of consumer surveys are not discussed as only 2% (10/502) of responders participated in the DAA program[[7]](#footnote-7), and thus results from the consumer surveys do not reflect consumers’ satisfaction with the DAA service.

Table 4.7 Main findings of the 2015 5CPA combined review, 2011-2014

|  |  |
| --- | --- |
| Measure/domain | Key findings |
| Program results |  |
| PPI participating pharmacies | Overall, a total of 6,216 pharmacies (with unique registration numbers) submitted claims for PPI services |
| DAA participating pharmacies and patients | 5,909 pharmacies submitted claims for DAAs delivered to 22,571,080 patientsa. |
| Total expenditure on PPI | $126,507,909 |
| Total expenditure on DAA initiative | $71,225,306 (56% of total funds allocated) |
| Total expenditure on SS initiative | $11,231,152 (9% of total funds allocated) |
| Total expenditure on CI initiative | $44,051,451 (35% of total funds allocated) |
| Practitioner focus group themes raised |  |
| Addressing consumer need | DAAs were seen as an essential part of medication management in RACFs by all participants involved in RMMRs. All participants commented that DAAs address medication adherence needs in the community and reduce medication misadventure. |
| Eligibility criteria and targeting | There were no specific marketing strategies or recruitment activities directed at those most in need of the 5CPA programs. |
| Program implementation | A multidisciplinary, collaborative approach to programs/services would aid in the implementation of the programs and benefit the impacts and outcomes for consumers. It was also suggested that funding should be allocated to support implementation to prevent inconsistencies in the way that programs are delivered. |
| Policy and strategy | Participants agreed that generally the 5CPA programs/services added value and should be part of the overall preventative strategy for consumers. |
| Practitioners/providers survey results |  |
| Interaction between programs | Less than half (42%) of total survey respondents agreed or strongly agreed that the linkages/pathways between the programs/services were clearly identified. More than half (60%) agreed that there were gaps in the services provided, resulting in unmet needs of the consumer. |
| Screening/diagnostic/intervention tools | DAA services were viewed as being purpose specific, with nonadherence the main reason for recommending a DAA (78%), followed by age/frailty (42%). |
| Provider satisfaction | The majority (77%) reported being satisfied with their involvement in DAA programs/ services. The majority (95%) reported being satisfied with the benefit their consumers receive through the DAA program. |
| Collaboration | There was very little collaboration between GPs and pharmacists for DAAs, apart from brief phone calls or faxes to confirm a prescription or dosage. |

Source: PricewaterhouseCoopers Combined Review of 5CPA Medication Management Programmes (2015)

Abbreviations: 5CPA, Fifth Community Pharmacy Agreement; DAA, Dose Administration Aid; GP, general practitioner; PPI, Pharmacy Practice Incentives; QUM, Quality Use of Medicines; RACF, residential aged care facility; RMMR, Residential Medication Management Review.

**a** This does not refer to individual consumers, as one consumer may have received multiple DAA services over the data collection period.

Note 1: PPI Program data were analysed using claims data. Claims for multiple DAA services may be submitted by one pharmacy on the same claim, generating the same claim ID for these two services.

Note 2: Consumer survey results are not representative as there were only ten DAA participants among survey respondents.

Overall, practitioners reported being reasonably satisfied with their involvement in the Medication Management programs and services. They also reported being satisfied with the benefit their consumers received through Medication Management programs and services, and they saw clear benefit in the suite of Medication Management programs and services as contributing towards improving the health outcomes of consumers.

However, stakeholders and practitioners indicated that 5CPA programs were difficult to access for consumers due to low consumer awareness, information on programs not being readily available to consumers, and low GP engagement and awareness to refer consumers to the relevant programs, particularly for ATSI and culturally and linguistically diverse (CALD) peoples.

There were a number of limitations relevant to program data analysis. These included:

* Data collected as part of the claims process provided limited insight on uptake and volume of programs and services since multiple services could be submitted under one claim. The authors presented service level data where possible, merging accepted, rejected and claims datasets to conduct more accurate analyses.
* Consumer level data was de-identified and not linked to other data sources (e.g. Medicare and hospital data); therefore, it was not possible to determine the impact of participating in specific programs on consumer outcomes, outside of that particular episode of care.
* Consumer demographic data, such as age and gender, was not available for any of the PPI Program initiatives, including DAA. Postcode was not captured at the consumer level within any program/service dataset, therefore analysis of the data could not be performed for socioeconomic indicator (SEIFA) or remoteness (ARIA).
* The number of medicines and health conditions of consumers was not captured in the PPI Program dataset, resulting in the inability to analyse trends over time and potential investment value, including impact, for other programs and services.
* Analysis of program data beyond 28th February 2014 was not performed, resulting in failure to capture the effects of administrative changes to programs and services implemented on 1st March 2014 on the uptake and volume of programs and services.

A CBA was not performed in this Review, thus direct and indirect benefits resulting from delivering medication management programs, such as the PPI Program, could not be inferred. The authors recommended that a baseline benefits analysis be conducted in a future review of the Program to inform the health, social and economic benefits that result from these program implemented as part of the 6CPA and evaluate the cost-benefits as a result of the 6CPA investment. A reliable CBA would require a more sophisticated approach towards collection of data, linking program data (multiple datasets, including at consumer level) combined with regular auditing and reporting requirements to enable consumer health outcomes to be more effectively monitored and measured over time.

# Published evidence relating to effectiveness and safety

This Section presents the evidence identified in the systematic literature review relating to the effectiveness and safety of DAAs in relation to the research questions and the PICO criteria outlined in Section 3.1.1. None of the included studies assessed the impact of an incentive payment to pharmacists for the provision of DAAs to community patients.

This section does not include evidence reported in previous evaluations of the PPI Program DAA incentive, which was summarised in Section 0.

## Evidence from systematic reviews

Table 5.1 presents a summary of the characteristics and quality of the three included systematic reviews, one of which was a Cochrane review (Mahtani et al, 2011). Table 5.2 summarises the overlap in included studies between systematic reviews. The most comprehensive systematic review was Boeni et al (2014).

The three systematic reviews included studies that evaluated DAAs in the form of a multipunch drug card, reminder blister pack, or reminder packaging. These interventions are in accordance with the DAAs service guidelines and standards for pharmacists (PSA, 2007), where DAA is described to be either in the form of a unit-dose packing, where the dose (single or multiple units) of a single type of medicine is packed in each compartment, blister or pouch pack; or a multi-dose packing (where doses of more than one medicine can be packed in one compartment, blister or pouch pack).

However, as mentioned in Section 3.1.4, the systematic reviews also included studies that evaluated DAAs as part of a comprehensive pharmacy care program that included patient education, pharmacist’s follow-up, and refill reminders. For example, the RCT by Valenstein et al (2009), which was discussed in both the Boeni et al (2014) and Zedler et al (2011) systematic reviews, evaluated the Meds-Help pharmacy-based intervention in patients with serious mental illness. The FAME study by Lee et al (2006) evaluated a pharmacy care program in community-based patients aged ≥65 years, who received standardised education, regular follow-up and multidrug punch cards covering at least four chronic medications.

The inclusion of studies that evaluated a combination of adherence-aimed interventions confounds the findings for DAAs. For this reason, studies that examined DAAs independent of other adherence enhancing programs were specifically selected and discussed individually in Section 5.2. However, as the systematic reviews included some relevant studies, a brief summary of each review is presented below.

Table 5.1 Summary of the included systematic reviews

|  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- |
| Study ID*Qualitya* | Search date | No. of studies | Population | DAA intervention | Medical conditions (No. of studies) | Outcome measures | Authors’ conclusions |
| Boeni (2014)*5/10* | Up until September 2013 | 30 (10 RCTs, 19 controlled clinical trials, 1 cohort study) | Patients taking one or more oral medication (prescribed or over-the-counter) without the assistance of a health-care professional | Drug reminder packagingb in any adherence-enhancing program (*7 RCTs*)* reusable multi-compartment adherence aids (plastic pillboxes with several compartments per day or per week filled by the patient or pharmacy staff)
* non-reusable multidrug punch cards (frame cards with plastic cavities, sealed with a foil backing, with typically 28 compartments, filled by pharmacy staff, by a specialised company or an automated system)
 | * hypertension (7)
* diabetes type 2 (3)
* geriatric conditions (3)
* HIV infection (2)
* *H. Pylori (2)*
* vitamin supplementation (2)
* chronic mental illness (2)
* hypercholesterolemia (1)
* epilepsy (1)
* pain relief in cancer patients (1)
* anticoagulation (1)
* chlamydia infection (1)
 | * adherence to medication (pill count
* patient self-report
* refill data
* therapeutic drug monitoring
* appointment keeping
* clinical measures (e.g. BP, glycated haemoglobin, psychiatric symptoms, LDL-C, pain reduction, number of seizures, viral load, CD4 cell count, hospitalisations, etc.)
* cost-effectiveness
* humanistic outcomes
* safety
 | Evidence from the included studies showed a positive effect of drug reminder packaging on adherence and clinical outcomes. However, poor reporting and important gaps like missing humanistic and economic outcomes and neglected safety issues limit the drawing of firm conclusions.  |
| Mahtani (2011)*10/11* | Up until September 2010 | 12 RCTs | Patients at any age taking medication (prescribed or over-the-counter) without the assistance of a health-care professional | Medication that was packaged by a pharmacist or a manufacturing company and in any setting:* Reminder packaging aidsc both pre-packed into blister packs (calendar blister, unit dose, monitored dosage system) and those packaged in pill boxes (multi-compartment compliance aid, DAAd) (*6 relevant studies*)
* Other reminders separate to the intervention (electronic via email, SMS) were excluded
 | * hypertension (5)
* non-insulin dependent diabetes (3)
* chronic mental illness (1)
* elderly people with multiple medical conditions (1)
* people with low literacy skills and chronic medical conditions (1)
* allergies (1)
* healthy adults (1)
 | * adherence to medication (number of pills taken and/or self-reported)
* health outcomes (BP, change in glycated haemoglobin, serum vitamin C and E levels, and psychological symptoms)
* clinical outcomes (hospitalisation rates and/or readmission rates)
* cost
* reduction in adverse drug events
* patient satisfaction
 | Reminder packing may represent a simple method for improving adherence for patients with selected conditions. However, there was a lack of evidence for the use of reminder packaging in the elderly population, and nine of the 12 included studies were undertaken in North America, therefore caution is warranted in generalising the results of this review to other settings. Further research is warranted to improve the design and targeting of these devices. |
| Zedler (2011)*5/10* | Up until September 2010 | 10 RCTs | Community dwelling adult patients aged ≥18 years old who took daily medication for any duration longer than one month | Medication packaged in blister packaging or a pill organiser that incorporated a reminder system for the day of the week as part of the packaging (*6 RCTs*).  | * hypertension (4)
* type 2 diabetes (1)
* epilepsy (1)
* serious mental illness (2)
* elderly people with multiple medical conditions (1)
* vitamin prophylaxis (1)
 | * adherence to medication (number of pills taken, number of missed doses, or pills taken as a percentage of the total number prescribed and dispensed) and prescription refill rates or blood concentrations of anticonvulsants
* clinical outcomes (BP, change in glycated haemoglobin, seizures and psychiatric symptoms, well-being and satisfaction scales,

and health care resource utilisation and associated costs) | Calendar packaging, especially in combination with education and other reminder strategies, may improve medication adherence. Methodological limitations preclude definitive conclusions about the effect size of adherence and clinical benefits or harms associated with CBP and CPO. High-quality trials of adequate size and duration are needed to assess the clinical effectiveness of such interventions. |

Abbreviations: BP, blood pressure; CBP, calendar blister package; CPO, calendar pill organiser; DAA, dose administration aid; HIV, human immunodeficiency virus; LDL, low density lipoprotein; RCT, randomised controlled trial.

**a** Quality was assessed using the AMSTAR (see Appendix 6)

**b** These included reusable multi-compartment adherence aids (plastic pillboxes with several compartments per day or per week filled by the patient or pharmacy staff), non-reusable multidrug punch cards (frame cards with plastic cavities, sealed with a foil backing, with typically 28 compartments, filled by pharmacy staff, by a specialised company or an automated system) and non-reusable unit-of-use packaging (e.g. blister pouches attached to form flexible chains, with an unrestricted number of separated daily dosing times, filled by automated systems)

**c** Reminder packaging refers to any assembly of medication/s, such as a pill box, blister pack, bottle or single-use container that physically incorporates a system for the day and/or time when the medication/s are to be taken. Reminder packaging falls into two distinct categories: those that are pre-packaged into blister packs (calendar blister, unit dose, monitored dosage system) or those that are packaged in pill boxes (multi-compartment compliance aid, dose administration aid). According to the Cochrane review, DAAs “are divided into days of the week. Each day of the week has a sliding lid, which covers compartments for different dosing times (usually four compartments for each day). They are commonly but not exclusively used for multiple medications. Examples of these are Dosett®, Medidos® and the Mediset”.

**d** A DAA was defined as “plastic trays or boxes that hold seven days of a patient’s medicine and are divided into days of the week. Each day of the week has a sliding lid, which covers compartments for different dosing times (usually four compartments for each day).”

Table 5.2 Studies included in the three systematic reviews

|  |  |  |  |
| --- | --- | --- | --- |
| Primary studies included in the included systematic reviews | Boeni (2014) | Mahtani (2011) | Zedler (2011) |
| Ascione (1984) | √ | Not identified | - |
| Azrin (1998) | √ | √ | √ |
| **Becker (1986)** | **√** | **√** | **√** |
| Binstock (1988) | √ | √ | - |
| Crome (1980) | √ | Excluded | - |
| Crome (1982) | √ | Excluded | - |
| Eshelman (1976) | √ | Excluded | - |
| Fairley (2003) | √ | Excluded | - |
| Henry (1999) | √ | Excluded | - |
| Huang TRACE (2000) | √ | √ | √ |
| **Huang VITAL (2000)** | **√** | **Excluded** | **√** |
| Jansen (2009) | - | √ | - |
| Kripalani (2007) | - | √ | - |
| Lee JK (2006) | √ | Not identified | √ |
| Lee M (1999) | √ | Excluded | - |
| MacDonald (1977) | √ | Excluded | - |
| Maier (2006) |  | Not identified | - |
| McPherson-Baker (2000) | √ | Not identified | - |
| Miaskowski (2004) | √ | Not identified | - |
| Murray (1993) | √ | Excluded | - |
| Nochowitz (2009) | √ | Not identified | - |
| Park (1992) | √ | Not identified | - |
| Peterson (1984) | √ | Excluded | √ |
| Rheder (1980) | √ | Excluded | √ |
| **Schneider (2008)** | **√** | **√** | **√** |
| **Simmons (2000)** | **√** | **√** | **√** |
| **Skaer (NIDDM, 1993b)** | **√** | **√** | **√** |
| **Skaer (Hypertension, 1993a)** | **√** | **√** | **√** |
| Solomon (1988) | √ | Not identified | - |
| Suppapitiporn (2005) | - | √ | - |
| Valenstein (2009) | √ | Not identified | √ |
| Ware (1991) | √ | Excluded | - |
| **Winland-Brown (2000)** | **√** | **√** | **√** |
| **Total** | **30** | **12** | **10** |

Abbreviations: NIDDM, noninsulin-dependent diabetes mellitus.

Note: Studies shown in bold include interventions that are relevant to the current review.

The systematic review by Boeni et al (2014) analysed the effect of drug reminder packaging on medication adherence, as well as clinical and economic outcomes. The objectives of this review were similar to the Cochrane review published in 2011 by Mahtani et al, but included a broader approach and included all study designs with a controlled setting, studies on short- and long-term therapies, on reminder packaging aids used alone or in combination with adherence enhancing programs, and without restriction to follow-up. Boeni (2014) included 30 studies: 10 RCTs, 19 controlled clinical trials, and 1 cohort study. Twenty-seven studies reported adherence, 17 studies reported clinical outcomes, and two studies reported humanistic outcomes. Only two studies reported economic outcomes; however, economic evaluation of the time-intensive process of repackaging medication was not performed. Only five studies were graded as methodologically strong. Quantitative data pooling was not performed because of marked heterogeneity among the identified studies in patient populations, medical conditions, calendar packaging specifications, and measures of adherence and clinical outcomes.

Evidence from methodologically strong studies showed that drug reminder packaging had a significant effect on adherence in a geriatric population (one study), for chronic mental illness (one study), and for cardiovascular disease (one study). Of two studies reporting hospital admissions (both methodologically weak), only one study showed that drug reminder packaging significantly reduced the mean hospitalisation rate.

The authors warned that the overall methodological quality of the included studies was poor and the reporting was incomplete, thus the overall effect of drug reminder packaging on adherence parameters remains inconclusive. Another concern was that some studies showed that while there was a significant improvement in adherence, this was not necessarily accompanied by clinically meaningful improvements in clinical outcomes. This raises the question as to how much adherence is necessary for altering treatment success and achieving clinical benefits for patients. The authors identified major research gaps in relation to economics, disease-unspecific clinical outcomes (such as hospitalisation) and humanistic outcomes. Safety issues and satisfaction with the intervention were marginally reported.

The Cochrane review by Mahtani et al (2011) examined the effects of reminder packaging aids on adherence and other outcomes. It included 12 RCTs published between 1986 and 2009, involving 1,196 participants taking self-administered medications for at least one month. Most of the studies included in the review were small and of low-to-moderate quality. The studies involved various prescription or over-the-counter medications for chronic health conditions, and several types of packaging. Patients in the studies included people with hypertension, diabetes, chronic mental illness or allergies. Some of the studies focused on specific populations such as healthy adults taking vitamin supplements, senior citizens with multiple medical conditions, and people with chronic medical conditions and low literacy skills. In most studies, the reminder packages consisted of prefilled pill boxes or foil-backed blister packaging. The review excluded studies involving reminder technology, such as packaging that transmits a wireless message when a dose is missed. Meta-analysis was performed for some of the outcomes; however, the meta-analyses included studies where DAAs were used in combination with a refill reminder. Only two of the included studies were judged to be of between adequate and high quality.

Four studies provided data on pill counts (pre-packed and self-packed) that showed an 11% mean increase in the percentage of pills taken, with 72% of the effect from two studies (four arms) in which the reminder packaging was prepared by a pharmacist. Combined analysis of data from two trials focusing on hypertension found that reminder packaging significantly improved diastolic blood pressure, however systolic pressure remained unchanged. The remaining studies were either of poor quality or showed no significant difference between people who received reminder packaging and those who did not. Further, due to a lack of consistent information on patient satisfaction, barriers to use, difficulties with using reminder devices, and costs to health services and consumers, the authors refrained from drawing any firm conclusions about the effects of reminder packaging on these outcomes.

The authors commented that the effects of reminder packs on adherence appears to be somewhat larger than the effects of reminder packs on clinical outcomes. This is to be expected; modest amounts of non-adherence may still leave patients within a therapeutic window, and hence proportional gains in compliance are likely to be more than the proportional gains in clinical outcomes. Even if pill counts are improved, they may have no effect on clinical outcomes. A patient must surpass the therapeutic threshold for clinically important differences in outcomes to occur. The authors concluded that there is some evidence to suggest that reminder packaging may improve clinical outcomes such as blood pressure in hypertensive patients, and that the use of appropriately designed reminder packaging may be preferred by individuals with low literacy levels. Due to the paucity of high-quality trials, further research is warranted to improve the design and targeting of these devices.

The systematic review by Zedler et al (2011) assessed the evidence of the adherence benefits and harms of calendar blister packaging and calendar pill organisers for self-administered long-term medication use. The review included 10 RCTs (492 subjects) published between 1980 and 2009, that compared calendar blister packaging or calendar pill organisers versus control receiving standard vial of loose pills. Included participants were community patients (aged ≥18 years old) taking daily medication for any duration longer than one month for hypertension, type 2 diabetes, epilepsy, serious mental illness or vitamin prophylaxis. Calendar pill organisers had to incorporate a reminder system for day of week as part of packaging. This review also included studies with concomitant interventions given alongside calendar blister packaging or calendar pill organisers such as education, mailed refill reminders, phone calls if missed refill and customised dosing schedule.

The quality of the included trials, as evaluated by the Jadad scale, was very poor to moderate. Trial sample size ranged from 13 to 89 patients, and study duration ranged from two to 12 months. Quantitative data pooling was not performed because of marked heterogeneity among the identified studies in patient populations, medical conditions, calendar packaging specifications, and measures of adherence and clinical outcomes. A narrative synthesis was presented with trials grouped by outcomes.

The review revealed that when compared with control, six out of eight included studies had positive adherence outcomes and only one out of nine studies had positive clinical outcomes. None of the trials provided suitable data to evaluate harms. The authors concluded that calendar reminder packaging, especially in combination with education and other reminder strategies, may improve medication adherence. However, almost all of the included studies had important methodological flaws such as insufficient information provided in the published study reports about key quality criteria, including randomisation, blinding, withdrawals and drop-outs, and statistical handling of missing data, all of which limited the validity of the results and precluded conclusions about effect sizes and clinical benefits or harms.

**Summary of findings**: *The identified systematic reviews did not draw firm conclusions in favour of any particular intervention aimed at improving adherence to medication. The published literature on medication adherence interventions is relatively small and heterogeneous. The authors of the reviews reflected on the poor methodological quality of the studies and the inadequacies in terms of reporting of results and missing information, leading to a high risk of bias. Very few studies report explicitly on the effectiveness of DAAs among the other frequent pharmacy interventions aimed at improving adherence, making it difficult to draw clear conclusions.*

## Evidence from primary studies

Nine studies published between 1986 and 2016 were identified for inclusion. The studies were mixed in design and included seven RCTs, one prospective cohort study, and one retrospective matched cohort study. One study was conducted in New Zealand, one in Canada, and the remaining seven studies were conducted in North America.

There were no Australian studies identified that evaluated the use of DAA on medication adherence or other health-related outcomes. However, the University of Queensland undertook an RCT designed to identify patients with poor medication-taking behaviour. A further aim of this study was to implement personalised interventions (including DAAs) to improve medication-taking behaviour. The trial has been completed, with improvement shown in medication adherence. A publication is expected during 2016 (personal communication, Cottrell, 2016).

The characteristics and results of the nine identified studies are presented in Table 5.3 and Table 5.4, respectively. Five studies assessed DAAs or similar compliance aids in people taking medications for hypertension (Dupclay, 2012; Schneider, 2008; Simmons, 2000; Skaer, 1993a; Becker, 1986), two studies were in people taking medications for diabetes (Simmons, 2000; Skaer, 1993b), one study was in elderly patients with multiple medical conditions (Winland-Brown, 2000), one study was in patients taking warfarin to prevent thromboembolic events (Dumas, 2016), and one study was in healthy elderly patients taking vitamin supplements (Huang, 2000). There were no studies that were specifically conducted in patients with cognitive or physical impairment or with chronic mental illness. None of the included studies reported results for patients taking only one medications compared with those concurrently using multiple medications (polypharmacy).

The two most recent studies, by Dumas et al (2016) and Dupclay et al (2012), were not included in the systematic reviews discussed in Section 5.1.

Table 5.3 Characteristics of the included studies

|  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- |
| Study IDCountry | Study design, duration and qualityf | Condition treated | Study medication | Population | Intervention | Control | Outcomes |
| Dumas (2016)Canada | Prospective cohort study (N=1069)12 months*Poor quality* | Prevention of thromboembolic events | Warfarin | Patients aged ≥18 years old who started warfarin, primarily due to a diagnosis of atrial fibrillation, mechanical valve replacement, or mitral stenosis | N=112aPillbox, packed by a pharmacist, consisting of compartments that correspond to a day or a period of the day. | N=382aNo pillboxN=354aSelf-prepared pillbox | Clinical outcomes (3, 6, 9, 12 mo):* TTR <60%b
* INR instability
 |
| Dupclay (2012)US | Retrospective matched cohort study (N=9266)11 months*Poor quality* | Hypertension | Valsartan-hydrochlorothiazide combination tablets | Patients ≥18 years old with at least two hypertension prescriptions | N=4633Monthly blister pack  | N=4633No reminder packaging | Adherence outcomesc:* MPR
* time to refill
* proportion of days covered
* time to discontinuation
 |
| Schneider (2008)US | Multicentre RCT (N=85)12 months*Fair quality* | Hypertension | Lisinopril | Patients aged ≥65 years, treated with lisinopril for hypertension | N=47Daily-dose adherence blister package (Pill Calendard) in four rows of seven tablets, pharmacy-filled | N=38Standard medicine vials | Adherence outcomes:* MPR
* self-report

Clinical outcomes (6, 12 mo):* dBP
* sBP
* absolute change in BP
 |
| Huang (VITAL) (2000) US | RCT (N=297)2 months*Fair quality* | Disease prevention | Vitamin E | Healthy subjects using antioxidant vitamin supplements | N=149Blister pack | N=148Pill organiser | Adherence outcomes: * pill count
* serum vitamin level
* self-report
 |
| Simmons (2000)New Zealand | RCT (N=68)8 months*Good quality* | Poorly controlled diabetes | Antidiabetic and antihypertensive medication | Diabetic patients with poorly controlled blood glucose levels, half of which were prescribed three or more medications per day | N=36Calendar blister package prepared at one pharmacy, marked with the days of the week and the time of dosage | N=32Original packaging | Clinical outcomes (4, 8 mo):* dBP
* sBP
* HbA1C

Humanistic outcome:* usability
 |
| Winland-Brown (2000)US | RCT (N=61)6 months*Poor quality* | Any chronic condition with medication mismanagement | Any long-term medication | Elderly patients who had a mismanagement episode, and were hospitalised for medication non-adherence or an illness in which therapeutic accuracy was necessary for its management | N=16Pillbox, pharmacy-filled on weekly basis, marked with the days of the week in which individual doses were stored. | N=21Standard medicine vial | Adherence outcomes:* pill count (missed doses)

Health care resource use:* hospital admissions
* home health visits
 |
| Skaer (1993a)US | RCT (N=304)12 months*Poor quality* | Hypertension | Verapamil | Medicaid beneficiaries <65 years old with untreated hypertension, prescribed calcium channel antagonist verapamil once daily | N=85Unit-of-use packaging, pharmacy-filled  | N=78Standard medicine vial | Adherence outcome:* MPR e

Health care resource use: * costs of prescriptions, lab, physician visits, hospitalisations
 |
| Skaer (NIDDM) (1993b)US | RCT (N=258)12 months*Poor quality* | Type 2 diabetes | Glyburide | Medicaid beneficiaries <65 years old prescribed sulfonylurea glyburide twice daily for Type 2 diabetes | N=53Unit-of-use packaging, pharmacy-filled | N=78Standard medicine vial | Adherence outcome: * MPRe

Health care resource use: * costs of prescriptions, lab, physician visits, hospitalisations
 |
| Becker (1986)US | RCT (N=180)12 months*Poor quality* | Poorly controlled diastolic hypertension | Any anti-hypertensive | Patients with poorly controlled diastolic hypertension (elevated BP >90 mmHg) | N=86Foil-backed blister packaging with 28 doses of medication marked with the days of the week | N=94Standard medicine vial | Adherence outcomes:* pill count
* self-report

Clinical outcome: * dBP
 |

Abbreviations: BP, blood pressure; d, day/s; dBP, diastolic blood pressure; HBA1c, glycated haemoglobin; INR, international normalised ratio;  mo, month/s; MPR, medication possession ratio; nd, not disclosed; NIDDM, non-insulin dependent diabetes mellitus; RCT, randomised controlled trial; sBP, systolic blood pressure; TTR, time in therapeutic range; US, United States; VITAL, Vitamins, Teachers, and Longevity. a TTR <60% was calculated using linear interpolation between available INR measures for each of the follow-up periods (3-6, 6-9, and 9-12 months).

**a** In this observational study, the number of patients reflects the 9- to 12-month time point. The publication does not report the number in each group at baseline.

**b** TTR <60% was calculated using linear interpolation between available INR measures for each of the follow-up periods (3-6, 6-9, and 9-12 months).

**c** MPR was calculated as the ratio of days’ supply of medication to total number of days between the first and last prescriptions. Proportion of days covered was calculated as the ratio of days’ supply of medication to total number of days in the follow-up period (11 months). Time to discontinuation (or patient length of therapy) measured continuous treatment without prolonged gaps in therapy. Patients were deemed to have discontinued therapy when more than 30 days had elapsed without a prescription refill. The mean time to refill measured the time between successive refills or relevant medications using all prescriptions within the defined analysis period.

**d** The Pill Calendar is a single card that does not allow separation of individual doses, and it therefore provides an ongoing visual record of doses taken or missed.

**e** MPR was calculated as the number of days’ supply of medication obtained over 360 days of the trial.

**f.** **Quality assessment** was undertaken for the purposes of this review and is presented in Appendix 6.

Table 5.4 Summary of results of the included studies

|  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- |
| Study IDCountry | Study design, duration and quality | Population | Relevant comparison | Effect | Authors’ conclusions |
| Dumas (2016)Canada | Prospective cohort study12 months*Poor quality* | Patients ≥18 years old starting warfarin | Pillbox packed by a pharmacist vs control (pillbox non users) | Clinical outcomes* TTR <60% at 3-6 mo 36.6% vs 30.4%
* TTR <60% at 6-9 mo: 24.1% vs 27.4%
* TTR <60% at 9-12 mo: 27.9% vs 28.5%
 | Pillbox use was not associated with TTR < 60% or a specific INR instability pattern. The impact of self-prepared pillbox use was greater among younger patients, but results were not clinically significant. |
| Dupclay (2012)US | Retrospective matched cohort study11 months*Poor quality* | Patients ≥18 years old with hypertension  | Monthly blister pack vs control (no reminder packaging) | Adherence * MPR: 80% vs 73%, P<0.001
* Proportion of days covered: 76% vs 63%, P<0.001
* Refill timing: 10 d vs 16 d, P<0.001
* Time to discontinuation: 196 d vs 174 d, P<0.001
 | Patients who used reminder packaging (RP) were more adherent and persistent with their treatment regimens and had a lower refill time than patients without RP.A higher proportion of RP patients remained on therapy compared with non-RP patients, with patients in the RP group being 17% less likely to discontinue therapy compared with patients in the non-RP group. |
| Schneider (2008)US  | Multicentre RCT12 months*Fair quality* | Patients aged ≥65 years with hypertension | Multidrug punch card-blister pack (Pill Calender) vs control (traditional medicine bottles) | Adherence * MPR: 0.93 vs 0.87 (P =0.039)
* Patients with their prescription refilled on-time (± 5 d): 80.4% vs 66.1% (P =0.012)

Clinical outcomes* dBP at 6 mo: 73.2 vs 77.7 (P =0.0367)
* dBP at 12 mo: n.s.
* No. of patients with decreased dBP at 12 mo: 12 vs 4 (P =0.031)
* sBP at 6 and 12 mo: n.s.
* Absolute change in BP: n.s.
 | The daily-dose blister pack (Pill Calender) improved treatment regimen adherence and treatment outcomes (e.g. improved BP values) in elderly patients. |
| Huang (VITAL) (2000) US | RCT2 months*Fair quality* | Healthy subjects using vitamin E supplements | Multidrug punch card-blister pack vsmulticompartment adherence aid | Adherence* Patients who took >90% of pills: 93% vs 87% (P =0.05)
* Serum vitamin levels: n.s.
* Self-report total score: n.s
* Positive answer to question ‘forgot to take pills’: 21 % vs 31 % (P =0.05)
 | When compared to pill organisers, the use of blister packs improved adherence as measured by pill counts (and not by serum vitamin levels) among those with lower adherence.  |
| Simmons (2000)New Zealand | RCT8 months*Good quality* | Patients with poorly controlled diabetes | Multi-drug punch card-calender blister pack vs control (usual medicine containers) | Clinical outcomes at 4 and 8 mo (blister pack vs control)* dBP at 8 mo: -5.8 mmHg vs 0.1 mmHg (P < 0.001)
* sBP at 8 mo: n.s.
* HbA1C: -0.95% vs -0.15% (P =0.026)
* Usability: 77% vs 27% (P < 0.001)
 | Calendar blister packs should be considered among diabetic patients with poor glycaemic control receiving multiple medications. |
| Winland-Brown (2000)US | RCT6 months*Poor quality* | Elderly patients who had were hospitalised due to a medicine mismanagement episode | Prefilled pillbox vs control (standard medicine vials) | Adherence* Pill count: n.s.

Health care resource use* Hospital admissions: 7 vs 4
* Home visits: 0 vs 0
* Mean (per patient) physician visits: 1.5 vs 1.5
* Transition to higher level of care: NR
 | Participants who self-administered their own medications had more frequent physician office visits and increased hospitalisations. |
| Skaer (Hypertension) (1993a)US | RCT12 months*Poor quality* | Patients <65 years old prescribed verapamil for untreated hypertension | Unit-of-use packaging with standard pharmaceutical care vs control (standard pharmaceutical care with standard medicine vial) | Adherence* MPR: 0.67 vs 0.56 (P ≤0.05)
 | The use of a unit-of-use reminder packaging (alone or in combination with a refill reminder) significantly increased the MPR for anti-hypertensive therapy relative to controls. |
| Skaer (NIDDM) (1993b)US | RCT12 months*Poor quality* | Patients <65 years old prescribed sulfonylurea glyburide for diabetes | Unit-of-use packaging) with standard pharmaceutical care vs control (standard pharmaceutical care with standard medicine vial) | Adherence* MPR: 0.71 vs 0.58 (P ≤0.05)
 | Unit-of-use packaging alone or in combination with refill reminders, significantly increased the MPR for sulfonylurea therapy relative to controls. |
| Becker (1985)US | RCT12 months*Poor quality* | Patients with poorly controlled diastolic hypertension | Drug reminder packaging:multidrug punch card | Adherence:* Pill count: n.s.
* Self-report: n.s.

Clinical outcomes:* dBP: n.s.
 | There was no significant improvement in compliance with special packaging of anti-hypertensive medications. |

Abbreviations: 13C-urea breath test; (s, d)BP, (systolic, diastolic) blood pressure; cg, control group; CI, confidence interval; FAME, Federal Study of Adherence to Medications in the Elderly; INR, international normalised ratio; LDL-C, low density lipoprotein-cholesterol; m, months; MPR, medication possession ratio; NIDDM, non–insulin–dependent diabetes mellitus; No., number; n.s., not significant; NR, not reported; RP, reminder packaging; TDM, therapeutic drug monitoring; TTR, time in therapeutic range.

Note: **Quality assessment** was undertaken for the purposes of this review and is presented in Appendix 6.

The study by Dumas et al (2016) is a prospective cohort study that examined the impact of a pharmacy-packed pillbox on two clinical outcomes, time in therapeutic range (TTR) and international normalised ratio (INR) instability, among warfarin users. The study also examined the effect of non-pillbox users, and users of a self-prepared pillbox, on the same outcomes. The study included 1,069 new warfarin users, with a mean age of 70 years, who initiated warfarin between May 2010 and July 2013 within 17 hospitals in Quebec, Canada. Nearly 76% had atrial fibrillation as warfarin’s primary indication, and 35.6% had a previous history of myocardial infarction or angina. The demographic and clinical characteristics differed between the pharmacist-packed pillbox users and nonusers, thus creating a source of bias. Pharmacist-prepared pillbox users were older, disproportionally female, less educated, differed in their alcohol and green vegetable intake, were less active, more diabetic, had a greater history of myocardial infarction or angina, and were less prone to have a mechanic valve replacement as a main indication for warfarin than nonusers.

A major limitation of this study was the growing number of losses to follow-up and exclusions from analysis by the time of the 12-month follow-up interview. The main cause was the discontinuation or temporary cessation of warfarin. The authors also noted that they were not able to directly measure the impact of pillbox use on adherence as there were potentially multiple warfarin dose adjustments and the use of electronic pillboxes. It is unclear from the publication whether the pillboxes prepared by pharmacists were tamper-evident devices.

A retrospective study by Dupclay et al (2012) evaluated the impact of reminder packaging on patient adherence and persistence to antihypertensive combination therapy over 11 months. The reminder packaging was a monthly blister-packaged container of 30 valsartan-hydrochlorothiazide combination tablets with clear labelling information (days supplied, brand/generic name, storage information, instructions for use) found on the front of the reminder packaging container. The study included a total of 9266 matched patients who switched to using a single-pill combination of valsartan-hydrochlorothiazide in reminder packaging at index date (6 months post-enrolment and starting antihypertensive combination therapy without packaging) compared with patients remaining on the combination without reminder packaging (n=4633). Patients were propensity score-matched on baseline adherence and background demographic variables, including comorbidities. A major limitation of the study is its retrospective nature, thus introducing selection bias that may confound the relationship between treatment and the outcomes of interest.

The multicentre RCT by Schneider et al (2008) evaluated medication adherence in elderly outpatients using daily-dose blister packaging (Pill Calendar) compared with medications packaged in bottles of loose tablets. The study included 85 participants aged 65 years or older, prescribed the antihypertensive medicine lisinopril. Forty-seven patients were randomised to receive daily-dose blister packaged medicine (Pill Calendar, a single card containing 28 days of therapy arranged in weekly rows, labelled with medication-specific instructions and the day of the week on which the dose was to be taken). Patients in the control group (n=38) received their antihypertensive medicine in traditional bottles of loose tablets. Patients returned for refills every 28 days during a 12 month period where the pharmacist would record the time between prescription refills for the medicine and any study-related problems. A major limitation of this study was the relatively small number of patients, the tracking of only one disease, and the short timeframe relative to some of the long-term outcomes measured. The imbalance in patient numbers in each study arm was not justified by the authors.

The Vitamins, Teachers, and Longevity (VITAL) RCT by Huang et al (2000) compared the effect of different types of pill packaging on adherence in healthy subjects taking vitamin E. The study included 297 individuals randomised to one of two types of pill packaging (blister pack or pill bottles along with organisers) and to one of two supplement groups (placebo or an antioxidant vitamin preparation that provided 400 international units/day of vitamin E). Participants in the blister-pack group (n=149) received four packs of 31 blisters labelled with dates, whereas participants in the pill organiser group (n=148) packed their own pills. Baseline patient characteristics were well matched in the two groups. Unlike the other included studies, this trial did not include a control arm with no reminder packaging. The results should be interpreted with this in mind, as not all community patients would use pill organisers for vitamin E supplements.

The RCT by Simmons et al (2000) examined the impact of calendar blister pack (CBP) use on glycaemic and blood pressure control. The study included 68 patients with an average age of 54 years, with poor blood glucose control (glycated haemoglobin [HbA1c] >9%). Thirty six patients were randomised to receive a CBP prepared at one pharmacy, marked with the days of the week and the time of dosage. The control group (n=32) received the same packaging but with the medication contained within the usual containers. Outcome measures included glycated haemoglobin (HbA1c), systolic and diastolic blood pressure levels at four and eight months’ follow-up.

A small study by Winland-Brown (2000) examined the effect of a prefilled pillbox on medication adherence. The pillbox was marked with the days of the week in which individual doses were stored and pre-filled by the pharmacist on a weekly basis. It is unclear from the publication whether the pillbox was tamper-evident. The study included 61 independent elders aged >70 years with a variety of medical conditions, who had experienced an episode of medication mismanagement. The intervention group (n=16) received a pillbox marked with the days of the week, which was prefilled on a weekly basis. The control group (n=21) dispensed their own medications.

The two Skaer trials (1993a; 1993b) examined the use of a unit-of-use packaging (with or without a refill reminder) on adherence in two separate patient populations: hypertension and non-insulin dependent diabetes mellitus (NIDDM). The two studies used a factorial design with a reminder package and a medication-refill reminder (sent by mail 10 days prior to each sequential refill date) as interventions. The unit-of-use packaging was pharmacy-filled, and was composed of a sequentially numbered 30-day supply inventory tray with easy access compartments, marked with the days of the week. It is not clear from the publication whether the compliance aid was a tamper-evident device. Each trial included four groups that provided comparisons made between the reminder pack versus control, and reminder pack plus refill reminder versus refill reminder only. Both studies used medication possession ratio (MPR) to measure adherence. Costs were also calculated as the sum of anticipated prescription, physician, hospital and laboratory costs, and are further discussed in Section 6 of this Report.

The trial by Skaer et al (1993a) examined the impact of reminder packaging on prescription refill compliance with antihypertensive therapy. The study included 304 patients <65 years old with untreated hypertension, prescribed calcium channel antagonist (verapamil) once daily. Patients were randomly assigned to one of the four groups described above. The intervention group (n=85) received standard pharmaceutical care and was provided unit-of-use reminder packaging with each prescription-refill request. Participants in the control cohort (n=78) received standard pharmaceutical care with each dispensing of antihypertensive therapy.

The Skaer (1993b) NIDDM RCT included a total of 258 patients aged <65 years of age prescribed glyburide twice daily. Study participants were not to have received an alternative sulphonylurea or have utilised insulin post receipt of the initial prescription, and were not to have prescription medicines for other disease states. Patients were randomly assigned to one of the four groups described above. Patients in the intervention group relevant to this assessment (n=53) received standard pharmaceutical care and were provided unit-of-use packaging with each prescription refill request. The control group (n=78) received standard pharmaceutical care with each dispensing of glyburide. Analysis occurred at 0 to 3 months prior to receipt of the initial glyburide prescription, and 0 to 12 months post receipt of the initial glyburide prescription.

A major limitation of the two Skaer RCTs is that they did not relate findings on medication adherence to other aspects of disease self-management (e.g. self-monitoring of blood glucose or patient self-efficacy). Another limitation of these two studies is selection bias due to the methods of randomisation being unclear, with unbalanced groups in the intervention and control groups.

The RCT by Becker et al (1986) evaluated the use of special packaging of antihypertensive medication on compliance and blood pressure control. The study included 180 patients aged 20 to 80 years taking medication for previously diagnosed hypertension. All patients had demonstrated poor blood pressure control (diastolic > 90 mm Hg) on at least one visit during the preceding two years. Patients in the intervention group (n=86) received their medications in a single plastic blister sealed pack sealed with a foil backing on which was printed the day of the week and the time of day at which each medication was to be taken. Patients in the control group received all of their antihypertensive medicines in the conventional pill vials (separate vials for each pill that were labelled with the medicine name, the dosage, the medicine instructions, and the physician’s name). All medicines for both groups were provided free of charge to ensure that all patients would receive their medicines.

### Adherence

Seven studies, all from the US, provided relevant information on adherence, measured either by MPR or pill count (see Table 5.5).

Table 5.5 Summary of adherence outcomes from included primary studies

|  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- |
|  |  |  |  | MPR |  | Pill  | count |  |
| Study ID*Quality* | Medical condition | N | Reminder pack | Control group | P value | Reminder pack | Control group | P value |
| Dupclay (2012)*Poor quality* | Hypertension | 9266 | 80% | 73% | <0.001 | NR | NR | NR |
| Schneider (2008)*Fair quality* | Hypertension | 85 | 93% | 87% | 0.039 | NR | NR | NR |
| Huang (2000) *Fair quality* | Disease prevention | 297 | NR | NR | NR | 93%a | 87%a | 0.05 |
| Winland-Brown (2000)*Poor quality* | Multiple comorbidities | 61 | NR | NR | NR | n.s. | n.s. | n.s. |
| Skaer (1993a)*Poor quality* | Hypertension | 304 | 67% | 56% | ≤0.05 | NR | NR | NR |
| Skaer (1993b)*Poor quality* | Diabetes | 258 | 71% | 58% | ≤0.05 | NR | NR | NR |
| Becker (1985)*Poor quality* | Hypertension | 180 | NR | NR | NR | n.s. | n.s. | n.s. |

Abbreviations: MPR, medication possession ratio; NR, not reported; n.s., not significant; US, United States.

**a** Patients with>90% pill intake.

Note: **Quality assessment** was undertaken for the purposes of this review and is presented in Appendix 6.

In the retrospective matched cohort study by Dupclay et al (2012), improvements in adherence were assessed by increases in MPR and proportion of days covered. An increase in persistence was measured by shorter gaps between successive refills (time to refill) in the reminder packaging cohort over an 11-month period. The study found that adherence was significantly higher in the reminder packaging cohort compared with patients in the non-reminder packaging cohort, with MPR of 80% in the reminder packaging group versus 73% in the non-reminder packaging group (P<0.001). The proportion of days covered for the reminder packaging group was reported to be 76% versus 63% in the non-reminder packaging group (P<0.001). Refill timing was 10 days for reminder packaging patients versus 16 days for non-reminder packaging patients (P<0.001). Similar trends were observed with respect to time to discontinuation (reminder packaging 196 days, non-reminder packaging 174 days; P<0.001). A higher proportion of reminder packaging patients remained on therapy compared with non-reminder packaging patients, with patients in the reminder packaging group being 17% less likely to discontinue therapy compared with patients in the non-reminder packaging group (hazards ratio 0.833; 95% CI 0.79–0.87). The authors concluded that the use of reminder packaging improved patients’ adherence and persistence to antihypertensive medication regimen.

In the RCT by Schneider et al (2008), adherence was measured using MPR, defined as the sum of the day’s supply for all prescriptions received during the study, divided by the number of days between the dates of the first and last prescription dispensing. MPR was significantly higher for the blister packaging group than the control group, although the absolute difference was small (6%). The study also found that the percentage of on-time refills was significantly higher by 13.7% for the blister packaging group than the control group. Both effects were retained after adjusting for age and gender. The authors concluded that reminder packaging significantly improved adherence to antihypertensive therapy.

In the VITAL RCT (Huang et al, 2000), adherence to pill taking was measured by pill counts, serum vitamin (alpha-tocopherol) levels, and self-reports using a standardised instrument (Morisky scale). Follow-up data was provided by 294 participants (99%). The study found that the percentage of participants who took 90% or more of pills was 93% in the blister-pack group versus 87% in the self-packed pill-organiser group. Distribution of pill counts were similar among healthy individuals and among persons who had at least one chronic medical condition. Adherence measured by serum vitamin levels was similar in the blister-pack and the pill organiser groups, while the pattern of adherence as measured by pill counts suggested that the use of blister packs may have improved adherence, particularly among those with lower adherence. This was also the finding of self-reported adherence, with the percentage of participants who reported having ever forgotten to take study pills being lower in the blister-pack group than in the organiser group. The authors concluded that the use of blister packs improved adherence as measured by pill counts among those with lower adherence, however neither pill delivery systems improved adherence as measured by serum vitamin levels.

The small study by Winland-Brown (2000) reported the number of missed doses of medications (pill count) in each group at one, three and six months. The study found no significant effect with the use of a prefilled pillbox on the mean number of missed doses; however, results from this study are inconclusive as there was insufficient information on the number of study medications taken by participants and substantial gaps in the information published.

The Skaer et al (1993a) hypertension RCT showed that patients receiving reminder packaging achieved a significant increase in the MPR for antihypertensive therapy relative to controls. The percentage of pills taken was 85% in the reminder packaging group versus 78% in the control group (P ≤0.05).

Results from the Skaer (1993b) NIDDM RCT showed that the use of specialised packaging significantly increased the MPR for sulfonylurea therapy relative to control. The percentage of pills taken was 71% in the reminder packaging group versus 58% in the control group (P ≤0.05).

The RCT by Becker et al (1986) did not find any statistically significant improvement in adherence for hypertensive therapy in patients receiving their medications in a single blister sealed pack compared with conventional pill vials (data not reported).

**Findings:** *The evidence on the effectiveness of DAAs on adherence to medication is mixed. Four studies (three RCTs and one retrospective matched cohort study) showed that the use of DAAs or similar medicine compliance aids significantly improved adherence to medication for diabetes and hypertension, as manifested by improvements in MPR. However, the evidence was less convincing for adherence measured by pill counts, with two of three studies showing no effect. The effect of drug reminder packaging was more pronounced when used in combination with other interventions such as a refill reminder.*

*The current evidence base consists of poor to fair quality studies with significant methodological limitation, inadequate length of follow-up, and moderate-to-high risk of bias. Therefore, findings from these studies should be interpreted with caution.*

*There are currently no studies that assessed the effect of the Australian DAA initiative on adherence to medication. Further high-quality studies of adequate size and duration, assessing the use of DAAs or similar medicine compliance aids on adherence to self-administered long-term medication use are required to draw firm conclusions.*

*It also appears that there is a lack of a thorough and patient-centred assessment tool that pharmacists can use to assist with determining if patient nonadherence is intentional or unintentional, as DAAs are probably not effective in improving intentional nonadherence.*

### Clinical outcomes

#### Warfarin use

Only one poor quality prospective cohort study (Dumas et al, 2016) reported on the results of pharmacist-packed pill box use on clinical outcomes in patients taking warfarin therapy for atrial fibrillation or other indications.

The primary outcome in the prospective cohort study was TTR <60%, which represents a low percentage of time in the INR therapeutic range or an unstable patient. The secondary outcome was the INR instability pattern (unstable below range; unstable over range; unstable with erratic pattern; and stable) to better describe patient INR profiles. The study found that pharmacist-prepared pillbox use was not associated with a TTR <60% or with a specific INR instability pattern at any time during follow-up (see Table 5.6). Similar results were obtained when the threshold to define INR instability was changed to TTR < 45% and using the same confounders.

Table 5.6 Association between pillbox use for warfarin and TTR <60%

|  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- |
|  | 3-6  | months | 6-9 | months | 9-12 | months |  |  |
| Independent variable | n (%) | TTR <60%n (%) | n (%) | TTR <60%n (%) | n (%) | TTR <60%n (%) | Adjusted ORa (95% CI) | P value |
| Self-prepared pillbox | 342 (32.0) | 104 (30.4) | 358 (33.5) | 92 (25.7) | 354 (33.1) | 97 (27.4) | 0.86 (0.70-1.05) | 0.129 |
| Pharmacist-prepared pillbox | 112 (10.5) | 41 (36.6) | 116 (10.9) | 28 (24.1) | 111 (10.4) | 21 (27.9) | 1.15 (0.85-1.56) | 0.357 |
| No pillbox | 519 (48.6) | 158 (30.4) | 431 (40.3) | 118 (27.4) | 382 (35.7) | 109 (28.5) | reference | reference |

Source: Dumas (2016), Table 2, p. 681

Abbreviations: CI, confidence interval; OR, odds ratio; TTR, time in therapeutic range.

**a** Adjusted with pillbox use, age, sex, warfarin’s indication, hypertension, dyslipidaemia, diabetes, myocardial infarction or angina history, stroke history, green vegetable intake, and genotype.

In the pharmacist-prepared pillbox group, the proportion of patients with stable TTR >60% increased from 48% at the first tertile of warfarin therapy (between three and six months) to 57% at the end of 12 months follow-up, whereas the proportion of unstable patients below range decreased from 21% to 12% over the same follow-up period. However, these changes were not statistically significant different from pillbox nonusers.

#### Hypertension

Three studies reported the effects of DAAs or similar medication compliance aids on blood pressure: Schneider et al, 2008 (fair quality); Simmons et al, 2000 (good quality); Becker et al, 1986 (poor quality).

The Schneider et al (2008) RCT reported a statistically significant difference in diastolic blood pressure at six months between blister package and control patients aged 65 years or over taking lisinopril for hypertension. The mean (± SD) diastolic blood pressure was 73.2 ± 8.8 mmHg in study patients compared with 77.7 ± 10.2 mmHg in control patients (P =0.0367). There was no statistically significant difference in systolic blood pressure at six months (132.7 ± 17.3 mmHg vs 138.2 ± 22.2 mmHg, P =0.2143). At 12 months there was no significant difference in both systolic and diastolic blood pressure between participants in the two groups.

The Simmons et al (2000) RCT reported a significant reduction in diastolic blood pressure at eight months (-5.8 ± 1.5 mmHg) in the CBP group, and an increase (0.1 ± 1.9 mmHg) in the control group (P <0.001). There was no significant change in systolic blood pressure at eight months (intervention -3.6 ± 2.3 mmHg versus control -2.6 ± 2.8 mmHg, P =0.89). According to the authors, it was unclear why the use of a CBP had an effect on diastolic but not systolic blood pressure.

The RCT by Becker et al (1986) did not find any statistically significant improvement at 12 months in blood pressure control for hypertensive patients receiving their medications in a single blister sealed pack compared with conventional pill vials (data not reported).

#### Glycated haemoglobin

The RCT by Simmons et al (2000) reported the effects of a reminder package intervention on HbA1c in patients with poor blood glucose control. The study found that HbA1c was reduced by 0.95 ± 0.22% in the intervention group, compared with 0.15 ± 0.25% in the control group (P =0.026.) at eight months of follow-up. The authors concluded that the use of CBPs in a group with poor glucose control was associated with a reduction in HbA1 c over an eight month period, which was equivalent to that required to achieve a clinically meaningful reduction in risk of complications.

**Findings:** *A single prospective cohort study of poor quality assessed the impact of pillbox use on clinical outcomes in warfarin users. The study found that pillbox use was not associated with TTR <60% or INR instability; however, these results may be biased by unmeasured confounders such as concomitant drug use. Therefore, the effect of pillbox on INR instability among warfarin users remains inconclusive and further research is still needed in this area.*

*Evidence from two RCTs (one fair quality and one good quality) showed that the use of reminder packaging in patients taking antihypertensive medication significantly decreased diastolic blood pressure but not systolic blood pressure, compared with control. An older study of poor quality failed to demonstrate an effect of reminder packaging on blood pressure control (or on adherence).*

*Evidence from a good quality RCT of small size showed that in patients with poorly controlled diabetes, reminder packaging significantly decreased glycated haemoglobin at eight months of follow up compared with original packaging.*

*High quality studies of adequate size and duration assessing the clinical effectiveness of reminder packaging interventions are required before firm conclusions can be drawn.*

### Adverse drug reactions

None of the included studies specifically reported outcomes relating to adverse drug events, adverse drug reactions or medication-related problems.

### Mortality

None of the included studies reported deaths.

### Health care resource use

The study by Winland-Brown et al (2000) examined the effect of a prefilled pillbox on health care resource utilisation (hospitalisation and admission rates) in elderly patients with a variety of medical conditions, who had experienced a previous episode of medication mismanagement. However, the effect of the intervention could not be determined as there was insufficient information to draw a useful conclusion.

Studies reporting the impact of DAAs on health care costs (prescription, physician, hospital and laboratory costs) are shown in Section 6.1.

### Patient satisfaction

Three of the included studies reported on the usefulness of medication compliance aids from the patients’ perspective. The remaining six studies provided no information on patients’ satisfaction, harms or barriers to use with their medication packaging.

The Simmons et al (2000) RCT reported that 77% (26/34) of the calendar blister package group found the packaging to be useful, as opposed to 27% (7/26) in the group that received original packaging (P <0.001). The authors did not describe the tool used to collect this information.

The VITAL RCT by Huang et al (2000) collected data on self-reported adherence to pill taking (vitamin E supplementation) through a self-administered questionnaire that contained questions about how frequently (never, rarely, sometimes, most of the time, all of the time) participants ever decided not to take study pills, forgot to take pills, skipped taking pills, took pills incorrectly because of carelessness, or took more than the assigned pills. The study found that the percentage of participants who reported any problem with pill taking was somewhat higher in the pill organiser group than in the blister pack group (39.3% vs 28.7%, P =0.06). A higher percentage of persons in the pill organiser group reported the problem of forgetting to take their pills (31.0% vs 21.0%, P =0.05).

The RCT by Becker et al (1986) reported on patient satisfaction in regards to using the reminder blister pack. Patients in this study found that the “special package” was more difficult and less convenient to use than did patients who received their medications in the regular format; however, the study reported no actual data to support this. The authors suggested that “future studies might compare different forms of the more streamlined packages now becoming available.”

**Findings:** *There is insufficient evidence to assess patient acceptance or satisfaction with pharmacist-prepared DAAs or similar medicine compliance aids. Patient satisfaction was marginally reported, with only three of the included studies reflecting on this outcome. Future research into adherence aids should incorporate the opinions of study participants to identify what they would desire in a medicine compliance aid and how they evaluate current devices available, with consideration given to their ease of opening, transportability and display features.*

### Health-related quality of life

None of the included studies reported health-related quality of life outcomes.

### Safety

None of the included studies provided information on the safety or harms associated with DAA use, such as dispensing or packaging errors.

# Published evidence relating to cost and cost-effectiveness

This Section presents the evidence identified in the systematic literature review relating to the cost and cost-effectiveness of DAAs in relation to the research questions and the PICO criteria outlined in Section 3.1.1. None of the included studies assessed the impact of an incentive payment to pharmacists for the provision of DAAs to community patients.

This section does not include evidence reported in previous evaluations of the PPI Program DAA incentive, which was summarised in Section 4.

## Evidence for impact of medicine compliance aids on health care expenditure

Two studies by Skaer et al examined the use of reminder packaging on health care resource costs in hypertensive (1993a) and diabetic (1993b) patients in the US. Total health care costs were calculated as the sum of prescription, physician, hospital and laboratory costs. Neither of the included studies reported the cost of the reminder packaging intervention itself.

A summary of the results from the two studies is presented in Table 6.1.

Table 6.1 Summary of included studies that examined health care expenditure

|  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- |
| Study IDCountry | Study design*Quality* | Population | Comparison | Economic outcomes | Results (relative to control) | Authors’ conclusions |
| Skaer (Hypertension) (1993a)US | RCT12 monthsN=304*Poor* | Medicaid beneficiaries <65 years old with untreated hypertension, prescribed verapamil once daily | Pharmacy-filled unit-of-use packaging (n=85) vs standard medicine vial (n=78) | * prescription expenditure
* all other expenditure (physician, laboratory, hospital)
 | * Adjusted mean annual prescription costs per person: US$48.17 increase (P ≤0.05)
* Adjusted mean annual total health care costs per person: US$13.66 decrease (n.s.)
* Adjusted mean annual physician costs per person: US$32.85 decrease (n.s.)
* Adjusted mean annual laboratory costs per person: US$3.06 decrease (n.s.)
* Adjusted mean annual hospital costs per person: US$25.92 decrease (n.s.)
 | Receipt of unit-of-use packaging resulted in a significant increase in program expenditures for antihypertensive therapy relative to patients provided with standard pharmaceutical care. There was a non-significant reduction in total health care costs relative to patients provided with standard pharmaceutical care.Patients receiving the unit-of-use packaging together with a refill reminder recorded significant reductions in the use of physician and hospital services relative to patients provided with standard pharmaceutical care. |
| Skaer (NIDDM) (1993b)US | RCT12 monthsN=258*Poor* | Medicaid beneficiaries <65 years old prescribed sulfonylurea glyburide twice daily for Type 2 diabetes | Pharmacy-filled unit-of-use packaging (n=53) vs standard medicine vial (n=78) | * prescription expenditure
* all other expenditure (physician, laboratory, hospital)
 | * Adjusted mean annual prescription costs per person: US$74.09 increase (P ≤0.05)
* Adjusted mean annual total health care costs per person: US$22.94 increase (n.s.)
* Adjusted mean annual physician costs per person: US$19.51 decrease (n.s.)
* Adjusted mean annual laboratory costs per person: US$6.73 decrease (n.s.)
* Adjusted mean annual hospital costs per person: US$22.91 decrease (n.s.)
 | Receipt of unit-of-use packaging resulted in a significant increase in program expenditures for sulfonylurea therapy relative to patients provided with standard pharmaceutical care.There was a non-significant reduction in the use of physician, laboratory and hospital services relative to patients provided with standard pharmaceutical care.Patients receiving the unit-of-use packaging together with a refill reminder recorded significant reductions in the use of physician, laboratory and hospital services relative to patients provided with standard pharmaceutical care. |

Abbreviations: CI, confidence interval; mo, month/s; NIDDM, noninsulin-dependent diabetes mellitus; n.s.; not significant; RCT, randomised controlled trial; US, United States.

Note: In the two studies by Skaer et al (1993a and 1993b), results relating to refill reminders used alone or with a drug reminder packaging are excluded from this Review.

Note: **Quality assessment** was undertaken for the purposes of this review and is presented in Appendix 6.

Skaer et al (1993a) conducted an RCT of 304 patients with mild to moderate hypertension receiving Medicaid benefits. The intervention group (n=78) received pharmaceutical care and unit-of-use packaging (30-day supply inventory tray with easy access compartments), whereas the control group received standard pharmaceutical care. Information regarding health service utilisation was derived from the state of South Carolina’s Medicaid computer archive. Patient-level paid claims data files contained extensive information regarding the health services received, including type of service (e.g. hospitalisation), date of service, units of service (e.g. days), and ICD-9-CM code. The date of service for the first verapamil prescription was used to partition the patient level data into pre and post time periods. The Medicaid program authorised the dispensing of prescription medication in 30-day supplies of therapy. The MPR for verapamil therapy was defined at the patient-level as the number of days’ supply of medication obtained throughout the 360-day (12-month) study period. Thus, the optimal outcome would result in a ratio of 1:1 (360 days’ supply of therapy obtained over a 360-day period); a less desirable outcome would be a ratio of <1:1. A higher MPR was hypothesised as being correlated with an increase in prescription expenditure and a decrease in expenditure for physician, laboratory and hospital services.

The study showed that patients receiving units-of-use packaging achieved a significant (P ≤0.05) increase in the mean number of days’ supply of therapy obtained, and thus MPR, relative to controls. The use of reminder packaging resulted in a small but statistically significant increase in prescription expenditure (adjusted mean annual prescription costs per patient of +US$48.17, P ≤0.05), and a non-significant decrease in total costs in the reminder packaging group (adjusted mean annual total health care costs per patient of -US$13.66) when compared to the control group, which implied the potential for cost savings.

The Skaer (1993b) NIDDM RCT included 258 Medicaid patients with NIDDM. The intervention group (n=53) received standard pharmaceutical services and unit-of-use packaging (30-day supply inventory tray with easy access compartments). The control group (n=78) received standard pharmaceutical care. Patients receiving units-of-use packaging achieved a significant (P ≤0.05) increase in the mean number of days’ supply of therapy obtained, and thus MPR, relative to controls. The study found a non-significant increase in total costs in the reminder packaging group (adjusted mean annual total health care costs per patient of +US$22.9). However, the study reported that patients receiving a reminder packaging in combination with a mailed refill reminder achieved a significant reduction in the use of physician, laboratory, and hospital services relative to patients provided standard pharmaceutical care (adjusted mean annual total health care costs per patient of -US$67.67, P ≤0.05).

The two studies by Skaer showed that the use of unit-of-use packaging alone resulted in a non-significant trend to reduced total health care expenditures associated with an increase in medication adherence (adherence outcomes measured by MPR are discussed previously in Section 5.2.1). However, both studies showed that combining the unit-of-use packaging with a mailed refill reminder was associated with a significantly greater improvement in adherence (MPR), which was reflected in higher mean annual prescription costs per patient than for either intervention alone, and a significant reduction in mean physician, hospital and total health care expenditures.

It is important to note that the two studies by Skaer (1993a; 1993b) were conducted in the context of the US Medicaid system, with patient-level archive data regarding the use of, and expenditure for, healthcare services derived from the South Carolina Medicaid computer archive. These studies therefore have limited applicability to the Australian context. The two studies were also of poor methodological quality and their results should be interpreted with caution.

## Evidence for cost-effectiveness of medicine compliance aids

No studies were identified that assess the cost-effectiveness of DAAs or similar medicine compliance aids.

# DAA utilisation analysis

## DAA initiative participating pharmacies and claims made

Between 2012 and 2016, 7,509 pharmacies have participated in the DAA incentive program, peaking in 2014 at 5,857 pharmacies[[8]](#footnote-8). As 2016 is a part year, it is under-represented in the data and thus largely excluded in the analysis (Table 7.1).

Table 7.1 Summary of pharmacy DAA claims 2012 – 2016

| **Claim year** | **No of pharmacies with claims** | **Value of claims** | **Volume of patient DAAs supplied** | **Average claim amount per DAA** | **Average claim per participating pharmacy** |
| --- | --- | --- | --- | --- | --- |
| 2012 | 4,931 | $38,066,849 | 9,826,102 | $3.87 | $7,720 |
| 2013 | 4,910 | $22,292,547 | 9,435,206 | $2.36 | $4,540 |
| 2014 | 5,857 | $33,520,542 | 11,391,921 | $2.94 | $5,723 |
| 2015 | 5,000 | $42,245,894 | 13,237,575 | $3.19 | $8,449 |
| 2016 | 46 | $158,705 | 41,381 | $3.84 | $3,450 |
| **Total**  | **7,509** | **$136,284,537** | **43,932,185** | **$3.10** | **$18,149** |

Source: Claims payment data supplied in PPI Total Data Compilation\_Copy.xls

Table 7.1 shows that the volume of patient DAAs supplied has increased 34.7% from 9.8 million in 2012 to 13.2 million in 2015, matched to corresponding increase of 1.4% in the number of participating pharmacies indicating that participating pharmacies have substantially increased their volumes. It also shows that the average amount earned by pharmacies per patient DAA has decreased by 17.6%, going from $3.87 in 2012 to $3.19 in 2015, however the average total annual amount claimed by participating pharmacies has increased from $7,720 to $8,449 (9.4% increase), which has been driven by the higher volumes.

Table 7.2 deconstructs the same data by Australian Bureau of Statistics (ABS) remoteness. Pharmacies classified as Major Cities of Australia have consistently received greater claims payments per patient DAA than the other remoteness classifications (with an average of $3.25 over the period). Remote Australia and Very Remote Australia have received the least per patient DAA supplied (with an averages of $2.40 and $2.29 respectively. This variation arises as a result of the weighting for the number of prescriptions dispensed per pharmacy used in the claims calculation, since patient DAA volumes tend to be higher in metropolitan areas.

Table 7.2 Summary of pharmacy DAA claims 2012 – 2016 by ABS Remoteness

| **ABF Remoteness** | **Claim year** | **No of pharmacies with claims** | **Value of claims** | **Volume of patient DAAs supplied** | **Average claim amount per DAA** | **Average claim per participating pharmacy** |
| --- | --- | --- | --- | --- | --- | --- |
| Inner Regional Australia | 2012 | 1,002 | $9,132,733 | 2,477,867 | $3.69 | $9,115 |
| 2013 | 973 | $5,183,295 | 2,274,457 | $2.28 | $5,327 |
| 2014 | 1,188 | $8,062,823 | 2,852,121 | $2.83 | $6,787 |
| 2015 | 978 | $10,195,463 | 3,328,392 | $3.06 | $10,425 |
| 2016 | 6 | $29,108 | 7,872 | $3.70 | $4,851 |
| **Total**  | **1,555** | **$32,603,422** | **10,940,709** | **$2.98** | **$20,967** |
| Major Cities of Australia | 2012 | 3,356 | $23,971,788 | 5,844,431 | $4.10 | $7,143 |
| 2013 | 3,357 | $14,126,713 | 5,739,105 | $2.46 | $4,208 |
| 2014 | 4,021 | $20,711,856 | 6,722,413 | $3.08 | $5,151 |
| 2015 | 3,374 | $26,111,172 | 7,858,296 | $3.32 | $7,739 |
| 2016 | 34 | $114,589 | 29,521 | $3.88 | $3,370 |
| **Total**  | **5,120** | **$85,036,118** | **26,193,766** | **$3.25** | **$16,609** |
| Outer Regional Australia | 2012 | 479 | $4,274,802 | 1,250,919 | $3.42 | $8,924 |
| 2013 | 484 | $2,506,270 | 1,165,976 | $2.15 | $5,178 |
| 2014 | 618 | $3,805,897 | 1,396,423 | $2.73 | $6,158 |
| 2015 | 539 | $4,815,529 | 1,611,050 | $2.99 | $8,934 |
| 2016 | 5 | $13,953 | 3,689 | $3.78 | $2,791 |
| **Total**  | **791** | **$15,416,451** | **5,428,057** | **$2.84** | **$19,490** |
| Remote Australia | 2012 | 61 | $402,641 | 137,354 | $2.93 | $6,601 |
| 2013 | 60 | $285,697 | 152,581 | $1.87 | $4,762 |
| 2014 | 83 | $556,285 | 246,721 | $2.25 | $6,702 |
| 2015 | 73 | $731,511 | 286,423 | $2.55 | $10,021 |
| 2016 | 1 | $1,055 | 299 | $3.53 | $1,055 |
| **Total**  | **105** | **$1,977,188** | **823,378** | **$2.40** | **$18,830** |
| Very Remote Australia | 2012 | 33 | $284,884 | 115,531 | $2.47 | $8,633 |
| 2013 | 36 | $190,573 | 103,087 | $1.85 | $5,294 |
| 2014 | 51 | $383,681 | 174,243 | $2.20 | $7,523 |
| 2015 | 44 | $392,219 | 153,414 | $2.56 | $8,914 |
| **Total**  | **62** | **$1,251,358** | **546,275** | **$2.29** | **$20,183** |
| **Total**  |  | **7,509** | **$136,284,537** | **43,932,185** | **$3.10** | **$18,149** |

Source: Claims payment data supplied in PPI Total Data Compilation\_Copy.xls in conjunction with ABS postcode to remoteness.xls available from [http://www.abs.gov.au/AUSSTATS/abs@.nsf/DetailsPage/1270.0.55.006July%202011?OpenDocument](http://www.abs.gov.au/AUSSTATS/abs%40.nsf/DetailsPage/1270.0.55.006July%202011?OpenDocument) (accessed 5th October, 2016)

Abbreviations: ABS, Australian Bureau of Statistics; DAA, Dose Administration Aids.

The Very Remote Australia classification has experienced the highest relative increase in participating pharmacies, with numbers growing 33% (from 33 to 44) between 2012 and 2015 and Remote Australia classification, growing 20% (from 61 to 73).

It is evident from the claims payment data that the volume of patient DAAs supplied has increased substantially between 2012 and 2015 nationally, and that the number of participating pharmacies has also increased, especially in remote and very remote regions. Growth in the program suggests it is considered effective, but the available data do not allow a determination of the reasons for growth (e.g. motivation for take-up of the incentive payment, or favourable patient feedback on the program, or both).

## DAA initiative reach to target populations

The claims data do not include any information on the characteristics of the patients receiving the DAA service such as age, or indicators of frailty, mental faculties or health status; or indeed any other data that would assist in determining whether the patient population reached by the DAA program is consistent with what is intended (PSA Guidelines) and/or whether the program is effective.

Nonetheless, assuming that the program is reaching the intended target groups, it should be possible to observe a relationship between, for example, chronic disease prevalence and the per-capita volumes of DAAs claimed for pharmacies at geographic area level (i.e. it might be expected that areas with high chronic disease prevalence would also have a high per capita incidence of DAA services and claims).

To illustrate, Table 7.3 looks at the distribution across PHNs areas for DAA service volumes against estimated diabetes (as an illustrative chronic disease) prevalence (i.e. proportion of the population in the PHN area with diabetes). Please note that the high, medium and low groupings in Table 7.3 are calculated by dividing the values for each of the metrics into three even segments between the highest and lowest values for all PHNs. Microsoft Excel is used to apply heat map colour coding to show where the range of values for each metric fall.

Table 7.3 Diabetes prevalence and DAA service volumes and dollars claimed per capita, 2015

|  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- |
| **Primary Health Network** | **Diabetes prevalence** | **Diabetes prevalence range** | **Average DAA services per capita** | **DAA services /capita range** | **Average DAA claim per capita** | **DAA claim /capita range** |
| Western Queensland | 2.1% | Low | 0.442 | Low | $1.27 | Low |
| Northern Queensland | 2.8% | Low | 0.594 | Low | $1.81 | Low |
| Eastern Melbourne | 3.1% | Low | 0.406 | Low | $1.43 | Low |
| Northern Territory | 3.1% | Low | 1.350 | High | $3.27 | High |
| Brisbane North | 3.2% | Low | 0.500 | Low | $1.63 | Low |
| Country WA | 3.2% | Low | 0.785 | Mid | $2.16 | Mid |
| South Eastern Melbourne | 3.2% | Mid | 0.442 | Low | $1.50 | Low |
| Australian Capital Territory | 3.3% | Mid | 0.663 | Low | $1.75 | Low |
| Murray | 3.3% | Mid | 0.880 | Mid | $2.78 | High |
| Northern Sydney | 3.3% | Mid | 0.396 | Low | $1.32 | Low |
| Western Victoria | 3.3% | Mid | 0.864 | Mid | $2.60 | Mid |
| Perth North | 3.4% | Mid | 0.469 | Low | $1.50 | Low |
| Gippsland | 3.5% | Mid | 0.773 | Mid | $2.49 | Mid |
| Gold Coast | 3.5% | Mid | 0.396 | Low | $1.42 | Low |
| Perth South | 3.5% | Mid | 0.427 | Low | $1.38 | Low |
| Brisbane South | 3.6% | Mid | 0.464 | Low | $1.55 | Low |
| Darling Downs and West Moreton | 3.6% | Mid | 0.764 | Mid | $2.40 | Mid |
| Nepean Blue Mountains | 3.6% | Mid | 0.565 | Low | $1.91 | Low |
| Western NSW | 3.8% | Mid | 1.190 | High | $3.52 | High |
| North Western Melbourne | 3.9% | Mid | 0.368 | Low | $1.34 | Low |
| Hunter New England and Central Coast | 4.0% | Mid | 0.904 | Mid | $2.79 | High |
| Murrumbidgee | 4.0% | Mid | 1.110 | High | $3.32 | High |
| Central Queensland, Wide Bay, Sunshine Coast | 4.1% | Mid | 0.643 | Low | $2.09 | Mid |
| Central and Eastern Sydney | 4.2% | Mid | 0.384 | Low | $1.31 | Low |
| Tasmania | 4.3% | Mid | 0.773 | Mid | $2.27 | Mid |
| Western Sydney | 4.3% | Mid | 0.389 | Low | $1.43 | Low |
| North Coast | 4.6% | High | 0.896 | Mid | $2.74 | Mid |
| South Eastern NSW | 4.8% | High | 0.979 | Mid | $2.90 | High |
| Country SA | 4.9% | High | 0.956 | Mid | $2.86 | High |
| Adelaide | 5.2% | High | 0.670 | Low | $2.14 | Mid |
| South Western Sydney | 5.5% | High | 0.465 | Low | $1.63 | Low |
| **Total** | **3.8%** |  | **0.554** |  | **$1.77** |  |

Source: Claims payment data supplied in PPI Total Data Compilation\_Copy.xls in conjunction with Phidu\_data\_pha\_aust.xls available from <http://www.phidu.torrens.edu.au/social-health-atlases/indicators-and-notes-on-the-data/social-health-atlases-of-australia-contents#population-projections> (accessed 5th October, 2016)

Abbreviations: DAA, Dose Administration Aids.

Visual examination of Table 7.3 reveals that there is little relationship between diabetes prevalence and DAA services provided or DAA resources applied. It shows that only 10 of 31 PHNs have the same banding for both disease prevalence, and average DAA service volume per capita and average DAA resources (claims) per capita. In fact, none of the five highest prevalence diabetes PHNs feature as high DAA services PHNs. The degree of similarity in the heat map coloration of each column is negligible.

As another illustration, Table 7.4 looks at the distribution across PHNs areas for DAA service volumes against estimated mental health issues prevalence (i.e. proportion of the population in the PHN area with a mental health issue. The same heat mapping approach is used.

Table 7.4 Mental health prevalence and DAA service volumes and dollars claimed per capita, 2015

|  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- |
| **Primary Health Network** | **Mental health prevalence** | **Mental health prevalence range** | **Average DAA services per capita** | **DAA services /capita range** | **Average DAA claim per capita** | **DAA claim /capita range** |
| Northern Territory | 7.9% | Low | 1.350 | High | $3.27 | High |
| Western Queensland | 8.2% | Low | 0.442 | Low | $1.27 | Low |
| Western Sydney | 10.8% | Mid | 0.389 | Low | $1.43 | Low |
| Northern Queensland | 11.1% | Mid | 0.594 | Low | $1.81 | Low |
| North Western Melbourne | 11.1% | Mid | 0.368 | Low | $1.34 | Low |
| Country WA | 11.3% | Mid | 0.785 | Mid | $2.16 | Mid |
| Eastern Melbourne | 11.4% | Mid | 0.406 | Low | $1.43 | Low |
| Northern Sydney | 11.4% | Mid | 0.396 | Low | $1.32 | Low |
| South Western Sydney | 11.5% | Mid | 0.465 | Low | $1.63 | Low |
| South Eastern Melbourne | 11.7% | Mid | 0.442 | Low | $1.50 | Low |
| Perth North | 11.8% | Mid | 0.469 | Low | $1.50 | Low |
| Central and Eastern Sydney | 11.8% | Mid | 0.384 | Low | $1.31 | Low |
| Nepean Blue Mountains | 11.9% | Mid | 0.565 | Low | $1.91 | Low |
| Perth South | 12.4% | Mid | 0.427 | Low | $1.38 | Low |
| Western NSW | 12.7% | Mid | 1.190 | High | $3.52 | High |
| Brisbane South | 12.8% | Mid | 0.464 | Low | $1.55 | Low |
| Murrumbidgee | 12.8% | Mid | 1.110 | High | $3.32 | High |
| Brisbane North | 13.3% | High | 0.500 | Low | $1.63 | Low |
| Western Victoria | 13.3% | High | 0.864 | Mid | $2.60 | Mid |
| South Eastern NSW | 13.3% | High | 0.979 | Mid | $2.90 | High |
| Murray | 13.4% | High | 0.880 | Mid | $2.78 | High |
| Gold Coast | 13.7% | High | 0.396 | Low | $1.42 | Low |
| Darling Downs and West Moreton | 13.7% | High | 0.764 | Mid | $2.40 | Mid |
| Hunter New England and Central Coast | 13.7% | High | 0.904 | Mid | $2.79 | High |
| Australian Capital Territory | 14.0% | High | 0.663 | Low | $1.75 | Low |
| Country SA | 14.0% | High | 0.956 | Mid | $2.86 | High |
| Adelaide | 14.0% | High | 0.670 | Low | $2.14 | Mid |
| Gippsland | 14.2% | High | 0.773 | Mid | $2.49 | Mid |
| Central Queensland, Wide Bay, Sunshine Coast | 14.5% | High | 0.643 | Low | $2.09 | Mid |
| Tasmania | 14.5% | High | 0.773 | Mid | $2.27 | Mid |
| North Coast | 15.3% | High | 0.896 | Mid | $2.74 | Mid |
| **Total** | **12.5%** |  | **0.554** |  | **$1.77** |  |

Source: Claims payment data supplied in PPI Total Data Compilation\_Copy.xls in conjunction with Phidu\_data\_pha\_aust.xls available from <http://www.phidu.torrens.edu.au/social-health-atlases/indicators-and-notes-on-the-data/social-health-atlases-of-australia-contents#population-projections> (accessed 5th October, 2016)

Abbreviations: COPD, chronic obstructive pulmonary disease; DAA, Dose Administration Aids

Visual examination of Table 7.4 reveals a slightly stronger relationship at PHN area level between the prevalence of mental health issues, and DAA services provided per capital and DAA resources applied per capita. The heat map colouration does pool many of the PHNs with the lowest and highest per capita DAA service rate into the same half of the table possibly suggesting an underlying connection. That said, just 2 of 31 PHNs share the same bandings for mental health issues prevalence, and average DAA service volume per capita and average DAA resources (claims) per capita.

As another illustration, using the same heat map approach, Table 7.5 examines for each PHN area, the proportion of the population that is aged over 65 years against the DAA services volume per capita (only for those aged over 65 years). Please note that the Northern Territory has been excluded from the heat mapping as it is an outlier in terms of the proportion of the population aged over 65 years.

Table 7.5 Proportion of population over 65 and DAA service volumes and dollars claimed per capita (age over 65), 2015

|  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- |
| **Primary Health Network** | **% aged over 65 years** | **% aged over 65 years range** | **Average DAA services per capita** | **DAA services /capita range** | **Average DAA claim per capita** | **DAA claim /capita range** |
| Northern Territory | 7.0% | Low | 19.17 | High | $46.47 | High |
| North Western Melbourne | 11.1% | Low | 3.31 | Low | $12.10 | Low |
| Western Queensland | 11.5% | Low | 3.85 | Low | $11.07 | Low |
| Australian Capital Territory | 11.9% | Low | 5.57 | High | $14.70 | Mid |
| Brisbane South | 12.1% | Low | 3.84 | Low | $12.79 | Mid |
| Northern Queensland | 12.2% | Low | 4.89 | Mid | $14.87 | Mid |
| Perth North | 12.3% | Low | 3.82 | Low | $12.24 | Low |
| Western Sydney | 12.3% | Low | 3.18 | Low | $11.66 | Low |
| Country WA | 12.7% | Low | 6.16 | High | $16.92 | High |
| Central and Eastern Sydney | 12.8% | Low | 3.00 | Low | $10.26 | Low |
| Brisbane North | 13.1% | Low | 3.82 | Low | $12.43 | Low |
| Nepean Blue Mountains | 13.3% | Low | 4.26 | Mid | $14.41 | Mid |
| Perth South | 13.3% | Low | 3.22 | Low | $10.39 | Low |
| South Western Sydney | 13.4% | Low | 3.48 | Low | $12.19 | Low |
| South Eastern Melbourne | 14.7% | Low | 3.00 | Low | $10.19 | Low |
| Darling Downs and West Moreton | 14.8% | Low | 5.15 | Mid | $16.16 | High |
| Northern Sydney | 14.8% | Low | 2.67 | Low | $8.89 | Low |
| Gold Coast | 15.4% | Mid | 2.57 | Low | $9.27 | Low |
| Eastern Melbourne | 15.6% | Mid | 2.60 | Low | $9.15 | Low |
| Adelaide | 16.5% | Mid | 4.05 | Mid | $12.95 | Mid |
| Western NSW | 17.8% | Mid | 6.67 | High | $19.71 | High |
| Tasmania | 18.2% | Mid | 4.25 | Mid | $12.49 | Low |
| Western Victoria | 18.4% | Mid | 4.70 | Mid | $14.17 | Mid |
| Central Queensland, Wide Bay, Sunshine Coast | 18.6% | Mid | 3.46 | Low | $11.23 | Low |
| Murrumbidgee | 18.9% | High | 5.89 | High | $17.61 | High |
| Hunter New England and Central Coast | 19.1% | High | 4.73 | Mid | $14.60 | Mid |
| Murray | 19.3% | High | 4.57 | Mid | $14.45 | Mid |
| Country SA | 19.4% | High | 4.93 | Mid | $14.73 | Mid |
| South Eastern NSW | 20.0% | High | 4.89 | Mid | $14.50 | Mid |
| Gippsland | 20.8% | High | 3.72 | Low | $11.98 | Low |
| North Coast | 22.5% | High | 3.98 | Mid | $12.17 | Low |
| **Total**  | **14.9%** |  | **3.71** |  | **$11.85** |  |

Note: Northern Territory has been excluded from the heat-map colouration in this table, due to the impact the relative variations in metrics had on readability.

Source: Claims payment data supplied in PPI Total Data Compilation\_Copy.xls in conjunction with Phidu\_data\_pha\_aust.xls available from <http://www.phidu.torrens.edu.au/social-health-atlases/indicators-and-notes-on-the-data/social-health-atlases-of-australia-contents#population-projections> (accessed 5th October, 2016)

Abbreviations: COPD, chronic obstructive pulmonary disease; DAA, Dose Administration Aids

Visual examination of Table 7.5 reveals little relationship between the proportions of the population aged over 65 years and the DAA services provided or DAA resources applied. However, nearly half (15 of the 31) of the PHNs have the same banding for proportion of population over 65 years, and average DAA service volume per capita and average DAA resources (claims) per capita. But there is little consistency, as illustrated by the fact that only one of the seven PHNs (Murrumbidgee) with the highest proportion of population aged over 65 years, is also amongst the highest per capita users of DAA services.

Overall, these results are insufficient to demonstrate a clear relationship between the factors that describe the target population according to the PSA Guidelines and the take up rates for the DAA services. To shed further light on the issue, parametric statistical analysis using correlation coefficients was attempted, but this work was similarly inconclusive, and therefore is not presented here.

It is clear that to make a more robust assessment of the impact of the DAA program, more comprehensive data are required. Such data should include the characteristics of patients receiving the DAA services to enable funders and providers to be confident that the initiative is applying resources to the intended target populations.

Ideally the additional data collected should also include measures of interim and final clinical outcomes, as well as patient reported measures of experience with the program, to enable an assessment of clinical and cost effectiveness. It is acknowledged that this type\s of data could probably only be collected in the context of a structured trial of the DAA program.

# APPENDIX 1 **References**

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# APPENDIX 2 Working Group Members

The Department of Health established a Working Group of nominated representatives (Table A-2.1) to provide advice to the Department and the Assessment Group on the research questions and PICO criteria for the literature review, the literature search terms, utilisation data and analysis.

Table A-2.1 Members of the Working Group for the evaluation of the medication adherence PPI Programs

|  |  |
| --- | --- |
| Name | Representing |

# APPENDIX 3 Search strategy

The DAA search strategies for Embase, Medline, International Pharmaceutical Abstracts and Cochrane databases are outlined in Table A-3. 1, Table A-3. 2, Table A-3. 3, Table A-3. 4.

Table A-3. 1 Embase search strategy (23rd August 2016)

|  |  |  |
| --- | --- | --- |
| # | Search term | Number of citations |
| 1 | dose administration aid\*.mp. | 21 |
| 2 | reminder system.mp. or reminder system/ | 2177 |
| 3 | drug packaging.mp. | 8649 |
| 4 | drug delivery system.mp. | 98641 |
| 5 | webster pack.mp. | 1 |
| 6 | webster pak.mp. | 6 |
| 7 | webstercare.mp. | 2 |
| 8 | unit dose pack.mp. | 4 |
| 9 | multi dose pack.mp. | 0 |
| 10 | PacMED.mp. | 5 |
| 11 | Meditech.mp. | 665 |
| 12 | medico pack.mp. | 0 |
| 13 | Mediwheel.mp. or Medi-wheel.mp. | 1 |
| 14 | Medichest.mp. | 0 |
| 15 | automated packing.mp | 1 |
| 16 | drug administration management.mp. | 1 |
| 17 | medication pack.mp | 3 |
| 18 | venalink.mp | 9 |
| 19 | blister pack.mp. or exp blister pack/ | 568 |
| 20 | (blister adj2 (pack\* or pak\*)).mp. | 770 |
| 21 | (calendar adj2 (pack\* or pak\*)).mp. | 50 |
| 22 | (c-pak or c-pack or c-cap\*).mp. | 929 |
| 23 | (bubble adj2 (pack\* or pak\*)).mp | 25 |
| 24 | ((pil\* or medication\*) adj2 (pack\* or organi?er\* or delivery system\* or container\* or box\* or dispenser\* or device\*)).mp.. | 1697 |
| 25 | ((multicompartment or multi-compartment) adj2 (pack\* or organi?er\* or delivery system\* or container\* or box\* or dispenser\* or device\*)).mp. | 19 |
| 26 | pillbox\*.mp. | 187 |
| 27 | doset\*.mp. | 220 |
| 28 | ((prescription\* or refill\* or medication\*) adj2 reminder\*).mp. | 307 |
| 29 | ((prescription\* or medication\* or drug\* or compliance or adherence) adj2 refill\*).mp. | 1607 |
| 30 | ((adherence or compliance or persist\* or accept\* or reminder or prompt\*) adj (device\* or aid\*)).mp. | 439 |
| 31 | mediset.mp | 9 |
| 32 | medidos.mp. | 30 |
| 33 | manrex.mp. | 1 |
| 34 | pre-pack\*.mp. | 469 |
| 35 | nomad\*.mp. | 1399 |
| 36 | 1 or 2 or 3 or 4 or 5 or 6 or 7 or 8 or 9 or 10 or 11 or 12 or 13 or 14 or 15 or 16 or 17 or 18 or 19 or 20 or 21 or 22 or 23 or 24 or 25 or 26 or 27 or 28 or 29 or 30 or 31 or 32 or 33 or 34 or 35 | 116704 |
| 37 | (complian\* or noncomplian\* or non-complian\*).mp. | 259463 |
| 38 | (adhere\* or nonadhere\* or non-adhere\*).mp. | 208984 |
| 39 | persist\*.mp. | 496503 |
| 40 | accept\*.mp. | 455644 |
| 41 | concordance.mp. | 48227  |
| 42 | 37 or 38 or 39 or 40 or 41 | 1378644 |
| 43 | pharmac\*.mp. | 1199299  |
| 44 | community pharmac\*.mp. | 9142 |
| 45 | 43 or 44 | 1199299 |
| 46 | 36 and 42 and 45 | 3513 |
| 47 | limit 46 to (human and english language) | 2447 |
| 48 | limit 47 to (book or book series or conference proceeding or "conference review" or editorial or erratum or letter or note) | 689 |
| 49 | 47 not 48 | 1758 |

mp = title, abstract, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword

Table A-3. 2 Medline search strategy (23rd August 2016)

|  |  |  |
| --- | --- | --- |
| # | Search term | Number of citations |
| 1 | dose administration aid\*.mp. | 6 |
| 2 | reminder system.mp. or reminder system/ | 323 |
| 3 | drug packaging.mp. | 4623 |
| 4 | drug delivery system.mp. | 6331 |
| 5 | webster pack.mp. | 0 |
| 6 | webster pak.mp. | 1 |
| 7 | webstercare.mp. | 0 |
| 8 | unit dose pack.mp. | 0 |
| 9 | multi dose pack.mp. | 0 |
| 10 | PacMED.mp. | 2 |
| 11 | Meditech.mp. | 79 |
| 12 | medico pack.mp. | 0 |
| 13 | Mediwheel.mp. or Medi-wheel.mp. | 0 |
| 14 | Medichest.mp. | 0 |
| 15 | automated packing.mp | 1 |
| 16 | drug administration management.mp. | 1 |
| 17 | medication pack.mp | 2 |
| 18 | venalink.mp | 2 |
| 19 | blister pack.mp. or exp blister pack/ | 64 |
| 20 | (blister adj2 (pack\* or pak\*)).mp. | 207 |
| 21 | (calendar adj2 (pack\* or pak\*)).mp. | 37 |
| 22 | (c-pak or c-pack or c-cap\*).mp. | 791 |
| 23 | (bubble adj2 (pack\* or pak\*)).mp | 9 |
| 24 | ((pil\* or medication\*) adj2 (pack\* or organi?er\* or delivery system\* or container\* or box\* or dispenser\* or device\*)).mp.. | 942 |
| 25 | ((multicompartment or multi-compartment) adj2 (pack\* or organi?er\* or delivery system\* or container\* or box\* or dispenser\* or device\*)).mp. | 16 |
| 26 | pillbox\*.mp. | 89 |
| 27 | doset\*.mp. | 12 |
| 28 | ((prescription\* or refill\* or medication\*) adj2 reminder\*).mp. | 149 |
| 29 | ((prescription\* or medication\* or drug\* or compliance or adherence) adj2 refill\*).mp. | 792 |
| 30 | ((adherence or compliance or persist\* or accept\* or reminder or prompt\*) adj (device\* or aid\*)).mp. | 274 |
| 31 | mediset.mp | 7 |
| 32 | medidos.mp. | 14 |
| 33 | manrex.mp. | 0 |
| 34 | pre-pack\*.mp. | 250 |
| 35 | nomad\*.mp. | 1096 |
| 36 | 1 or 2 or 3 or 4 or 5 or 6 or 7 or 8 or 9 or 10 or 11 or 12 or 13 or 14 or 15 or 16 or 17 or 18 or 19 or 20 or 21 or 22 or 23 or 24 or 25 or 26 or 27 or 28 or 29 or 30 or 31 or 32 or 33 or 34 or 35 | 15635 |
| 37 | (complian\* or noncomplian\* or non-complian\*).mp. | 136678 |
| 38 | (adhere\* or nonadhere\* or non-adhere\*).mp. | 153962 |
| 39 | persist\*.mp. | 350334 |
| 40 | accept\*.mp. | 346076 |
| 41 | concordance.mp. | 29735 |
| 42 | 37 or 38 or 39 or 40 or 41 | 964630 |
| 43 | pharmac\*.mp. | 694696 |
| 44 | community pharmac\*.mp. | 4989 |
| 45 | 43 or 44 | 694696 |
| 46 | 36 and 42 and 45  | 716 |
| 47 | limit 46 to (human and english language) | 577 |
| 48 | limit 47 to (case reports or comment or editorial or letter or published erratum) | 23 |
| 49 | 47 not 48 | 554 |

mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier

Table A-3. 3 International Pharmaceutical Abstracts (IPA) search strategy (23rd August 2016)

|  |  |  |
| --- | --- | --- |
| # | Search term | Number of citations |
| 1 | dose administration aid\*.mp. | 3 |
| 2 | reminder system.mp. | 34 |
| 3 | drug packaging.mp. | 76 |
| 4 | drug delivery system.mp. | 2516 |
| 5 | webster pack.mp. | 0 |
| 6 | webster pak.mp. | 3 |
| 7 | webstercare.mp. | 0 |
| 8 | unit dose pack.mp. | 43 |
| 9 | multi dose pack.mp. | 0 |
| 10 | PacMED.mp. | 0 |
| 11 | Meditech.mp. | 17 |
| 12 | medico pack.mp. | 0 |
| 13 | Mediwheel.mp. or Medi-wheel.mp. | 0 |
| 14 | Medichest.mp. | 0 |
| 15 | automated packing.mp | 0 |
| 16 | drug administration management.mp. | 0 |
| 17 | medication pack.mp | 1 |
| 18 | venalink.mp | 1 |
| 19 | blister pack.mp. or exp blister pack/ | 27 |
| 20 | (blister adj2 (pack\* or pak\*)).mp. | 176 |
| 21 | (calendar adj2 (pack\* or pak\*)).mp. | 11 |
| 22 | (c-pak or c-pack or c-cap\*).mp. | 17 |
| 23 | (bubble adj2 (pack\* or pak\*)).mp | 4 |
| 24 | ((pil\* or medication\*) adj2 (pack\* or organi?er\* or delivery system\* or container\* or box\* or dispenser\* or device\*)).mp.. | 407 |
| 25 | ((multicompartment or multi-compartment) adj2 (pack\* or organi?er\* or delivery system\* or container\* or box\* or dispenser\* or device\*)).mp. | 1 |
| 26 | pillbox\*.mp. | 20 |
| 27 | doset\*.mp. | 13 |
| 28 | ((prescription\* or refill\* or medication\*) adj2 reminder\*).mp. | 51 |
| 29 | ((prescription\* or medication\* or drug\* or compliance or adherence) adj2 refill\*).mp. | 593 |
| 30 | ((adherence or compliance or persist\* or accept\* or reminder or prompt\*) adj (device\* or aid\*)).mp. | 93 |
| 31 | mediset.mp | 1 |
| 32 | medidos.mp. | 2 |
| 33 | manrex.mp. | 0 |
| 34 | pre-pack\*.mp. | 12 |
| 35 | nomad\*.mp. | 9 |
| 36 | 1 or 2 or 3 or 4 or 5 or 6 or 7 or 8 or 9 or 10 or 11 or 12 or 13 or 14 or 15 or 16 or 17 or 18 or 19 or 20 or 21 or 22 or 23 or 24 or 25 or 26 or 27 or 28 or 29 or 30 or 31 or 32 or 33 or 34 or 35 | 3982 |
| 37 | (complian\* or noncomplian\* or non-complian\*).mp. | 13047 |
| 38 | (adhere\* or nonadhere\* or non-adhere\*).mp. | 5855 |
| 39 | persist\*.mp. | 6418 |
| 40 | accept\*.mp. | 10250 |
| 41 | concordance.mp. | 361 |
| 42 | 37 or 38 or 39 or 40 or 41 | 31738 |
| 43 | pharmac\*.mp. | 195014 |
| 44 | community pharmac\*.mp. | 9583 |
| 45 | 43 or 44 | 195014 |
| 46 | 36 and 42 and 45  | 409 |
| 47 | limit 46 to (human and english language) | 191 |
| 48 | limit 47 to (editorials or letters or notes) | 1 |
| 49 | 47 not 48 | 190 |

mp = title, subject heading word, registry word, abstract, trade name/generic name.

Table A-3. 4 Cochrane Library search strategy (17th August 2016)

|  |  |  |
| --- | --- | --- |
| # | Search term | Number of citations |
| 1 | dose administration aid\*.mp. | 2675 |
| 2 | reminder system.mp. | 723 |
| 3 | drug packaging.mp. | 489 |
| 4 | drug delivery system.mp. | 4092 |
| 5 | webster pack.mp. | 32 |
| 6 | webster pak.mp. | 7 |
| 7 | webstercare.mp. | 0 |
| 8 | unit dose pack.mp. | 339 |
| 9 | multi dose pack.mp. | 205 |
| 10 | PacMED.mp. | 0 |
| 11 | Meditech.mp. | 16 |
| 12 | medico pack.mp. | 15 |
| 13 | Mediwheel.mp. or Medi-wheel.mp. | 2 |
| 14 | Medichest.mp. | 0 |
| 15 | automated packing.mp | 12 |
| 16 | drug administration management.mp. | 16352 |
| 17 | medication pack.mp | 454 |
| 18 | venalink.mp | 0 |
| 19 | blister pack.mp. or exp blister pack/ | 85 |
| 20 | Medication pack | 454 |
| 21 | (calendar adj2 (pack\* or pak\*)).mp. | 31 |
| 22 | (c-pak or c-pack or c-cap\*).mp. | 103 |
| 23 | (bubble adj2 (pack\* or pak\*)).mp | 11 |
| 24 | Pill pack | 93 |
| 25 | ((multicompartment or multi-compartment) adj2 (pack\* or organi?er\* or delivery system\* or container\* or box\* or dispenser\* or device\*)).mp. | 2 |
| 26 | pillbox\*.mp. | 20 |
| 27 | doset\*.mp. | 14 |
| 28 | Reminder pack\* | 200 |
| 29 | Medicine compliance aid | 466 |
| 30 | Adherence aid | 234 |
| 31 | mediset.mp | 2 |
| 32 | medidos.mp. | 22 |
| 33 | manrex.mp. | 1 |
| 34 | pre-pack\*.mp. | 1 |
| 35 | nomad\*.mp. | 18 |
| 36 | 1 or 2 or 3 or 4 or 5 or 6 or 7 or 8 or 9 or 10 or 11 or 12 or 13 or 14 or 15 or 16 or 17 or 18 or 19 or 20 or 21 or 22 or 23 or 24 or 25 or 26 or 27 or 28 or 29 or 30 or 31 or 32 or 33 or 34 or 35 | 21848 |
| 37 | (complian\* or noncomplian\* or non-complian\*).mp. | 30203 |
| 38 | (adhere\* or nonadhere\* or non-adhere\*).mp. | 14594 |
| 39 | persist\*.mp. | 7720 |
| 40 | accept\*.mp. | 3038 |
| 41 | concordance.mp. | 1778 |
| 42 | 37 or 38 or 39 or 40 or 41 | 48720 |
| 43 | pharmac\*.mp. | 164978 |
| 44 | community pharmac\*.mp. | 4807 |
| 45 | 43 or 44 | 164978 |
| 46 | 36 and 42 and 45  | 439 |

# APPENDIX 4 Excluded publications

Table A-4. 1 Citation details for other identified reviews excluded from the current evaluation

|  |  |
| --- | --- |
| Citation | Reasons for exclusion |
| Conn VS, Ruppar TM, Chan KC, Dunbar-Jacob J, Pepper GA, De Geest S (2015). Packaging interventions to increase medication adherence: Systematic review and meta-analysis. Current Medical Research and Opinion, 31(1):145-60. | Examines any intervention, including DAAs that directly improve medication adherence in patients with any medical condition. A pooled analysis of 47/52 included studies was performed. No new evidence was identified from hand searching the reference list |
| Elliott RA (2014). Appropriate use of dose administration aids. Australian Prescriber, 37(2):46-50. | Narrative review. No new evidence was identified from hand searching the reference list. |
| Ryan R, Santesso N, Lowe D, Hill S, Grimshaw J, Prictor M, et al. (2014). Interventions to improve safe and effective medicines use by consumers: an overview of systematic reviews. The Cochrane database of systematic reviews, (4):CD007768. | A systematic review of 75 other systematic reviews, which included the Mahtani (2011) Cochrane review. The objectives and scope of included reviews varied, although almost primarily aimed to improve adherence to medicines or uptake of immunisations using any intervention. No new evidence was identified from hand searching the reference list. |
| Gwadry-Sridhar FH, Manias E, Lal L, Salas M, Hughes DA, Ratzki-Leewing A, et al. (2013). Impact of interventions on medication adherence and blood pressure control in patients with essential hypertension: A systematic review by the ISPOR medication adherence and persistence special interest group. Value in Health, 16(5):863-71. | Examines any intervention that may improve adherence to antihypertensive medication. No new evidence was identified from hand searching the reference list. |
| Hersberger KE, Boeni F, Arnet I (2013). Dose-dispensing service as an intervention to improve adherence to polymedication. Expert Review of Clinical Pharmacology, 6(4):413-21. | Narrative review. No new evidence was identified from hand searching the reference list. |
| George J, Elliott RA, Stewart DC (2008). A systematic review of interventions to improve medication taking in elderly patients prescribed multiple medications. Drugs and Aging, 25(4):307-24. | Examines any pharmacy intervention that may enhance adherence in the elderly with a focus on patient education, medication review, and pharmacist follow-up. No new evidence was identified from hand searching the reference list. |
| Heneghan CJ, Glasziou P, Perera R (2006). Reminder packaging for improving adherence to self-administered long-term medications. Cochrane Database of Systematic Reviews, (1):CD005025. | Superseded by the Mahtani (2011) Cochrane review. |
| Lindenmeyer A, Hearnshaw H, Vermeire E, Van Royen P, Wens J, Biot Y (2006). Interventions to improve adherence to medication in people with type 2 diabetes mellitus: A review of the literature on the role of pharmacists. Journal of Clinical Pharmacy and Therapeutics, 31(5):409-19. | Focusses on a range of diabetes care interventions delivered by pharmacists to improve adherence to medication. The studies reviewed formed a subgroup of those reported in the Vermiere (2005) Cochrane review. This included the study by Skaer et al (1993a), which was included in the Mahtani (2011) Cochrane review, the Zedler (2011) and the Boeni (2014) systematic reviews. |
| Connor J, Rafter N, Rodgers A (2004). Do fixed-dose combination pills or unit-of-use packaging improve adherence? A systematic review. Bull World Health Organ, 82(12):935-9. | Presents a narrative discussion only, thus presenting difficulties with data extraction. No new evidence was identified from hand searching the reference list. |
| Krueger KP, Felkey BG, Berger BA (2003). Improving adherence and persistence: a review and assessment of interventions and description of steps toward a national adherence initiative. Journal of the American Pharmacists Association: JAPhA, 43(6):668-78; quiz 78-79. | Focusses on adherence-related interventions and their effectiveness. No new evidence was identified from hand searching the reference list. |

Table A-4. 2 Citation details for other identified primary studies excluded from the current evaluation

|  |  |
| --- | --- |
| Citation | Reason for exclusion |
| Mosca C, Castel-Branco MM, Ribeiro-Rama AC, Caramona MM, Fernandez-Llimos F, Figueiredo IV (2014). Assessing the impact of multi-compartment compliance aids on clinical outcomes in the elderly: A pilot study. International Journal of Clinical Pharmacy, 36(1):98-104. | Participants received medication follow-up from the community pharmacist. |
| Zillich AJ, Jaynes HA, Snyder ME, Harrison J, Hudmon KS, de Moor C, et al. (2012). Evaluation of specialized medication packaging combined with medication therapy management: adherence, outcomes, and costs among Medicaid patients. Medical Care, 50(6):485-93. | Intervention included specialised medication packaging and telephonic medication therapy management. |
| Jansen A, Andersen KF, Bruning H (2009). Evaluation of a compliance device in a subgroup of adult patients receiving specific immunotherapy with grass allergen tablets (GRAZAX) in a randomized, open-label, controlled study: an a priori subgroup analysis. Clinical Therapeutics, 31(2):321-7. | Automated compliance device. |
| Nochowitz B, Shapiro NL, Nutescu EA, Cavallari LH. (2009). Effect of a warfarin adherence aid on anticoagulation control in an inner-city anticoagulation clinic population. Ann Pharmacother, (43):1165–1172. | Drug reminder packaging in combination with other aids. |
| Valenstein M, Kavanagh J, Lee T, Reilly P, Dalack GW, Grabowski J, Smelson D, Ronis DL, Ganoczy D, Woltmann E, Metreger T, Wolschon P, Jensen A, Poddig B, Blow FC (2009). Using a pharmacy-based intervention to improve antipsychotic adherence among patients with serious mental illness. Schizophr Bull, 37:727–736. | Multifaceted pharmacy intervention, consisting of a unit-of-use packaging, medication and packaging education session, refill reminders and notification of clinicians when patients failed to fill antipsychotic prescriptions within 7–10 days of a fill date. |
| Kripalani S, Robertson R, Love-Ghaffari MH, Henderson LE, Praska J, Strawder A, et al. (2007). Development of an illustrated medication schedule as a low-literacy patient education tool. Patient Education and Counseling, 66(3):368-77. | Examined the use of an illustrated medication schedule (pill card). |
| Murray MD, Young J, Hoke S, Tu W, Weiner M, Morrow D, et al. (2007). Pharmacist intervention to improve medication adherence in heart failure: a randomized trial. Annals of Internal Medicine 2007; 146(10):714–25. | The intervention group were given care from a pharmacist who provided a 9-month multilevel intervention, with a 3-month post study phase. Control group received standard care. |
| Lee JK, Grace KA, Taylor AJ (2006). Effect of a pharmacy care program on medication adherence and persistence, blood pressure, and low-density lipoprotein cholesterol: a randomized controlled trial. JAMA, 296:2563–2571 | Multifaceted pharmacy intervention, consisting of individualised medication education (using standardised scripts), medications dispensed using blister packs, and regular follow-up with clinical pharmacists every 2 months. |
| Suppapitiporn S, Chindavijak B, Onsanit S (2005). Effect of diabetes drug counseling by pharmacist, diabetic disease booklet and special medication containers on glycemic control of type 2 diabetes mellitus: a randomized controlled trial. Journal of the Medical Association of Thailand; 88 Suppl 4:S134–41. | Multiple interventions (included disease counselling and education). Participants were recruited from Endocrine Clinics in King Chulalongkorn Memorial Hospital, Bangkok. |
| Huang HA, Maguire MG, Miller ER, Appel LJ (2000). Impact of pill organizers and blister packs on adherence to pill taking in two vitamin supplement trials (TRACE). American Journal of Epidemiology, 152:780–7. | Pill organisers packed by the study participants. |
| Henry A, Batey RG (1999). Enhancing compliance not a prerequisite for effective eradication of Helicobacter Pylori: the HelP study. American Journal of Gastroenterology, 94(3):811–5. | Patient received a package of “compliance enhancing measures” including a dose dispensing unit, medication chart, an information sheet about H. pylori treatment, and phone call 2 days after starting therapy. Treatment extended over ten days. |
| Azrin NH, Teichner G (1998). Evaluation of an instructional program for improving medication compliance for chronically mentally ill outpatients. Behaviour Research and Therapy, 36:849–61. | Drug reminder packaging used in combination with other interventions.Pillbox, not tamper-evident. |
| Murray MD, Birt JA, Manatunga AK, Darnell JC. Medication compliance in elderly outpatients using twice daily dosing and unit-of-use packaging. Annals of Pharmacotherapy 1993; 27:616–21. | Unit-of-use packaging, with no clear use of a calendar device. A colour system was used for labelling medication packages. |
| Ware GJ, Holford N, Davison JG (1991). Unit dose calendar packaging and elderly compliance. New Zealand Medical Journal, 104:495–7. | The unit dose calendar packaging (Webster-Pak) was provided to inpatients that were followed-up three months after discharge to the community.  |
| Binstock ML, Franklin KL (1988). A comparison of compliance techniques on the control of high blood pressure. American Journal of Hypertension, 1:192S–4S. | Drug reminder packaging used in combination with other interventions. |
| Peterson GM, McLean S, Millingen KS (1984). A randomised trial of strategies to improve patient compliance with anticonvulsant therapy. Epilepsia, 25(4):412-7. | Participants were given a combination of “compliance-improving strategies” for the treatment of epilepsy. |
| Crome P, Curl B, Boswell M, Corless D, Lewis RR (1982). Assessment of a new calendar pack: the C-Pak. Age and Ageing, 11:275–9. | In-hospital patients. |
| Rehder TL, McCoy LK, Blackwell B, et al. (1980). Improving medication compliance by counseling and special prescription container. Am J Hosp Pharm; (37):379–85. | Special medication containers used in combination with counselling. |
| Eshelman FN, Fitzloff J (1976). Effect of packaging on patient compliance with an antihypertensive medication. Curr Ther Res Clin Exp, 20(2):215-9. | Study published 40 years ago and the study package was not described in the publication. |

# APPENDIX 5 Medication adherence measures

Table A-5. 1 Summary of medication adherence measures, self-report and questionnaires used in the literature

| Outcome measure | Definition | Equation/function | Target population | For primary or secondary nonadherence | Advantages | Disadvantages |
| --- | --- | --- | --- | --- | --- | --- |
| Pill count | This measures adherence by comparing the number of doses remaining in the patient’s supply with the number of doses that should be present, if the patient has taken all doses on schedule. | (Number of dosage units dispensed − number of dosage units remained)/(prescribed number of dosage unit per day × number of days between 2 visits) | Routine clinical practice | Primary nonadherence | * Low cost
* Simple
* Can be used in various formulations
* Highly accurate
 | * Not for non-discrete dosages or prn medications
* Underestimation due to early refill
* Arbitrary cut-off value
* Unable to identify medication-taking pattern
 |
| Medication Possession Ratio (MPR) | This measures the percentage of time a patient has access to medication | Number of days of medication supplied within the refill interval / number of days in refill interval | Routine clinical practice | Measures compliance | Calculated as both a continuous and dichotomous measure | * Can overestimate adherence due to summing the days’ supply because patients usually refill their medication before completing the current fill.
* Does not consider the gaps in refills
* There are differences in MPR denominator definition in the literature, thus complicating comparisons across studies
 |
| Patient estimates of adherence-self report | Direct questioning of patients to assess adherence can be an effective method. Patients who admit to non-adherence are generally accurate in their assessment. They can be administered as structured interviews, online assessments, written questionnaires, voice response system, etc. | - | * Routine clinical practice
* Less suitable for research
 | It depends on the type of assessments and questionnaires used | * Low cost
* Easy to administer
* Real-time feedback Available
* Flexible to accommodate different conditions
* Identify belief and barriers to adherence
* Well-validated
 | * Least reliable
* Relatively poor sensitivity and specificity
* Affected by communication skills of interviewers and questions in the questionnaire
* Patient’s desirability can bias
 |
| **Scaled questionnaire** |  |  |  |  |  |  |
| Morisky Medication Adherence Scale | This is an 8-item scaled questionnaire to assess adherence. The first seven items are Yes/No responses while the last item is a 5-point Likert response. The additional items focus on medication taking behaviours, especially related to underuse, such as forgetfulness.  | * Patient’s medication-taking behaviour
* Barriers to adherence
 | All validated conditions | - | Higher validity and reliability in patients with chronic diseases than MAQ | - |

Source: Adapted from Lam and Fresco (2015), Table 1, p. 3; Table 2, pp. 8-9

Note: Proportion of Days Covered (PDC) is a measure of persistence to the medication therapy, instead of adherence

# APPENDIX 6 Quality Assessment

## Systematic reviews

Table A-6.1 shows the 11 items considered in the AMSTAR tool. The results of the quality assessment for the three included systematic reviews are presented in Table A-6.1.

For each of the included systematic reviews, an overall score was calculated (simply the sum of the individual item scores), with a maximum possible score of 11/11. When one or more of the AMSTAR items were not applicable to a particular publication, the denominator was reduced to reflect the number of relevant criteria. For example, if a systematic review did not conduct a meta-analysis, the item pertaining to the appropriate pooling of results was not applicable and the overall quality score was out of 10.

Table A-6.1 The AMSTAR measurement tool for assessing the methodological quality of SRs

|  |  |
| --- | --- |
| Question | Answer |
| 1. Was an 'a priori' design provided?The research question and inclusion criteria should be established before the conduct of the review.Note: Need to refer to a protocol, ethics approval, or pre-determined/a priori published research objectives to score a “yes.” | * Yes
* No
* Can’t answer
* Not applicable
 |
| 2. Was there duplicate study selection and data extraction?There should be at least two independent data extractors and a consensus procedure for disagreements should be in place.Note: 2 people do study selection, 2 people do data extraction, consensus process or one person checks the other’s work. | * Yes
* No
* Can’t answer
* Not applicable
 |
| 3. Was a comprehensive literature search performed?At least two electronic sources should be searched. The report must include years and databases used (e.g., Central, EMBASE, and MEDLINE). Key words and/or MESH terms must be stated and where feasible the search strategy should be provided. All searches should be supplemented by consulting current contents, reviews, textbooks, specialized registers, or experts in the particular field of study, and by reviewing the references in the studies found.Note: If at least 2 sources + one supplementary strategy used, select “yes” (Cochrane register/Central counts as 2 sources; a grey literature search counts as supplementary). | * Yes
* No
* Can’t answer
* Not applicable
 |
| 4. Was the status of publication (i.e. grey literature) used as an inclusion criterion?The authors should state that they searched for reports regardless of their publication type. The authors should state whether or not they excluded any reports (from the systematic review), based on their publication status, language etc.Note: If review indicates that there was a search for “grey literature” or “unpublished literature,” indicate “yes.” SIGLE database, dissertations, conference proceedings, and trial registries are all considered grey for this purpose. If searching a source that contains both grey and non-grey, must specify that they were searching for grey/unpublished lit. | * Yes
* No
* Can’t answer
* Not applicable
 |
| 5. Was a list of studies (included and excluded) provided?A list of included and excluded studies should be provided.Note: Acceptable if the excluded studies are referenced. If there is an electronic link to the list but the link is dead, select “no.” | * Yes
* No
* Can’t answer
* Not applicable
 |
| 6. Were the characteristics of the included studies provided?In an aggregated form such as a table, data from the original studies should be provided on the participants, interventions and outcomes. The ranges of characteristics in all the studies analyzed e.g., age, race, sex, relevant socioeconomic data, disease status, duration, severity, or other diseases should be reported.Note: Acceptable if not in table format as long as they are described as above. | * Yes
* No
* Can’t answer
* Not applicable
 |
| 7. Was the scientific quality of the included studies assessed and documented?'A priori' methods of assessment should be provided (e.g., for effectiveness studies if the author(s) chose to include only randomized, double blind, placebo controlled studies, or allocation concealment as inclusion criteria); for other types of studies alternative items will be relevant.Note: Can include use of a quality scoring tool or checklist, e.g., Jadad scale, risk of bias, sensitivity analysis, etc., or a description of quality items, with some kind of result for EACH study (“low” or “high” is fine, as long as it is clear which studies scored “low” and which scored “high”; a summary score/range for all studies is not acceptable). | * Yes
* No
* Can’t answer
* Not applicable
 |
| 8. Was the scientific quality of the included studies used appropriately in formulating conclusions?The results of the methodological rigor and scientific quality should be considered in the analysis and the conclusions of the review, and explicitly stated in formulating recommendations.Note: Might say something such as “the results should be interpreted with caution due to poor quality of included studies.” Cannot score “yes” for this question if scored “no” for question 7. | * Yes
* No
* Can’t answer
* Not applicable
 |
| 9. Were the methods used to combine the findings of studies appropriate?For the pooled results, a test should be done to ensure the studies were combinable, to assess their homogeneity (i.e., Chi-squared test for homogeneity, I2). If heterogeneity exists a random effects model should be used and/or the clinical appropriateness of combining should be taken into consideration (i.e., is it sensible to combine?).Note: Indicate “yes” if they mention or describe heterogeneity, i.e., if they explain that they cannot pool because of heterogeneity/variability between interventions. | * Yes
* No
* Can’t answer
* Not applicable
 |
| 10. Was the likelihood of publication bias assessed?An assessment of publication bias should include a combination of graphical aids (e.g., funnel plot, other available tests) and/or statistical tests (e.g., Egger regression test, Hedges-Olken).Note: If no test values or funnel plot included, score “no”. Score “yes” if mentions that publication bias could not be assessed because there were fewer than 10 included studies. | * Yes
* No
* Can’t answer
* Not applicable
 |
| 11. Was the conflict of interest included?Potential sources of support should be clearly acknowledged in both the systematic review and the included studies.Note: To get a “yes,” must indicate source of funding or support for the systematic review AND for each of the included studies. | * Yes
* No
* Can’t answer
* Not applicable
 |

Source: Shea et al (2007), Table 2

Abbreviations: SR, systematic review

Table A-6.2 below shows AMSTAR scores of included systematic reviews.

Table A-6.2 AMSTAR scores of included systematic reviews

|  |  |  |  |  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
| Author, Year | Overall AMSTAR score a | (1)Provided study design | (2)Duplicate study selection | (3)Broad literature search | (4)Considered status of publication | (5)List of studies | (6)Provided study character-istics | (7)Assessed scientific quality | (8)Considered quality in report | (9)Methods to combine appropriate | (10)Assessed publication bias | (11)Stated conflict of interest |
| Boeni (2014) | 5/10 | 0 | 1 | 1 | 0 | 0 | 1 | 1 | 1 | NA | 0 | 0 |
| Mahtani (2011) | 10/11 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 0 |
| Zedler (2011) | 5/10 | 0 | 1 | 1 | 0 | 0 | 1 | 1 | 1 | NA | 0 | 0 |

Abbreviations: AMSTAR, Assessment of Multiple Systematic Reviews; CA, can’t answer; HTA, health technology assessment; NA, not applicable.

**a** 1 = Yes, 0 = No; maximum possible score is 11. Details of AMSTAR Score are described in Shea et al (2007).

## Primary studies

Table A-6.3 below shows quality analysis of primary studies adapted from NHMRC 2000 toolkit – How to use the evidence: assessment and application of scientific evidence.

Table A-6.3 Quality analysis of primary studies – Dumas (2016)

| **Y** | **N** | **NR** | **NA** | **Study type: Prospective cohort study** |
| --- | --- | --- | --- | --- |
|  |  |  |  | Study ID: **Dumas (2016)** |
|  |  |  |  | **Quality criteria** |
|  |  |  |  | A. Was the selection of subjects appropriate? |
|  | 🗸 |  |  | Were the two groups being studied selected from source populations that are comparable in all respects other than the factor under investigation? |
|  |  |  | 🗸 | Was the likelihood that some eligible subjects might have the outcome at the time of enrolment adequately accounted for in the analysis? |
|  |  |  |  | B. Were all recruited participants included in the analysis? |
| 🗸 |  |  |  | Does the study report whether all people who were asked to take part did so, in each of the groups being studied? |
| 🗸 |  |  |  | Was loss to follow-up and exclusions from analysis reported? |
|  | 🗸 |  |  | Was loss to follow-up and exclusions from analysis appropriately accounted for in the analysis? |
|  |  |  |  | C. Does the study design/analysis adequately control for potential confounding variables? |
|  | 🗸 |  |  | Does the study adequately control for demographic characteristics, clinical features, and other potential confounding variables in the study design or analysis? |
|  |  |  |  | D. Was outcome assessment subject to bias? |
| 🗸 |  |  |  | Were all relevant outcomes measured in a standard, valid, and reliable way? |
|  | 🗸 |  |  | Was outcome assessment blinded to exposure status? |
|  |  |  | 🗸 | If outcome assessment was not blinded, were outcomes objective and unlikely to be influenced by blinding of assessment? |
|  |  |  |  | E. Was follow-up adequate? |
|  |  | 🗸 |  | Was follow-up long enough for outcomes to occur? |
|  |  |  |  | Comments: The demographic and clinical characteristics were different between nonusers and pharmacist-prepared pillbox users. Dropouts and losses-to-follow-up were reported, however, an intention-to-treat analysis was not carried out as final analysis was only carried out on the participants that completed the study. Healthy user bias may have been present in this study as pillbox users could have had generally healthier behaviours than nonusers. Concomitant drug use is a potential confounder which was not accounted for in the results and thus may bias the results. |
|  |  |  |  | Quality rating [Good/Fair/Poor]: Poor |

Note: Quality criteria adapted from NHMRC (2000) How to use the evidence: assessment and application of scientific evidence. NHMRC, Canberra.

Assess criterion using Y (yes), N (no), NR (not reported) or NA (not applicable).

Table A-6.4 Quality analysis of primary studies – Dupclay (2012)

| **Y** | **N** | **NR** | **NA** | **Study type: Retrospective cohort study** |
| --- | --- | --- | --- | --- |
|  |  |  |  | Study ID: **Dupclay (2012)** |
|  |  |  |  | **Quality criteria** |
|  |  |  |  | A. Was the selection of subjects appropriate? |
| 🗸 |  |  |  | Were the two groups being studied selected from source populations that are comparable in all respects other than the factor under investigation? |
|  |  |  | 🗸 | Was the likelihood that some eligible subjects might have the outcome at the time of enrolment adequately accounted for in the analysis? |
|  |  |  |  | B. Were all recruited participants included in the analysis? |
| 🗸 |  |  |  | Does the study report whether all people who were asked to take part did so, in each of the groups being studied? |
|  |  | 🗸 |  | Was loss to follow-up and exclusions from analysis reported? |
|  |  | 🗸 |  | Was loss to follow-up and exclusions from analysis appropriately accounted for in the analysis? |
|  |  |  |  | C. Does the study design/analysis adequately control for potential confounding variables? |
|  |  | 🗸 |  | Does the study adequately control for demographic characteristics, clinical features, and other potential confounding variables in the study design or analysis? |
|  |  |  |  | D. Was outcome assessment subject to bias? |
| 🗸 |  |  |  | Were all relevant outcomes measured in a standard, valid, and reliable way? |
|  | 🗸 |  |  | Was outcome assessment blinded to exposure status? |
|  |  |  | 🗸 | If outcome assessment was not blinded, were outcomes objective and unlikely to be influenced by blinding of assessment? |
|  |  |  |  | E. Was follow-up adequate? |
|  |  | 🗸 |  | Was follow-up long enough for outcomes to occur? |
|  |  |  |  | Comments:  |
|  |  |  |  | Quality rating [Good/Fair/Poor]: Retrospective design introduces selection bias that may confound the relationship between treatment and the outcomes of interestPoor |

Note: Quality criteria adapted from NHMRC (2000) How to use the evidence: assessment and application of scientific evidence. NHMRC, Canberra.

Assess criterion using Y (yes), N (no), NR (not reported) or NA (not applicable).

Table A-6.5 Quality analysis of primary studies – Schneider (2008)

| **Y** | **N** | **NR** | **NA** | **Study type: Randomised controlled trial** |
| --- | --- | --- | --- | --- |
|  |  |  |  | Study ID: **Schneider (2008)** |
|  |  |  |  | **Quality criteria** |
|  |  |  |  | A. Was assignment of subjects to treatment group randomised? |
| 🗸 |  |  |  | Was the use of randomisation reported? |
| 🗸 |  |  |  | Was the method of randomisation reported? |
| 🗸 |  |  |  | Was the method of randomisation appropriate? |
|  |  |  |  | B. Was allocation to treatment groups concealed from those responsible for recruiting subjects? |
| 🗸 |  |  |  | Was a method of allocation concealment reported? |
|  | 🗸 |  |  | Was the method of allocation concealment adequate? |
|  |  |  |  | C. Was the study double-blinded? |
|  | 🗸 |  |  | Were subjects and investigators blinded to treatment arm? |
|  |  |  |  | D. Were patient characteristics and demographics similar between treatment arms at baseline? |
| 🗸 |  |  |  | Were baseline patient characteristics and demographics reported? |
|  | 🗸 |  |  | Were the characteristics similar between treatment arms? |
|  |  |  |  | E. Were all randomised participants included in the analysis? |
| 🗸 |  |  |  | Was loss to follow-up reported? |
| 🗸 |  |  |  | Was loss to follow-up appropriately accounted for in the analysis? |
|  |  |  |  | F. Was outcome assessment likely to be subject to bias? |
| 🗸 |  |  |  | Were all relevant outcomes measured in a standard, valid, and reliable way? |
|  | 🗸 |  |  | Was outcome assessment blinded to treatment allocation? |
|  |  |  | 🗸 | If outcome assessment was not blinded, were outcomes objective and unlikely to be influenced by blinding of assessment? |
|  |  |  |  | G. Were the statistical methods appropriate? |
| 🗸 |  |  |  | Were the methods used for comparing results between treatment arms appropriate? |
|  |  | 🗸 |  | If the study was carried out at more than one site, are the results comparable for all sites? |
|  |  |  |  | H. If appropriate, were any subgroup analyses carried out? |
|  |  |  | 🗸 | Were subgroup analyses reported? |
|  |  |  | 🗸 | Were subgroup analyses appropriate? |
|  |  |  |  | Comments: The method of randomisation was described. Blinding of key study participants and personnel attempted, but likely that the blinding could have been broken. There is selection bias as participants or investigators enrolling participants could possibly foresee assignments. An intention-to-treat analysis was attempted. However it is not clear if the 112 participants evaluated for eligibility were randomised before inclusion. No baseline assessment of adherence. Dropout rate: 22% blister pack group and 27% control groups |
|  |  |  |  | Quality rating [Good/Fair/Poor]:Fair |

Note: Quality criteria adapted from NHMRC (2000) How to use the evidence: assessment and application of scientific evidence. NHMRC, Canberra.

Assess criterion using Y (yes), N (no), NR (not reported) or NA (not applicable).

Table A-6.6 Quality analysis of primary studies – Huang (2000)

| **Y** | **N** | **NR** | **NA** | **Study type: Randomised controlled trial** |
| --- | --- | --- | --- | --- |
|  |  |  |  | Study ID: **Huang (2000)** |
|  |  |  |  | **Quality criteria** |
|  |  |  |  | A. Was assignment of subjects to treatment group randomised? |
| 🗸 |  |  |  | Was the use of randomisation reported? |
| 🗸 |  |  |  | Was the method of randomisation reported? |
| 🗸 |  |  |  | Was the method of randomisation appropriate? |
|  |  |  |  | B. Was allocation to treatment groups concealed from those responsible for recruiting subjects? |
| 🗸 |  |  |  | Was a method of allocation concealment reported?  |
| 🗸 |  |  |  | Was the method of allocation concealment adequate? |
|  |  |  |  | C. Was the study double-blinded? |
| 🗸 |  |  |  | Were subjects and investigators blinded to treatment arm? |
|  |  |  |  | D. Were patient characteristics and demographics similar between treatment arms at baseline? |
| 🗸 |  |  |  | Were baseline patient characteristics and demographics reported? |
| 🗸 |  |  |  | Were the characteristics similar between treatment arms? |
|  |  |  |  | E. Were all randomised participants included in the analysis? |
|  |  | 🗸 |  | Was loss to follow-up reported? |
|  |  | 🗸 |  | Was loss to follow-up appropriately accounted for in the analysis? |
|  |  |  |  | F. Was outcome assessment likely to be subject to bias? |
| 🗸 |  |  |  | Were all relevant outcomes measured in a standard, valid, and reliable way? |
| 🗸 |  |  |  | Was outcome assessment blinded to treatment allocation? |
|  |  |  | 🗸 | If outcome assessment was not blinded, were outcomes objective and unlikely to be influenced by blinding of assessment? |
|  |  |  |  | G. Were the statistical methods appropriate? |
| 🗸 |  |  |  | Were the methods used for comparing results between treatment arms appropriate? |
|  |  |  | 🗸 | If the study was carried out at more than one site, are the results comparable for all sites? |
|  |  |  |  | H. If appropriate, were any subgroup analyses carried out? |
|  |  |  | 🗸 | Were subgroup analyses reported? |
|  |  |  | 🗸 | Were subgroup analyses appropriate? |
|  |  |  |  | Comments: Random allocation was generated by computer and issued by opening an opaque, sealed envelope. Participants and investigators enrolling participants could not foresee assignment. Blinding of participants and key study personnel ensured. Intention-to-treat analysis was not carried out as final analysis was only carried out on the participants that completed the study. No baseline assessment of adherence. Duration too short to determine adherence to long-term treatment. Dropout rate: 3% calendar pack and 10% control groups. |
|  |  |  |  | Quality rating [Good/Fair/Poor]:Fair |

Note: Quality criteria adapted from NHMRC (2000) How to use the evidence: assessment and application of scientific evidence. NHMRC, Canberra.

Assess criterion using Y (yes), N (no), NR (not reported) or NA (not applicable).

Table A-6.7 Quality analysis of primary studies – Simmons (2000)

| **Y** | **N** | **NR** | **NA** | **Study type: Randomised controlled trial** |
| --- | --- | --- | --- | --- |
|  |  |  |  | Study ID: **Simmons (2000)** |
|  |  |  |  | **Quality criteria** |
|  |  |  |  | A. Was assignment of subjects to treatment group randomised? |
| 🗸 |  |  |  | Was the use of randomisation reported? |
| 🗸 |  |  |  | Was the method of randomisation reported? |
| 🗸 |  |  |  | Was the method of randomisation appropriate? |
|  |  |  |  | B. Was allocation to treatment groups concealed from those responsible for recruiting subjects? |
| 🗸 |  |  |  | Was a method of allocation concealment reported? |
| 🗸 |  |  |  | Was the method of allocation concealment adequate? |
|  |  |  |  | C. Was the study double-blinded? |
| 🗸 |  |  |  | Were subjects and investigators blinded to treatment arm? |
|  |  |  |  | D. Were patient characteristics and demographics similar between treatment arms at baseline? |
| 🗸 |  |  |  | Were baseline patient characteristics and demographics reported? |
| 🗸 |  |  |  | Were the characteristics similar between treatment arms? |
|  |  |  |  | E. Were all randomised participants included in the analysis? |
| 🗸 |  |  |  | Was loss to follow-up reported? |
| 🗸 |  |  |  | Was loss to follow-up appropriately accounted for in the analysis? |
|  |  |  |  | F. Was outcome assessment likely to be subject to bias? |
| 🗸 |  |  |  | Were all relevant outcomes measured in a standard, valid, and reliable way? |
| 🗸 |  |  |  | Was outcome assessment blinded to treatment allocation? |
|  |  |  | 🗸 | If outcome assessment was not blinded, were outcomes objective and unlikely to be influenced by blinding of assessment? |
|  |  |  |  | G. Were the statistical methods appropriate? |
| 🗸 |  |  |  | Were the methods used for comparing results between treatment arms appropriate? |
|  |  |  | 🗸 | If the study was carried out at more than one site, are the results comparable for all sites? |
|  |  |  |  | H. If appropriate, were any subgroup analyses carried out? |
|  |  |  | 🗸 | Were subgroup analyses reported? |
|  |  |  | 🗸 | Were subgroup analyses appropriate? |
|  |  |  |  | Comments: The method of randomisation was described. Adequate blinding was attempted. A third party was used to allocate patients to each group An intention-to-treat analysis was attempted. It is unclear whether the final analysis was carried out on all the subjects that were randomised. Follow-up was up to eight months. |
|  |  |  |  | Quality rating [Good/Fair/Poor]:Good |

Note: Quality criteria adapted from NHMRC (2000) How to use the evidence: assessment and application of scientific evidence. NHMRC, Canberra.

Assess criterion using Y (yes), N (no), NR (not reported) or NA (not applicable).

Table A-6.8 Quality analysis of primary studies – Winland-Brown (2000)

| **Y** | **N** | **NR** | **NA** | **Study type: Randomised controlled trial** |
| --- | --- | --- | --- | --- |
|  |  |  |  | Study ID: **Winland-Brown (2000)** |
|  |  |  |  | **Quality criteria** |
|  |  |  |  | A. Was assignment of subjects to treatment group randomised? |
| 🗸 |  |  |  | Was the use of randomisation reported? |
|  |  | 🗸 |  | Was the method of randomisation reported? |
|  |  |  | 🗸 | Was the method of randomisation appropriate? |
|  |  |  |  | B. Was allocation to treatment groups concealed from those responsible for recruiting subjects? |
|  |  | 🗸 |  | Was a method of allocation concealment reported?  |
|  |  |  | 🗸 | Was the method of allocation concealment adequate? |
|  |  |  |  | C. Was the study double-blinded? |
|  | 🗸 |  |  | Were subjects and investigators blinded to treatment arm? |
|  |  |  |  | D. Were patient characteristics and demographics similar between treatment arms at baseline? |
|  |  | 🗸 |  | Were baseline patient characteristics and demographics reported? |
|  |  | 🗸 |  | Were the characteristics similar between treatment arms? |
|  |  |  |  | E. Were all randomised participants included in the analysis? |
|  |  | 🗸 |  | Was loss to follow-up reported? |
|  |  | 🗸 |  | Was loss to follow-up appropriately accounted for in the analysis? |
|  |  |  |  | F. Was outcome assessment likely to be subject to bias? |
|  |  | 🗸 |  | Were all relevant outcomes measured in a standard, valid, and reliable way? |
|  |  | 🗸 |  | Was outcome assessment blinded to treatment allocation? |
|  |  |  | 🗸 | If outcome assessment was not blinded, were outcomes objective and unlikely to be influenced by blinding of assessment? |
|  |  |  |  | G. Were the statistical methods appropriate? |
|  |  | 🗸 |  | Were the methods used for comparing results between treatment arms appropriate? |
|  |  |  | 🗸 | If the study was carried out at more than one site, are the results comparable for all sites? |
|  |  |  |  | H. If appropriate, were any subgroup analyses carried out? |
|  |  |  | 🗸 | Were subgroup analyses reported? |
|  |  |  | 🗸 | Were subgroup analyses appropriate? |
|  |  |  |  | Comments: The method of randomisation was not described clearly. Allocation concealment was not described. It was unclear if patients or outcome assessors were blinded to the intervention. Intention-to-treat analysis was carried out. Drop-out rate was not reported. No baseline assessment of adherence. |
|  |  |  |  | Quality rating [Good/Fair/Poor]:Poor |

Note: Quality criteria adapted from NHMRC (2000) How to use the evidence: assessment and application of scientific evidence. NHMRC, Canberra.

Assess criterion using Y (yes), N (no), NR (not reported) or NA (not applicable).

Table A-6.9 Quality analysis of primary studies – Skaer (1993a) hypertension

| **Y** | **N** | **NR** | **NA** | **Study type: Randomised controlled trial** |
| --- | --- | --- | --- | --- |
|  |  |  |  | Study ID: **Skaer (1993a) hypertension** |
|  |  |  |  | **Quality criteria** |
|  |  |  |  | A. Was assignment of subjects to treatment group randomised? |
| 🗸 |  |  |  | Was the use of randomisation reported? |
|  |  | 🗸 |  | Was the method of randomisation reported? |
|  |  |  | 🗸 | Was the method of randomisation appropriate? |
|  |  |  |  | B. Was allocation to treatment groups concealed from those responsible for recruiting subjects? |
|  |  | 🗸 |  | Was a method of allocation concealment reported?  |
|  |  |  | 🗸 | Was the method of allocation concealment adequate? |
|  |  |  |  | C. Was the study double-blinded? |
|  | 🗸 |  |  | Were subjects and investigators blinded to treatment arm? |
|  |  |  |  | D. Were patient characteristics and demographics similar between treatment arms at baseline? |
|  |  | 🗸 |  | Were baseline patient characteristics and demographics reported? |
|  |  | 🗸 |  | Were the characteristics similar between treatment arms? |
|  |  |  |  | E. Were all randomised participants included in the analysis? |
|  |  | 🗸 |  | Was loss to follow-up reported? |
|  |  | 🗸 |  | Was loss to follow-up appropriately accounted for in the analysis? |
|  |  |  |  | F. Was outcome assessment likely to be subject to bias? |
| 🗸 |  |  |  | Were all relevant outcomes measured in a standard, valid, and reliable way? |
|  |  | 🗸 |  | Was outcome assessment blinded to treatment allocation? |
|  |  |  | 🗸 | If outcome assessment was not blinded, were outcomes objective and unlikely to be influenced by blinding of assessment? |
|  |  |  |  | G. Were the statistical methods appropriate? |
| 🗸 |  |  |  | Were the methods used for comparing results between treatment arms appropriate? |
|  |  |  | 🗸 | If the study was carried out at more than one site, are the results comparable for all sites? |
|  |  |  |  | H. If appropriate, were any subgroup analyses carried out? |
|  |  |  | 🗸 | Were subgroup analyses reported? |
|  |  |  | 🗸 | Were subgroup analyses appropriate? |
|  |  |  |  | Comments: The method of randomisation was not described clearly. Allocation concealment was not described. It was unclear if patients or outcome assessors were blinded to the intervention. Analysis carried out on the 304 participants enrolled into the trial. Drop-out rate was not reported. No baseline assessment of adherence or clinical outcomes. Quality of reporting difficult to ascertain as very little data was presented. |
|  |  |  |  | Quality rating [Good/Fair/Poor]:Poor |

Note: Quality criteria adapted from NHMRC (2000) How to use the evidence: assessment and application of scientific evidence. NHMRC, Canberra.

Assess criterion using Y (yes), N (no), NR (not reported) or NA (not applicable).

Table A-6.10 Quality analysis of primary studies – Skaer (1993a) NIDDM

| **Y** | **N** | **NR** | **NA** | **Study type: Randomised controlled trial** |
| --- | --- | --- | --- | --- |
|  |  |  |  | Study ID: **Skaer (1993a) NIDDM** |
|  |  |  |  | **Quality criteria** |
|  |  |  |  | A. Was assignment of subjects to treatment group randomised? |
| 🗸 |  |  |  | Was the use of randomisation reported? |
|  |  | 🗸 |  | Was the method of randomisation reported? |
|  |  |  | 🗸 | Was the method of randomisation appropriate? |
|  |  |  |  | B. Was allocation to treatment groups concealed from those responsible for recruiting subjects? |
|  |  | 🗸 |  | Was a method of allocation concealment reported?  |
|  |  |  | 🗸 | Was the method of allocation concealment adequate? |
|  |  |  |  | C. Was the study double-blinded? |
|  | 🗸 |  |  | Were subjects and investigators blinded to treatment arm? |
|  |  |  |  | D. Were patient characteristics and demographics similar between treatment arms at baseline? |
|  |  | 🗸 |  | Were baseline patient characteristics and demographics reported? |
|  |  | 🗸 |  | Were the characteristics similar between treatment arms? |
|  |  |  |  | E. Were all randomised participants included in the analysis? |
|  |  | 🗸 |  | Was loss to follow-up reported? |
|  |  | 🗸 |  | Was loss to follow-up appropriately accounted for in the analysis? |
|  |  |  |  | F. Was outcome assessment likely to be subject to bias? |
| 🗸 |  |  |  | Were all relevant outcomes measured in a standard, valid, and reliable way? |
|  |  | 🗸 |  | Was outcome assessment blinded to treatment allocation? |
|  |  |  | 🗸 | If outcome assessment was not blinded, were outcomes objective and unlikely to be influenced by blinding of assessment? |
|  |  |  |  | G. Were the statistical methods appropriate? |
| 🗸 |  |  |  | Were the methods used for comparing results between treatment arms appropriate? |
|  |  |  | 🗸 | If the study was carried out at more than one site, are the results comparable for all sites? |
|  |  |  |  | H. If appropriate, were any subgroup analyses carried out? |
|  |  |  | 🗸 | Were subgroup analyses reported? |
|  |  |  | 🗸 | Were subgroup analyses appropriate? |
|  |  |  |  | Comments: The method of randomisation was not described clearly. Allocation concealment was not described. It was unclear if patients or outcome assessors were blinded to the intervention. Analysis carried out on the 258 participants enrolled into the trial. Drop-out rate was not reported. No baseline assessment of adherence or clinical outcomes. Quality of reporting difficult to ascertain as very little data was presented. |
|  |  |  |  | Quality rating [Good/Fair/Poor]:Poor |

Note: Quality criteria adapted from NHMRC (2000) How to use the evidence: assessment and application of scientific evidence. NHMRC, Canberra.

Assess criterion using Y (yes), N (no), NR (not reported) or NA (not applicable).

Table A-6. Quality analysis of primary studies – Becker (1986)

| **Y** | **N** | **NR** | **NA** | **Study type: Randomised controlled trial** |
| --- | --- | --- | --- | --- |
|  |  |  |  | Study ID: **Becker (1986)** |
|  |  |  |  | **Quality criteria** |
|  |  |  |  | A. Was assignment of subjects to treatment group randomised? |
| 🗸 |  |  |  | Was the use of randomisation reported? |
|  |  | 🗸 |  | Was the method of randomisation reported? |
|  |  |  | 🗸 | Was the method of randomisation appropriate? |
|  |  |  |  | B. Was allocation to treatment groups concealed from those responsible for recruiting subjects? |
|  |  | 🗸 |  | Was a method of allocation concealment reported?  |
|  |  |  | 🗸 | Was the method of allocation concealment adequate? |
|  |  |  |  | C. Was the study double-blinded? |
|  | 🗸 |  |  | Were subjects and investigators blinded to treatment arm? |
|  |  |  |  | D. Were patient characteristics and demographics similar between treatment arms at baseline? |
|  |  | 🗸 |  | Were baseline patient characteristics and demographics reported? |
|  |  | 🗸 |  | Were the characteristics similar between treatment arms? |
|  |  |  |  | E. Were all randomised participants included in the analysis? |
| 🗸 |  |  |  | Was loss to follow-up reported? |
|  | 🗸 |  |  | Was loss to follow-up appropriately accounted for in the analysis? |
|  |  |  |  | F. Was outcome assessment likely to be subject to bias? |
| 🗸 |  |  |  | Were all relevant outcomes measured in a standard, valid, and reliable way? |
|  | 🗸 |  |  | Was outcome assessment blinded to treatment allocation? |
|  |  |  | 🗸 | If outcome assessment was not blinded, were outcomes objective and unlikely to be influenced by blinding of assessment? |
|  |  |  |  | G. Were the statistical methods appropriate? |
| 🗸 |  |  |  | Were the methods used for comparing results between treatment arms appropriate? |
|  |  |  | 🗸 | If the study was carried out at more than one site, are the results comparable for all sites? |
|  |  |  |  | H. If appropriate, were any subgroup analyses carried out? |
|  |  |  | 🗸 | Were subgroup analyses reported? |
|  |  |  | 🗸 | Were subgroup analyses appropriate? |
|  |  |  |  | Comments: The method of randomisation was not described clearly. Allocation concealment was not described. It was unclear if patients were blinded to the intervention. Dropout rate was 9% overall. Although reasons for drop out are stated, final analysis was carried out only on those participants that completed the trial. No baseline assessment of adherence. |
|  |  |  |  | Quality rating [Good/Fair/Poor]:Poor |

Note: Quality criteria adapted from NHMRC (2000) How to use the evidence: assessment and application of scientific evidence. NHMRC, Canberra.

Assess criterion using Y (yes), N (no), NR (not reported) or NA (not applicable).

1. Pharmacy Guild of Australia. Professional Pharmacy Services: Dose Administration Aids. Accessed 19 July 2016. Available from: http://www.guild.org.au/pps/content.asp?id=1425 [↑](#footnote-ref-1)
2. Available at http://www.psa.org.au/downloads/community-pharmacy-agreements/dose-administration-aids/dose-administration-service-guidelines.pdf [↑](#footnote-ref-2)
3. Agency for Healthcare Research and Quality (AHRQ) at [AHRQ](http://www.ahrq.gov/); Canadian Agency for Drugs and Technologies in Health (CADTH) at [CADTH Reports](https://www.cadth.ca/reports); National Institute for Health and Care Excellence (NICE) at [NICE, UK](http://www.nice.org.uk/) [↑](#footnote-ref-3)
4. Including Pharmacy Guild of Australia; Pharmaceutical Society of Australia; and Australian Association of Consultant Pharmacy. [↑](#footnote-ref-4)
5. Automated dispensing devices are drug storage devices that electronically dispense medications in a controlled fashion based on an in-built alarm system and track medication use. These devices are considerably more expensive than a blister pack, and require more technical assistance, and thus may not be widely used in the patient population. A systematic review by Sinnemaki et al (2013) indicated that automated dispensing devices are more commonly used in nursing home settings. [↑](#footnote-ref-5)
6. ABS postcode to remoteness.xls available from [http://www.abs.gov.au/AUSSTATS/abs@.nsf/DetailsPage/1270.0.55.006July%202011?OpenDocument](http://www.abs.gov.au/AUSSTATS/abs%40.nsf/DetailsPage/1270.0.55.006July%202011?OpenDocument) (accessed 5th October, 2016) [↑](#footnote-ref-6)
7. None of the survey respondents were participants in the SS and CI initiatives. [↑](#footnote-ref-7)
8. Pharmacies are counted according to unique S90 and /or Organisation Number identifiers. [↑](#footnote-ref-8)