A randomised controlled trial of Home Medicines Reviews following acute coronary syndromes

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**Declaration of Originality**

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**Statement of Ethical Conduct**

The research associated with this thesis abides by the international and Australian codes on human and animal experimentation, and the rulings of the Safety, Ethics and Institutional Biosafety Committees of the University.

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Abstract

Coronary heart disease (CHD) is a global healthcare problem. Sometimes fatal for the individual, but always life-changing, and for the wider healthcare system, CHD causes an unprecedented financial burden. CHD commonly presents as an acute coronary syndrome (ACS), which is a prevalent cause of mortality. However, better symptom awareness, a shorter time between symptom onset and acute treatment, and a higher quality of routinely accessible treatments has significantly improved mortality and morbidity in the period soon after ACS.

The disease pathway continues after the point of acute treatment and there are multiple behaviours that patients can adopt to prevent further coronary events. This includes lifestyle modification and the use of guideline-recommended medications. There are currently four main classes of medication recommended by consensus-based guidelines following ACS. This includes antiplatelet therapies (aspirin and a P2Y12 antagonist), statins, angiotensin-pathway inhibitors, and beta-blockers. The combination of these four medications has been shown to be more effective at reducing the risk of future ACS by comparison to those who stop one or more medications. Many patients struggle with the task of taking these medications as accurately as prescribed (non-adherence) and others stop taking some or all medications (non-persistence). Despite well-established advances in the acute treatment phases of ACS, successful strategies to improve medication adherence and persistence have been lacking.

The aim of the current study was to determine if an existing, pharmacist-led home-visit service could be tailored toward the needs of patients following ACS and improve medication adherence and persistence at six months post-discharge. The currently funded Home Medicines Review (HMR) service was utilised. Patients with ACS are eligible for HMR referral, however, to what extent this service is utilised by, or beneficial for patients following ACS is unknown.
To tailor the service toward the needs of patients with a recent ACS, accredited pharmacists (APs) who undertake HMRs were invited to participate in an online education package. This included five lectures covering: disease introduction and trial overview; in-hospital management of ACS; lifestyle modifications, cardiac rehabilitation (CR), and chest pain action plans; medication management following ACS; and strategies to improve adherence to therapy. Once viewing all lectures, APs sat a multiple-choice quiz and were required to achieve a 75% pass mark. The education package was peer-reviewed and also underwent a participant evaluation. Successful completion of the education package was a requirement of the trial protocol. The tailored service was termed a directed Home Medicines Review (dHMR). Twenty-seven Tasmanian APs completed the education package, 22 APs (81%) passed the quiz on their first attempt. Twenty-one APs (78%) who successfully completed the education package participated in the trial as described below.

A conceptual framework was utilised to design and evaluate a randomised controlled trial of a dHMR delivered at two months post-discharge compared with usual care. The primary outcome was the proportion of patients who were adherent and persistent to a guideline-concordant regimen at six months. This outcome was assessed by a modified medication possession ratio (MMPR). The MMPR was calculated by applying a specialised algorithm to compare the available supply of medication, as obtained through dispensing records, against that required to be fully adherent. Modifications to the algorithm utilised in the current study allowed for determination of adherence and persistence as unique behaviours. Secondary outcomes included mortality, hospital readmissions, length of stays, cardiac rehabilitation completion, smoking cessation, quality of life, survey outcomes, and process outcomes. Data collection was undertaken at hospital discharge, six weeks for baseline surveys, two months for dHMR reports, and follow-up at six months post discharge. Statistical analysis was conducted using SPSS, following standard
procedures. The primary outcome was assessed by both univariate chi-square analysis and binary logistic regression to control for potential confounding.

Three-hundred and fifty-nine patients with suspected ACS from two Tasmanian public hospitals were screened for enrolment. After exclusion criteria and informed consent, 184 patients were randomised to receive either usual care or a dHMR at two months following hospital discharge. Due to withdrawals and incomplete records a total of 76 control patients and 75 intervention patients were followed to the study endpoint at six months post-discharge. An intention-to-treat analysis was used, however, an on-treatment secondary analysis was also conducted, excluding those who had not followed the trial protocol with regards to timing of the intervention and completion of the education package. There were no significant differences between the study groups for baseline demographics or rates of guideline-concordant prescribing on discharge, which was relatively low at 60.0%.

There were only 90 patients who were discharged as guideline-concordant, meaning they could be assessed against the primary outcome. There were no significant differences in the primary outcome with 26 (59.1%) control patients and 22 (47.8%) intervention patients adhering and persisting with guideline-concordant therapy to six months (p=0.284). There was, however, a trend toward a lower proportion of persistence among patients in the intervention group versus the control group at six months (56.5% vs 75.0%, p=0.065). Multivariate analysis supported this finding with an odds ratio for persistence of 3.7 (1.1-12.3, p=0.035) in favour of allocation to the control group. There were no significant changes detected in the secondary outcomes.

Similarly, there were few significant changes in the questionnaire results, however, the specific concerns scale of the beliefs about medications questionnaire decreased among intervention patients from six weeks to six months (p=0.034). It was unclear, however, if this decrease occurred as a result of information conveyed that relieved
concerns or if medications for which the patient was concerned were stopped, and if so, what degree of impact the intervention had on this action.

Analysis of DRPs and review of individual dHMR reports did not clearly support or oppose the finding of lower persistence among intervention patients. Although this analysis did highlight that issues with medication adherence were being identified among some patients, it was interesting to find that other ACS-related problems, not related to adherence, were identified four times as often. This suggested that adherence may not have been given an adequate amount of attention during the dHMR, but also that there may have been improvements in medication management that were not adequately assessed by the primary outcome.

Based on assessment of process outcomes, the implementation of the intervention was poor with a large proportion of dHMRs occurring much later than two months post-discharge and over 50% not obtaining GP follow-up. Interestingly this appeared to be somewhat provider specific, suggesting a potential benefit from the use of peer-support and mentorship in future models of research as well as a need to better evaluate the perceptions of the stakeholders involved, such that barriers and enablers to on time completion could be identified. Somewhat similarly, comparisons to other studies suggested that future models of research involving the HMR service may benefit from better integration within the healthcare system and better engagement with the patient. This could be achieved by starting the intervention in hospital and having follow-up sooner after discharge and future research should investigate these options.

There were several study limitations. The small sample size limited the confidence in assessing the primary outcome, particularly the assessment of both adherence and persistence. The confidence in assessment of the persistence component, however, was improved by controlling for confounding from a wide variety of baseline variables and this was a positive aspect of the study design. There were also
limitations in the collection of complete dispensing records, an inability to assess for improvements in guideline-concordant prescribing, and a lack of quality control over the dHMRs conducted. Each of these factors potentially limits the generalisation of these results to routine practice.

This study concluded by finding that the methods used did not adequately tailor the current model of the HMR service to improve adherence or persistence to guideline-recommended medications following ACS. Future research should explore ways of targeting the patients most in need of intervention, utilising highly flexible interventions to suit a wide variety of needs, monitoring for a variety of outcomes that are not solely related to adherence, and providing support for the practitioners involved to deliver the highest quality service possible. Guidance from conceptual frameworks has proved valuable in the design and evaluation of the current study and such an approach could be bolstered with input from all stakeholders involved when designing and evaluating future research of similar interventions.
Publications

Peer-reviewed journal publications


*The methodology described in the paper above cites six and twelve month follow-up. Data collection was incomplete for the twelve month follow-up due to time and resource limitations, therefore it is not reported within this thesis.

Bernal D, Chalmers L, Bereznicki LR, Castelino RL, Davidson PM, Peterson G. An online education package for pharmacists delivering a home medication review service to patients following acute coronary syndromes. European Journal for Person Cetered Healthcare 2014;2(3)


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Abbreviations

AACP – Australian Association of Consultant Pharmacists
ACC/AHA – American College of Cardiology/American Heart Association
ACEI – angiotensin-converting-enzyme inhibitors
ACS – acute coronary syndrome
ADR – adverse drug reaction
AF – angina frequency (relating to a domain of the Seattle Angina Questionnaire)
AIHW – Australian Institute of Health and Welfare
AP – accredited pharmacist
ARB – angiotensin receptor blockers
AS – angina stability (relating to a domain of the Seattle Angina Questionnaire)
BB – beta blockers
BMS – bare metal stent
BMQ – beliefs about medicines questionnaire
CABG – coronary artery bypass grafting
CCS – Charlson comorbidity score
CCSUA – Charlson comorbidity score, updated and age-adjusted
CCU – coronary care unit
CE – change in estimate
CI – contraindication (re: medication tolerance)
CI – 95% confidence interval (re: statistical analysis)
CP – community pharmacist
CR – cardiac rehabilitation
CS – controlling symptoms domain of self-efficacy questionnaire
DAA – dose administration aid
DAPT – dual antiplatelet therapy
DES – drug eluting stent
dHMR – directed Home Medicines Review
DMACS – Discharge Management of Acute Coronary Syndromes
DOT – directly observed therapy
DRP – drug-related problem
Eq-5D-3L – Euroqol five domain, three-point Likert scale, quality of life questionnaire
FMPR – fixed-interval medication possession ratio
FTND – Fagerstrom Test for Nicotine Dependence
GC – guideline-concordant
GP – general practitioner
GR – guideline-recommended
GRACE – Global Registry of Acute Coronary Syndromes
GTN – glyceryl trinitrate
HMR – Home Medicines Review
IPQ – illness perception questionnaire
ITT – intention-to-treat
LGH – Launceston General Hospital
LoS – length of stay(s)
LR – logistic regression
MACE – major adverse cardiovascular events
MAQ – Morisky adherence questionnaire
MEMS – medication event monitoring systems
MF – maintaining function domain of self-efficacy questionnaire
MI – myocardial infarction
MMPR – modified medication possession ratio
MPR – medication possession ratio
MUR – medication use review
N or n – number
NSTEACS – non-ST-elevation acute coronary syndrome
NSTEMI – non-ST-elevation myocardial infarction
NYHA – New York Heart Association
OR – odds ratio
OT – on-treatment
PCI – percutaneous coronary intervention
PLS – physical limitation score (relating to a domain of the Seattle Angina Questionnaire)
PHRQ – Perceived Heart Risk Questionnaire
PSA – Pharmaceutical Society of Australia
QoL – quality of life
RCT – randomised controlled trial
RHH – Royal Hobart Hospital
RMMR – residential medication management review
SAQ – Seattle Angina Questionnaire
SD – standard deviation
SE – standard error
SR – self-report
STEMI – ST-elevation myocardial infarction
TABS – tool for adherence behaviour screening
TS – treatment satisfaction (relating to a domain of the Seattle Angina Questionnaire)
TT – triple therapy (as in aspirin, warfarin, and a P2Y₁₂ antagonist)
TTO – time trade-off
TTR – time in therapeutic range
UA/UAP – unstable angina / unstable angina pectoris
VAS – visual analogue scale
VMPR – variable-interval medication possession ratio
Chapter One: Introduction

1.1 Introduction

Acute coronary syndrome (ACS) is a term used to cover a spectrum of disease that results from an insufficient supply of oxygen to the muscular tissue of the heart.\(^1\) On the less severe end, unstable angina (UA) occurs when the oxygen supply is partially decreased, but not enough to cause permanent heart-muscle damage or “myocardial ischaemia”\(^2\). In contrast, a complete lapse in oxygen supply causes death of muscular tissue and a potentially life-threatening episode, commonly referred to as a heart attack or an acute myocardial infarction (AMI)\(^2,3\).

In clinical practice, ACS is used as a preliminary diagnosis that should be updated once further investigations confirm disease severity\(^1\). Such classification is important in guiding acute management; however, all patients with confirmed ACS should be considered for ongoing medication therapy aimed at reducing the risk of recurrent disease\(^1,2,4\). This includes the prescription of dual antiplatelet therapy (DAPT), a statin, an angiotensin-converting-enzyme inhibitor/angiotensin receptor blocker (ACEI/ARB), and a beta-blocker\(^1,5\). To ensure the full benefit, the patient has to adhere to this regimen for at least a year, with certain medications often prescribed lifelong\(^6\). This is not an easy habit to develop and many struggle to adhere to this routine of regular medication-taking\(^7\).

It is important to recognise that the act of taking prescribed medication is often executed with some degree of imperfection and this should be further described. The term ‘adherence’ aims to assess how well a patient is following the instructions of their health professional and could relate to any prescribed therapy that requires the patient to undertake a prescribed task\(^8\). When referring to medication, adherence assesses how accurately the patient takes their medication in accordance with the prescribed instructions\(^9\). Common errors in adherence may include skipping doses,
either as ‘unintentional non-adherence’, for example, due to forgetfulness, or ‘intentional non-adherence’, for example, when there is poor understanding of the importance of the medicine or if there is a fear of side effects.\textsuperscript{10} ‘Persistence’ refers to the time for which a specific medication has been taken continually, but without regard to how accurately the dosing has been during this period.\textsuperscript{9} When someone discontinues a medication without a recommendation to do so, they have become ‘non-persistent’. Accurately identifying this type of behaviour as unique from other types of non-adherence has an important clinical implication as there is no further benefit gained from the medication once it has been stopped, whereas a patient who is persistent, but poorly adherent may still gain some degree of benefit. When referring to the treatment of patients with ACS, the term ‘guideline non-adherence’ is often used to described deviation away from guideline-recommended therapy and it is important to recognise that both patient and prescriber actions may contribute to this outcome.

Despite best intentions, patients with ACS are at a high risk of suffering future ischaemic events and disease recurrence contributes a large proportion of the overall burden of ACS.\textsuperscript{11} The incidence of recurrence is higher among those who are non-adherent,\textsuperscript{12} and while acute treatments have progressed substantially;\textsuperscript{13} understanding adherence barriers, and the development of interventions to overcome them, has been somewhat elusive.\textsuperscript{10}

\textbf{1.2 The burden of disease from ACS and the impact of recent therapeutic advances}

\textit{“I am pleased to see that at present the devastating effects of AMI have been ameliorated by the combined efforts of the clinician, the interventional cardiologist and the cardiovascular surgeon.”}\textsuperscript{13}
Upon reflection of thirty years’ developments in surgical techniques, open heart surgery pioneer, Rene G. Favaloro (1923 – 2000), described the significant advances in patient survival following AMI. Despite the clear survival benefit resulting from acute interventions, the devastating effects of AMI were perhaps underestimated based on a paucity of information to quantify morbidity following ACS at the time. Further research was required to better understand the severity and duration of morbidity among those receiving successful surgical intervention.

1.2.1 Insights into morbidity and guideline non-adherence from “GRACE” and “DMACS”

The establishment of the “Global Registry of Acute Coronary Syndromes (GRACE)” just prior to the turn of the 21st century enabled a more robust understanding of disease recurrence by observing patients for six months following ACS. The registry initially included a sample of 24,055 patients from 14 countries, recruited between 1999 and 2002, and highlighted that nearly 20% of patients would be readmitted with further heart-related illness within six months after an ACS, regardless of disease subtype. Approximately 75% of these readmissions were severe enough to warrant further surgical management. This finding provided a ripe landscape for the development of treatments that could improve morbidity following ACS.

While low-dose aspirin was an established antiplatelet agent, evidence for improved outcomes following the addition of clopidogrel, the first in a new class of antiplatelet medications mediated by P2Y12 receptor inhibition, saw dual-antiplatelet therapy (DAPT) become a mainstay of management for three to six months post-ACS. The development of drug-eluting stents (DES) followed, and this technological advance saw reduced six-month restenosis by comparison to that from bare metal stenting (BMS) in a population of 176 symptomatic patients (mean six-month stenosis of 14% for DES versus 39% for BMS, p<0.001). However, repeated concerns over late-stent restenosis after cessation of DAPT; temporarily halted the uptake of the DES
The optimal length of DAPT was revisited and a recommendation for twelve months’ therapy was proposed for all patients following ACS.22 Ironically, this recommendation was based largely on the evidence from post-PCI studies undertaken during the pre-DES era (PCI-CURE15 and CREDO16). The recommendation for 12 months of DAPT for all patients following ACS would soon be adopted by expert consensus guidelines.5

While these therapeutic innovations saw improvements in morbidity, the impact from medication non-adherence, and specifically the non-persistence component of this behaviour, became more apparent as it was shown to significantly increase mortality following ACS.6 Compounding the issue, the use of acute interventions that required ongoing medication management in order to be successful, such as DES placement, were becoming commonplace.23 In spite of a growing dependence on medication therapy, interventions targeted at improving adherence and persistence had yet to show great promise.24

Australian research into the problem of guideline non-adherence found that there was a significant opportunity to improve the discharge management of ACS, by focussing on the prescribing component of this task.25 The Discharge Management of Acute Coronary Syndrome (DMACS) study was a pre and post intervention, quality improvement initiative recruiting over 3000 patients from 45 hospitals across Australia.26 The delivery of an academic detailing intervention to 3034 hospital staff saw a 12% pre to post intervention improvement in guideline-concordant prescribing, which was defined as the combination of all four classes of guideline-recommended medications (57% pre to 69% post, p<0.001). However, successful improvements in prescribing at hospital discharge appeared short-lived as a result of early non-persistence, with 17% of patients having stopped at least one guideline-recommended medication at three-month follow-up.26 Patient or prescriber reasons for discontinuation were not reported. Figure 1.1 shows that although there was a large decline in guideline-concordance by three months, the proportion of guideline-
The decline in medication adherence post-discharge was further explored by Chew et al who used an Australian subset of GRACE data to highlight the potential benefits from a shift in focus toward interventions aimed at improving guideline-concordant medication adherence. This research demonstrated that non-adherence to guideline-recommended medications was split almost 50:50 for patient-related versus prescribing-related barriers and, if non-adherence could be improved to 100% across the population, it could see 104 lives saved per 10,000 events by 12 months post-discharge. The authors compared this benefit to that from the addition of a theoretical innovation capable of reducing 12 month cardiovascular events by 30% on top of that already achievable with optimal care. Based on this hypothetical forecast, just four more lives per 10,000 events would be saved, clearly highlighting...
the need for further research and development into interventions that could improve current prescribing practices and medication adherence.27

1.2.2 The burden of disease from ACS in Australia

These findings are particularly important within the Australian context as the Australian Institute of Health and Welfare (AIHW) estimated that 17% of the population was suffering from cardiovascular disease (CVD) in 2008.28 Although this was not the most prevalent disease in Australia for that year, CVD resulted in the highest number of deaths by disease category, being responsible for 34% of all recorded deaths. Furthermore, CVD accounted for more healthcare expenditure than any other disease category in Australia, with the majority resulting from coronary heart disease (CHD) and stroke. The Australian population presents a suitable target with significant potential to reap benefits from interventions that can successfully improve medication-adherence and related outcomes following ACS.

1.3 Medication management of ACS and adherence to the regimen

Contemporary prescribing guidelines recommend the use of five medications following acute coronary syndrome (ACS).1,2,29 These include aspirin, a P2Y12 antagonist (eg. clopidogrel), an angiotensin converting enzyme inhibitor (ACEI) (eg. ramipril) or an angiotensin II receptor-blocker (ARB) (eg. irbesartan), a beta blocker (eg. metoprolol), and a statin (eg. atorvastatin).1 Assessing each class individually, there is strong evidence for improvement in a range of clinical outcomes, such as mortality and further cardiovascular events from high-potency statins following ACS.30-33 There is evidence for reduced major cardiovascular events with extended duration DAPT in patients undergoing PCI.15,16 There is evidence for a reduced rate of all-cause mortality from the use of ACE-inhibitors among moderate-risk patients with atherosclerosis.34 And there is conflicting evidence for a benefit from beta-blockers in patients with ACS or AMI.35-42 However, the greatest mortality benefits
are shown by effective use of combinations of at least three, and preferably four, guideline-recommended medications in long-term observational studies following ACS or AMI.\textsuperscript{6,12,43,44} Furthermore, combination therapy is associated with better patient-reported perceived health status.\textsuperscript{45} These studies demonstrate the impact of combination therapy in current medical practice, outside of the strictly monitored randomised controlled trial setting and support the guideline recommendation for all patients with ACS to be considered for the prescription of all four classes of medication at discharge.\textsuperscript{1,5} Therefore, when a person is admitted to hospital with ACS, they will almost certainly be discharged on a range of medicines and for those with their first episode of ACS, this may require them to rapidly adjust to a routine of regularly taking multiple medications. Very few other medical conditions increase medication burden as abruptly as ACS and this can create a number of challenges.

1.3.1 The World Health Organisation’s (WHO) model of adherence

The WHO has categorised the barriers to adherence that are commonly encountered by patients suffering chronic disease.\textsuperscript{8} These include condition, treatment, socioeconomic, health-system, and patient-related barriers. The model is designed to be holistic yet simple to remember, with the intention that barriers will be considered in conjunction with one another at an individual patient level.\textsuperscript{8} This is in contrast to traditional adherence assessments, whereby patient-related barriers are unfairly recognised as those that are most amenable to change and are addressed as a priority.\textsuperscript{46} Despite Morisky \textit{et al} eluding to flaws in this approach nearly 30 years ago,\textsuperscript{47} the systematic integration of a more holistic method to improving adherence in modern medical practice and research has not been widely adopted, and far too often, the sole burden of adherence is left hanging over the patient.\textsuperscript{46}

1.3.2 Applying the WHO model to ACS

Medication regimen complexity (MRC) is a term used to describe the cumulative patient effort required to take medication correctly.\textsuperscript{48} The notion of ‘change in MRC’
provides a useful foundation for understanding barriers to adherence following ACS. MRC increases each time a patient is required to make a decision about taking medication. For example, two tablets taken once daily requires only one decision and is a less complex regimen than taking one tablet twice a day. Increasing MRC is associated with poorer rates of adherence\(^6\) and the initiation of five new medications for patients after ACS typically leads to a significant increase in MRC, undoubtedly contributing to the difficulty in maintaining long-term adherence.\(^5\) Understandably, patients with ACS as their first major health condition may find the task of taking several new medications quite difficult.

When considering the WHO model, the burden attributable to medication-taking should be identified as a treatment-related barrier. However, adherence barriers overlap, and exploring the between-barrier connections can illustrate the complexities that exist within a regular medication-taking behaviour, for example:

- Most health systems require patients to contribute to the cost of their medications. When multiple medications are started simultaneously, this can create a significant socioeconomic barrier.\(^5,52\)
- There is a need for reliable information transfer processes between hospital and community settings to ensure newly initiated medications are continued. Failure of these processes could be considered a health-system barrier.\(^5,54\)
- Ten to thirty per cent of patients are known to suffer depression following ACS. This is often underdiagnosed and may add to the condition-related barriers to adherence.\(^5\)
- Multiple guideline-recommended behaviour changes typically confront a patient following ACS, such as dietary modification, developing exercise routines, and stress management.\(^1\) A large proportion of patients will start to question their ability to make the required changes to improve their own outcomes (psychologically defined as low “self-efficacy”) and this should be considered a patient-related barrier to adherence.\(^8,56\)
Figure 1.2 depicts the WHO adherence barriers with brief examples of how each barrier may relate to patients following ACS. While this figure helps to illustrate the broad range of root causes of adherence barriers, there is no weighting placed on the importance of different categories and it is important to recognise the essential role of the prescriber in maintaining medication adherence and persistence. There is now a wealth of information describing rates of discharge prescribing of guideline-recommended medications following ACS, however, data on non-prescription during the sub-acute recovery phase is poorly understood. Under prescribing, whether intentional or unintentional, may account for a large proportion of the problem and this needs to be acknowledged as a potential factor when considering studies of guideline non-adherence following ACS.

Figure 1.2: Five interacting dimensions of adherence proposed by the World Health Organisation, with relevance to acute coronary syndrome management
1.3.3 Complexities in measuring medication adherence

If a desirable health outcome is dependent upon regular medication consumption, a reliable method for measuring such a task is essential. If performed with 100% accuracy, directly observed therapy (DOT) can provide a true measure of adherence. However, this method is unsuitable for assessing adherence from practice-based interventions, as the presence of a third-party recording medication consumption adds a known variable that would inherently be expected to improve adherence.57

As a compromise, measurement of adherence typically involves the use of surrogate assessment tools, leading to a variety of assumptions about how the task being measured relates to the actual behaviour of adherence.8,58,59 For example, medication event monitoring systems (MEMS) involves the placement of sensors capable of detecting every time a dose of medication is removed from a container, and using this method to measure adherence assumes that consumption immediately follows the act of removing the medication from the container.60 The WHO accepts that the likelihood of this assumption failing is low and that MEMS give a very close estimation of adherence; however, their expense largely precludes widespread use.8

Further to this, Kolandaivelu et al have outlined the barriers that can be created by adopting complex adherence monitoring technologies designed to pinpoint minor deficits in adherence, when a genuine understanding of the impact from these small changes is not well established.61 Their review alludes to the potential to de-personalise the medication adherence journey by adopting such a technology-focussed approach, and Choudhry and Winkelmayer echo these principles, emphasising the value of the patient-provider relationship during the development of an individualised approach to improve adherence.24

As a more achievable option than MEMS for most researchers operating in a resource-limited environment, the combination of self-report and medication possession ratio (MPR) has been recognised by the WHO as “state of the art”.8 MPR is a calculated adherence estimate, derived by dividing the number of days of
medication supplied (as can be obtained from pharmacy dispensing records) by the number of days in an observed period. This measure relies on a more fallible assumption than for MEMS – assuming that collecting monthly medication supplies reflects a patient having taken the medication accurately on all of the days in between each supply.\textsuperscript{62} Similarly, if medication collection ceases, it is often unknown whether or not the patient or prescriber has been responsible for this decision. In contrast, self-report involves directly questioning the patient about their behaviour in relation to taking medication. For example, the Morisky Adherence Questionnaire (MAQ) uses four questions to qualify intentional and unintentional non-adherence.\textsuperscript{47} Although such measures can be limited by the provision of socially desirable, rather than honest answers, the MAQ has shown good predictive validity in patients at risk of cardiovascular disease.\textsuperscript{47,63} Figure 1.3 highlights some of the risks and benefits associated with various surrogate assessments of adherence.\textsuperscript{64} Notably, this figure highlights good reliability with the pharmacy refill method, but a similar limitation of sparse sampling for both methods exists and this must be considered when such methods are used to link adherence or persistence with clinical outcomes.
1.3.4 Non-persistence versus non-adherence

Both the MPR and the MAQ provide surrogate estimates of adherence, however, they are limited in their ability to specifically detect non-persistence; a unique behaviour and an important component of long-term medication therapy. To ensure persistence is not overlooked, additional methods for its detection are required.65 Persistence to individual medications can be self-reported as in the DMACS study,26 but more objectively, persistence can be assessed as a component of the MPR by specifying an interval of non-collection that qualifies the medication as discontinued.65 Importantly, this method must exclude non-persistence from contributing toward mean MPR values reported for the remainder of the cohort, thus minimising the risk of miss-labelling two unique medication-taking behaviours:

   a) Taking a medication for a period of time before stopping altogether (non-persistence), versus
b) Continuing the medication, but taking it haphazardly (low adherence). Both behaviours could result in similar MPR values if only an MPR is calculated, yet each behaviour is unique by definition and should be classified accordingly in order to fully understand the nature of the problem observed.

The clinical relevance of specifically assessing medication persistence was shown in a prospective study by Ho et al who observed 1,521 patients admitted to 19 hospitals in the United States of America and found 12.1% patients discharged on all three medications assessed (aspirin, beta blocker and statin) had discontinued all medications by one month post-discharge. The twelve-month mortality rate was 9% higher in this group compared to those who continued one or more medications. Similarly, Kuepper-Nybelen et al observed 3,008 patients post-AMI for a median follow-up of 4.2 years, using a definition of adherence as taking at least three guideline-recommended medications for 50% of the time observed. The proportion of days covered (PDC), which is similar to the MPR, was used to quantify adherence and the study showed a 28% reduction in mortality among the adherers. The authors state that the very low, 50% cut-off, reflected intermediate adherence. However, those falling into this group more likely represented a mixture of patients with unique, non-adherent behaviours; some will have continued their medication throughout the observed period, but with low adherence, whereas others will have taken their medication continuously for a period of time, before stopping altogether (non-persistence). Additionally, the authors reported an 8% decrease in mortality for every 10% increase in PDC. However, without knowing if the root of problem lay with non-persistence versus low adherence, it would be difficult to use this information to target interventions toward improving a specific behaviour. Nonetheless, this study expands on the findings of Ho et al, reinforcing the relationship between medication adherence and mortality following MI, while simultaneously illustrating the importance of defining persistence as a unique outcome and a sub-component of adherence. In this study electronic data collection
was key to enabling the granularity of the data, however, Figure 1.4 illustrates a different comparison of these terms, by compiling data from 16,907 patients enrolled in 95 different studies. This shows the large and absolute impact that non-persistence has on the measurement of overall adherence over time, by comparison to a relatively smaller, yet consistently present decrease in adherence, resulting from incorrectly taken or missed doses.67

Figure 1.4: Kaplan-Meier curves of adherence and persistence to medication recorded with MEMS devices from 16,907 patients enrolled in 95 studies, adapted from Blaschke et al, 2012, Annual Reviews in Pharmacology and Toxicology,67 reprinted with permission.

1.4 Options for improving medication adherence and persistence following ACS

As a result of the development of consensus-based guideline recommendations for acute interventions and secondary preventive therapy following ACS,1,2,4,29,68 there has been a strong focus on in-hospital care and discharge prescribing across a variety of healthcare settings.69-74 However, simple interventions, such as discharge
counselling and cardiologist follow-up that may prolong the benefits of in-hospital prescribing interventions, have only been explored through observational studies whereby a cause-effect relationship cannot be determined.\textsuperscript{75-79} Despite this relative lack of unbiased evidence, these services are common practice in many settings and the American College of Cardiology/American Heart Association (ACC/AHA) collaborative guidelines recommend that patients return to a cardiology clinic follow-up between 14 days and six weeks post-discharge, depending on risk assessment.\textsuperscript{2} In contrast, the Australian guidelines for the management of ACS are less prescriptive with regards to the timing or nature of ongoing follow-up, other than recommending referral to cardiac rehabilitation (CR).\textsuperscript{1} As a result, Australian national practice audits have not focussed on these areas and little is known about the quality of discharge counselling or the timing of cardiologist follow-up in Australia.\textsuperscript{25,80-82} While advanced clinical pharmacy services within the hospital setting have shown minimal benefit,\textsuperscript{83} a semi-structured intervention involving multiple opportunities for pharmacist input has shown the potential to improve medication adherence following ACS.\textsuperscript{84} However, unlike discharge counselling or cardiologist follow-up, these novel interventions are not a routine component of post-discharge care within the existing healthcare system, and wider implementation has been limited by a lack of financial viability.\textsuperscript{85} In contrast, CR is a well-established component of routine post-discharge care and has the potential to improve medication adherence following ACS.\textsuperscript{86}

An overview of 75 systematic reviews undertaken by The Cochrane Collaboration assessed a variety of interventions aiming to improve medication adherence and other medication-related outcomes.\textsuperscript{87} The most complex of the interventions included in this overview focussed on improving patients’ medication self-management, such as that involved with warfarin-based anticoagulation. While these interventions consistently showed positive outcomes, they could not be completed by all patients involved and their complexity may limit their applicability.
to a variety of healthcare settings. Ensuring the structure of a new intervention can fit within an existing healthcare system and be accessible to those in the greatest need are essential factors in determining the long-term success of interventions to improve chronic disease management.\textsuperscript{88,89} Systematic reviews of interventions targeted at reducing medication complexity and interventions involving pharmacist-led medication reviews were also included in this overview and were categorised as likely to be beneficial, however, further evidence was required before a definitive recommendation for wider use could be determined.\textsuperscript{87} A pharmacist-led medication review service that can be targeted toward specific patient groups at risk of medication misadventure, such as those with a recent ACS, would be an appropriate focus for future research.\textsuperscript{90} Although an intervention roughly fitting this description has been shown to be effective at improving medication adherence following ACS,\textsuperscript{84} further research is required to demonstrate if such a study can be effectively implemented into a healthcare system such that the wider majority of patients can benefit.\textsuperscript{85,89}

1.4.1 Cardiac rehabilitation (CR)

There is a range of benefits from successfully completing a CR program, from improvements in cardiovascular risk factors through to reductions in hospital readmission rates, and all patients should be encouraged to attend CR following ACS.\textsuperscript{86,91,92} However, rates of attendance are often low.\textsuperscript{93} Given the potential benefits, there has been significant research into the barriers to engagement with CR and approaches that could increase participation.\textsuperscript{94,95} Aiming to overcome the problems of sub-optimal access and low completion rates, programs that could be considered alternatives to CR have also been extensively trialled.\textsuperscript{92,96-98} However, the success of these programs has been variable and while research into the prospect of information and communication technology-enhanced solutions is promising,\textsuperscript{99} there is yet to be a sound alternative to traditional CR that has translated into widespread practice.\textsuperscript{100} Uncertainty over the long-term sustainability of such traditional services
creates further need to investigate how this well-accepted preventive intervention can be modified and improved to suit the needs of contemporary patients and healthcare systems.\textsuperscript{101}

In reference to medication adherence and persistence, this aspect of CR and related programs often varies, but typically only those that involve significant patient contact time have led to improvements in medication adherence.\textsuperscript{86,102,103} While CR completion has been shown to correlate with prolonging medication persistence,\textsuperscript{104} a causal effect has not been established and a ‘healthy-adherer’ effect\textsuperscript{105,106} cannot be ruled out as a confounder of such correlations. The healthy-adherer effect refers to a phenomena whereby adherent patients are observed to show better health outcomes as a result of adherence to a generally healthier lifestyle, rather than any specific treatment or intervention being tested.\textsuperscript{101,102} Given the extent of medication non-adherence following ACS, the inclusion of adherence screening and intervention components within future iterations of CR should be seen as essential.\textsuperscript{107} In turn, interventions aiming to improve post-discharge care of patients following ACS should not solely focus on medication management; they should also reinforce the importance of CR completion and, where possible, identify strategies to facilitate CR completion.

1.4.2 Home Medicines Reviews and their suitability following ACS

The Home Medicines Review (HMR) program is an existing community-based service that has the potential to be tailored to meet the needs of patients recently discharged from hospital following ACS. An HMR involves general practitioner (GP) referral of patients to an HMR-accredited pharmacist (AP), often through a community pharmacist (CP) liaison.\textsuperscript{108} The AP will visit the patient in their home, discuss their medication taking habits, and provide education or adherence interventions where required. Following the home visit, the AP writes a report for the GP noting their observations and any clinical adjustments that could be made to
the patient’s medication regimen. Based on this report, the GP is expected to complete an agreed management plan, selecting the AP’s recommendations that they agree to implement and/or follow up, ideally during the patient’s next appointment. The potential benefits of improving pharmaceutical care through post-discharge HMRs have not been fully realised in the past and a qualitative review identified a lack of pre-discharge referral mechanisms as a barrier to future expansion of the service into this domain.\textsuperscript{109} As a result of recommendations from this review, a process allowing GPs to refer directly to APs was developed. The direct-referral process aims to increase the uptake of the service by allowing GPs and patients to influence the selection of the AP undertaking the review, and relieves the community pharmacy from the requirement of sourcing an AP. Figure 1.5 shows the revised process of GP to AP direct-referral under the updated HMR guidelines.\textsuperscript{110}

\textit{Figure 1.5: Facilitation of a HMR following the GP to AP direct-referral process}

GP – general practitioner, DRPs – drug-related problems
The HMR service is currently available in Australia, free of charge to Australian citizens under funding arrangements through the public health system, Medicare Australia. The GP, AP and CP involved with an HMR service are paid by way of reimbursement from Medicare Australia. Until 2009, the service had seen a reasonable level of early acceptance with over 220,000 reviews conducted since its inception in 2001.\textsuperscript{111,112} However, from 2011 to 2013, service utilisation increased by 83.7\% with over 115,000 HMRs claimed during the 2012 to 2013 financial year, most likely reflecting the change in referral mechanisms allowing direct referral from GPs to APs.\textsuperscript{113} The value of this increased utilisation was unclear, and due to budgetary limitations, the service was capped to 20 HMRs per month, per AP. If such increased utilisation can be shown to benefit specific patient groups and reduce overall healthcare costs, this would form a strong argument toward uncapped services when provided to those likely to gain the most benefit. The HMR service has been shown to be feasible as a post-discharge service for patients following ACS in the Australian healthcare setting.\textsuperscript{114} However, the effect of this service on clinical outcomes following ACS is unknown and this warrants further investigation.

\section*{1.5 Justification for this trial}

Programs allowing pharmacists to provide formal medication review services exist across many countries. Although there are some regional differences in the structure of these programs, they are generally designed to improve the quality use of medicines and minimise the potential for medication-related harm. Previous studies assessing patient outcomes following post-discharge medication review services have found conflicting results. The HOMER trial questioned the value of the service as the intervention group had an increased hospitalisation rate at six months post-discharge.\textsuperscript{115} Similarly, Barker \textit{et al} trialled a home-based, post-discharge medication review service in patients with congestive heart failure (CHF) and found that patients in the intervention group had significantly longer CHF hospital stays,
incidence rate ratio = 2.34 (p < 0.001). There were no statistical differences in the other two primary outcomes of death and hospital readmission rates. Conversely, Stewart et al were able to demonstrate both a short and long-term benefit in reducing hospital readmissions and mortality following a post-discharge service targeted at a CHF population that was suspected to be at a high risk for readmission.

While the goal of reducing health-care costs through fewer and shorter hospitalisations appears appropriate, this outcome may not be a suitable measure for a service focusing specifically on medication management. A review by Benbassat et al questioned the validity of hospital readmissions as a marker for quality care and highlighted that the length of hospital stays, readmission rates, and death appear to be mostly predicted by unmodifiable causes, such as age, disease severity and comorbidity. The authors concluded by highlighting the importance of improving other clinical outcome measures, such as adherence to guideline-recommended therapy and improving patients’ self-management abilities.

Although the interventions trialled in their studies included a significant focus on improving medication adherence, neither Holland et al nor Barker et al measured changes in this outcome. As such, both authors were left to speculate over the causes of their paradoxical findings and what mechanisms may have led to the higher hospital readmission rates. Conversely, Stafford et al conducted a prospective, non-randomised, controlled cohort study of a pharmacist-led service aimed at improving warfarin therapy post-discharge and, while there were no significant changes in readmission or death rates over the 90-day follow-up period, the intervention was associated with a reduced rate of adverse bleeding events from warfarin therapy, 5.3% versus 14.7% (p = 0.03) and increased persistence with therapy, 95.4% versus 83.6% (p = 0.004). The pharmacists involved in this trial were HMR-accredited, but also received additional education, specific to the needs of patients taking warfarin. Although this study was more intensive than the standard HMR service as it involved multiple HMR-style home visits within the first couple of weeks post-
discharge, the ability to focus the HMR service on specific patient groups remains a likely avenue for improvement of the HMR service and this warrants further attention through future research.\textsuperscript{90,109} Ho \textit{et al} previously demonstrated the ability of a pharmacist-led service to improve adherence following ACS, however, their trial was almost exclusively in male war veterans limiting the relevance to the wider population, and any effects on medication persistence were not reported.\textsuperscript{84} Furthermore, their study did not have an existing funding stream, creating a research to practice translational barrier, whereas adaptations of the existing HMR service could be implemented immediately, such that the wider community can reap the benefits.\textsuperscript{100} The period following hospital discharge appears an appropriate time to target ACS patients due to their risk for harm that can result from premature medication discontinuation.\textsuperscript{6,53} A targeted service delivered by APs who were upskilled to address ACS-specific issues and to encourage positive patient behaviour change could lead to improved medication-related outcomes if delivered in a timely manner following ACS.

\textbf{1.6 Aims and objectives}

The aim was to investigate the effect of an adaptation of the currently available HMR service on adherence and persistence to a guideline-concordant medication regimen following ACS. The service was directed towards the needs of ACS patients by educating the APs involved about ACS-specific patient issues and by providing consistent information in a structured HMR referral letter, thus improving the continuum of care. As such, the trialled service was termed a directed Home Medicines Review (dHMR). Figure 1.6 highlights the intention to target both patient and prescribing adherence barriers as both are described as equally prevalent by Chew \textit{et al}.\textsuperscript{27}
In addition to assessing medication adherence and persistence, it was important to understand the effect of the intervention on clinical outcomes, such as hospital readmissions and mortality; patient-focussed outcomes, such as medication beliefs; and process outcomes, such as intervention fidelity, to ensure any changes in medication adherence or persistence could be further explained as a result of the intervention or due to other causes.
Chapter Two: Development and evaluation of an education package for accredited pharmacists delivering directed Home Medicines Reviews following acute coronary syndromes

2.1 Development

2.1.1 Design principles

The existing HMR service closely follows the Lemmens et al framework for developing and evaluating chronic disease management interventions,\textsuperscript{88} which is discussed in greater depth in Chapter Three. This structure highlights the importance of interventions targeting both the patient and their prescriber as a dyad. The HMR targets the patient through the home interview process and the GP through the follow-up report. Somewhat similarly, the education package was developed and structured to be applicable in a real-life situation, either while educating a patient in their home or writing a recommendation for a GP to consider. Given that the program for HMR accreditation is non-specific, with only a chance that pharmacists will be tested on their ACS-related knowledge, and that pharmacists can seek and complete accreditation for HMRs at any stage in their career, it was considered important to provide an overview of the inpatient management of ACS and an update on current guideline-recommended secondary prevention strategies following ACS. The well-established Kirkpatrick’s four-level model for training and evaluation (described below) was adopted to further guide the development and evaluation of the education package.\textsuperscript{122} By including a thorough evaluation of the education package within the framework of the overall trial, it was believed that the significance of the education package as a means of achieving the trial’s primary outcome would be better understood. Kirkpatrick’s model involves a four-pillar approach to designing and evaluating education packages or other training materials. Specifically, these pillars included assessment of pharmacists’ reactions to the material, their knowledge gained by participating,
changes in their behaviour while undertaking dHMRs, and the outcomes resulting from service delivery.

2.1.2 Content

The education package was centred around five online lectures:

1. Introduction to the program and the associated trial;

2. Inpatient ACS management and a case example;

3. Lifestyle changes, cardiac rehabilitation and chest pain action plans;

4. Medication management; and

5. Adherence to therapy following ACS.

While these topic headings were chosen to ensure broad coverage of ACS management, significantly more focus was given to the “medication management” and “adherence to therapy” sections of the education package, as discussed below. The material was developed using multiple resources and peer-reviewed literature, including the National Heart Foundation of Australia’s “Guidelines for the management of acute coronary syndromes”, the adherence toolkit “Improving adherence in cardiovascular care”, and the World Health Organisation’s “Adherence to long-term therapies”. The education package was delivered in a pre-recorded narrated PowerPoint® presentation format in order for the material to feel like a live lecture, but to also allow for convenience in terms of accessibility. The presentations were offered via an online learning module using the Moodle® system. In order to access the material, pharmacists were required to create an online username, request enrolment into the course, and download each presentation individually. The education package took a total of between three and four hours to complete.
The education package emphasised evidence-based recommendations following ACS according to the current Australian guidelines. Following the framework of medication reviews, there was an emphasis not only on medications that patients should be taking after ACS, but also appropriate resolutions for some of the likely DRPs that may be identified in this clinical context. Theoretically, providing scenario-specific education in this way would result in a change of behaviour that could be measured by APs’ competency in the development of relevant recommendations for DRPs found during the dHMR process. Although not entirely obvious to the pharmacists involved, assessment of behavioural changes is a major component of Kirkpatrick’s model and one that is often overlooked due to the difficulty associated with fairly measuring or quantifying behaviour change. This aspect was assessed within the process outcomes of this project, under section 4.4.2. The online lecture could also be used as a quick reference to return to for ideas when the pharmacist was writing the GP report. Table 2.1 provides examples of the topics and recommendations included in the medication management section.
Table 2.1 Examples of ACS-relevant topics covered and suggested management options provided in the education package.

PPI: proton pump inhibitors; PVD: peripheral vascular disease

<table>
<thead>
<tr>
<th>Topic</th>
<th>Description</th>
<th>Suggested management</th>
<th>References</th>
</tr>
</thead>
<tbody>
<tr>
<td>Clopidogrel and PPI interactions.</td>
<td>Early observational studies suggest some PPIs may decrease the activity of clopidogrel.</td>
<td>The COGENT study provides prospective evidence to suggest that if an interaction did occur that it is of minimal significance. Other studies suggest pantoprazole may be the safest option.</td>
<td>Bhatt et al 124, Juurlink et al 125, Cuisset et al 126</td>
</tr>
<tr>
<td>The use of beta-blockers in patients with comorbid diabetes, reactive airways disease, and/or PVD.</td>
<td>Historically, beta blockers would be avoided unless absolutely essential in these patient groups.</td>
<td>Provided the comorbid condition is under control, such patients should tolerate beta-blocker therapy long-term. In this situation, it is important to use beta-1 selective agents and a low starting dose.</td>
<td>Everly et al 38</td>
</tr>
<tr>
<td>The management of muscle aches associated with statin therapy.</td>
<td>Incidence of myalgia associated with statins in practice is around 10%, which is higher than initially reported in clinical trials.</td>
<td>Pharmacists can play a significant role in helping to differentiate between other possible causes of myalgia as well as recommending further options. Various strategies exist; however, further research is required to highlight which methods are most tolerable and offer the greatest long-term benefit.</td>
<td>Eckel 127</td>
</tr>
</tbody>
</table>
The material also explored the multiple ways of identifying and managing adherence-related problems. This included discussion of direct questioning techniques, such as “Do you ever forget to take your medicines?”, which could highlight unintentional non-adherence, and “Do you ever change the way you take your medicines to suit the way you feel?”, highlighting intentional non-adherence.

Further to this, the material explored the notion that the confronting wording of such questions can be of limited value in an HMR setting where the aim is to maintain a patient’s trust and rapport. The “Stages of Change” model was discussed in terms of smoking cessation, as well as a more general application of the model to aid in identifying the appropriate guidance to provide with regard to all types of lifestyle modification following ACS. Figure 2.1 is a pictorial representation of this model, adapted from Prochaska and Velicer, and it is also known as the transtheoretical model of health behaviour change.

Figure 2.1: Stages of Change model reflecting the psychological stages a patient progresses through when considering behavioural changes, adapted from Prochaska and Velicer, American Journal of Health Promotion, 1997, reprinted with permission.
However, the most unique part of this section was the use of the World Health Organisation’s “five dimensions of adherence”. This area was covered by providing examples of how each dimension of adherence could be investigated through the HMR process. Table 2.2 gives an overview of this section. By terming each dimension an “adherence barrier” the material encouraged pharmacists to discuss adherence in a less confronting and non-judgemental manner, by comparison to the direct questioning approach. This aligns with the notion of health professionals building and maintaining a strong rapport with a patient in order to have them gain trust in one’s opinions and recommendations.

**Table 2.2: Addressing adherence with HMRs**

<table>
<thead>
<tr>
<th>Adherence Barrier</th>
<th>When/how it may be noticed during the dHMR process</th>
</tr>
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</table>
| Condition related – for example, suffering from multiple conditions or from conditions that may contribute to a lack of motivation towards adherence. | • Pre-emptively – through assessment of the referral letter “conditions” and “notes” section.  
• Through recognition of the patient’s attitudes toward the review process and throughout the interview, particularly in the case of depression or anxiety-related condition barriers. |
| Treatment related – for example, treatment duration, regimen complexity, and treatment side effects. | • Assess the potential need to probe for this barrier, prior to the interview.  
• Direct questioning with regards to side effects or new symptoms during the interview. |
<p>| Healthcare system barriers – ranging from difficulty | • Assessing the patient’s awareness of available programmes, such as cardiac rehabilitation, during |</p>
<table>
<thead>
<tr>
<th>With access to medications, through to the quality of information transferred from hospital to the GP.</th>
<th>The interview.</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Identifying discrepancies between the patient’s medication list and that provided by the GP referral.</td>
<td></td>
</tr>
<tr>
<td>• Also a potential opportunity to help in rectifying accidental medication omissions following discharge.</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Socioeconomic – this may include the significance of the financial burden of seeking healthcare, health literacy issues, and the lack of a good social support network.</th>
<th>• Difficult to truly assess without direct questioning – potentially surrounding the cost of medicines or other possible access issues, such as the cost of GP appointments or travel to cardiology clinic appointments.</th>
</tr>
</thead>
<tbody>
<tr>
<td>• These are likely to be difficult for the pharmacist to change but they may be able to advise and reassure the patient surrounding the importance of their medicines in terms of improving their long-term health.</td>
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</table>

<table>
<thead>
<tr>
<th>Patient related – such as the patient’s perception of their disease, treatment, and side effects. May also include an assessment of any physical barriers to adherence.</th>
<th>• Assessing the patient’s attitude during the interview.</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Looking particularly for signs of denial/rejection of diagnosis, heightened concern over medication side effects, and low self-efficacy beliefs.</td>
<td></td>
</tr>
<tr>
<td>• May also find hints towards difficulty with dexterity, reading medication directions, or swallowing tablets based on the referral or during the interview.</td>
<td></td>
</tr>
</tbody>
</table>
2.1.3 Participation and assessment principles

Once a pharmacist had viewed each lecture in the education package, they could tick a completion box and move onto the next. Once all completion boxes had been ticked by the user, the assessment material was released. The boxes could be ticked without the pharmacist having viewed the presentation if they wished to premature move ahead. It was not possible to determine exactly how often this happened, but lecture download patterns and quiz attempt times suggested that only one participant attempted the quiz without sufficient time allowed for viewing of the lecture material.

The assessment component consisted of 16 multiple-choice questions relating to three hypothetical, case-based, ACS scenarios. A mark of 75% was required to pass. The assessment could be attempted over an unlimited time period with an unlimited number of attempts allowed, but there was a ten-minute lockout period between the first and second attempts, and a 24-hour lockout period between any attempts thereafter. In between each attempt, pharmacists were allowed a two-minute review of their answers and individual feedback was provided for each correct and incorrect answer. The feedback was carefully worded to ensure that it did not give away the correct answer, but highlighted why the option may have been incorrect for a patient at two months post-discharge after ACS. As the questions related to types of recommendations that could be made during the dHMR process, this format of assessment and feedback was a further opportunity for education surrounding the types of recommendations that could be anticipated from the post-ACS dHMR intervention.

In addition to the online lectures and to further assist with guiding the structure of ACS-specific dHMRs, a “dHMR checklist” (see Appendix A) and sample dHMRs from real patients were added to the education website. To assist with accessibility to the package, an administrator was available to guide pharmacists through any of
the stages of enrolment and to answer any questions relating to the material by telephone. The material was also available on compact disc by request.

2.1.4 Critical content review
The material was reviewed internally by three pharmacists: two expert cardiology clinical pharmacists and one professor of pharmacy who was also an accredited pharmacist. This was followed by an external review from an expert general medicine clinical pharmacist, clinical pharmacy lecturer and clinical staff educator. This resulted in multiple modifications and improvements to the material. The education package was then submitted for review and accreditation by the Pharmaceutical Society of Australia (PSA), Australia’s leading body for accreditation of continuing education material for pharmacists. This led to further, minor changes, as well as the specification of learning objectives. The education package was awarded formal accreditation and opened online for APs to access. The package was advertised to Tasmanian APs through emails from the Australian Association of Consultant Pharmacy (AACP), as most APs were likely to have been registered with this organisation.

2.1.5 Evaluation questionnaire
A questionnaire was developed to assess the pharmacists’ satisfaction and whether or not the material met the learning objectives developed through the accreditation process. Kirkpatrick’s model highlights the evaluation of participants’ “reactions” as one of the four pillars of assessing training and development programs.\textsuperscript{122} The questionnaire was face validated by the PSA and the three internal reviewers. The questionnaire was set as optional in order to reduce the barriers required to complete the package and increase the supply of trained APs ready to undertake dHMRs as a part of the subsequent trial. Questionnaire responses were recorded anonymously, with the online education software allowing for only one evaluation attempt per participant.
2.2 Assessment and evaluation results

2.2.1 Assessment results

From 91 Tasmanian accredited pharmacists, 36 registered an interest in the education package and followed through to completing the online enrolment process. Of those who enrolled, 27 completed the education package to the point of attempting the assessment quiz. Twenty-two APs (81%) passed the quiz on their first attempt, three passed on their second attempt, one AP passed on a third attempt, and one AP did not take any further attempts after their first unsuccessful attempt. The results of all attempts are shown in Figure 2.2. Seventeen of the 27 APs attempting the quiz (63%) also completed the evaluation questionnaire. Twenty-one of the 27 APs (78%) who successfully completed the education package went on to participate in dHMRs after ACS as a part of the trial for which the package was developed.

*Figure 2.2: Education package assessment quiz results*
2.2.2 Quantitative questionnaire results

Table 2.3 highlights the questions within the evaluation questionnaire that were assessed by a 3-level Likert scale response. It is worth noting that the feedback was consistently positive for all questions; with the exception of “How enjoyable was the format used?” where “partially enjoyable” was the highest response. Further to the Likert-scale questions, there were three questions with single phrase answers and more than one option could be selected by each participant. When participants were asked: “What would you like to have seen more of in the presentations?” 41% chose the option “nothing more required”. Similarly, for the question: “What would you like to have seen less of…?” 86% chose the option “nothing less”. There was a broad response to the question determining the driving factors behind participant motivation to complete the education package, but “personal desire to expand knowledge base” and “personal desire to improve HMR service” received the highest percentage of preferences at 25% and 23%, respectively.
### Table 2.3: Quantitative component of education package evaluation

<table>
<thead>
<tr>
<th>Question</th>
<th>0%</th>
<th>18%</th>
<th>82%</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Met learning objectives?</td>
<td>Not met</td>
<td>Partially met</td>
<td>Entirely met</td>
</tr>
<tr>
<td>2. Met personal learning needs?</td>
<td>Not met</td>
<td>Partially met</td>
<td>Entirely met</td>
</tr>
<tr>
<td>3. Relevant to your own practice?</td>
<td>Not relevant</td>
<td>Partially relevant</td>
<td>Entirely relevant</td>
</tr>
<tr>
<td>4. How enjoyable was the format used?</td>
<td>Not enjoyable</td>
<td>Partially enjoyable</td>
<td>Very enjoyable</td>
</tr>
<tr>
<td>5. Confidence in applying the material in practice?</td>
<td>Not at all confident</td>
<td>Partially confident</td>
<td>Completely confident</td>
</tr>
<tr>
<td>9. Overall quality?</td>
<td>Poor quality</td>
<td>Average quality</td>
<td>Very high quality</td>
</tr>
</tbody>
</table>

### 2.2.3 Qualitative questionnaire results

Each of the nine questions had a secondary space to allow participants to enter free text. Most of these responses were very positive, such as:

“Thank you for a very well presented education package. I found the information provided to be at just the right level for my current understanding and am very pleased with the knowledge that I’ve now gained” and

“I feel I am better equipped now to have more meaningful and beneficial discussions with my patients/customers who have ACS. I look forward to helping improve patient outcomes in the future.”
Some provided positive comments on the accessibility of the education package, such as:

“Appreciate the narration as attempting to read all of the information can be tedious and it can be easy to be distracted”

but conversely, others had technical difficulties in accessing some of the narration as evidenced by the responses:

“What narration?” and “Something wrong with my computer I think! Didn’t get the narration (but read it out loud from the bottom, so it was kinda the same ;-)”.

This correlates with the high response of “Partially enjoyable” to question 4 as mentioned above.

2.3 Discussion

The education package was developed following a review of evidence-based guidelines, consideration of behaviour change strategies and review by a panel of experts in pharmacy and medication review. Most APs who registered an interest could complete the resulting package and most of the feedback was positive. The strong assessment results and positive feedback suggest that the material covered was delivered at an appropriate level of difficulty and detail, allowing a good degree of learning and understanding; thus putting the participants in a good position to partake in real-life ACS-specific dHMRs. While this may partly reflect a well-developed product, it may be also due to the topic’s relevance within a pharmacist’s day-to-day practice. Whereas more complex topics, such as pharmacogenomics, have been shown to be difficult to teach using similarly brief education packages.131

A potentially negative aspect recognised through the analysis of the package was with accessibility. Online guides were provided to outline how to complete the material, as were a wide variety of viewing formats, and an author was accessible by
phone to assist with any technical difficulties. However, the online format still proved troublesome for some, and both qualitative and quantitative analyses highlighted this issue. In spite of this finding, technical difficulties were generally rare and encountered by only a small minority. It is likely that the attention given toward maintaining accessibility was actually a relative success of the education package and maintaining a high level of accessibility should be considered an important factor for any future service review or expansion.

The education and assessment package was evaluated against levels one and two of Kirkpatrick’s model for training and evaluation.122 Stafford et al followed a similar approach in utilising the HMR service to improve the post-discharge care of patients taking warfarin.120 The APs involved in the study were required to complete a thorough education package based on the principles of warfarin management and this included novel management approaches, such as point of care International Normalised Ratio (INR) monitoring.121 The APs involved with the warfarin management intervention were able to score highly on an assessment quiz and agreed strongly with an evaluation question measuring the perceived adequacy of the training offered. Although the approach described here is somewhat similar, the use of frameworks to guide the development, assessment and evaluation of this education package build on the research of Stafford et al, providing guiding principles to enable expansion of the package across a broader community of health professionals.

Evidence-based guidelines and training evaluation frameworks have governed the design of an education package for increasing the capacity of APs to improve medication management following ACS. The results following an assessment quiz and evaluation questionnaire suggest this may be suitable preparation toward directing the HMR service to the needs of patients following ACS.
Chapter Three: Methodology

3.1 Trial recruitment, randomisation, and the intervention

3.1.1 Overview
A randomised controlled trial (RCT) was conducted to compare a directed Home Medicines Review (dHMR) delivered at two months post-discharge to usual care following a hospital admission for acute coronary syndrome (ACS). Changes in the Home Medicines Review (HMR) referral process and an ACS-specific education package completed by study pharmacists made this program different to the standard HMR service. The primary outcome was the proportion of patients who were adherent and persistent to a guideline-concordant regimen of all four classes of recommended ACS medications, at six months post-discharge. Patients were enrolled in hospital during an admission for ACS. Figure 3.1 provides an overview of the trial protocol.
The design of the intervention and monitoring system was based on a conceptual framework for the standardised evaluation of chronic disease management interventions, as developed by Lemmens et al.\textsuperscript{88} Figure 3.2 is a summary of this framework that has been adjusted from the original model to better reflect the points of the framework that were considered relevant to the HMR service (shown in further detail in Figure 3.3). This framework highlights the importance of considering patient-related factors, professional-related factors and health-system
factors in both the design and evaluation of interventions targeted toward improving the management of chronic diseases. These considerations were particularly important throughout trial development.

**Figure 3.2: Summary of Lemmens et al framework**

Figure 3.3 provides an example of how the individual components of the trial aligned with the framework. The framework provided a fundamental set of recommendations to consider. For example, that a successful intervention should
have all three of a patient focus, professional focus, and be compatible with the existing organisational structure. The efforts to address these recommendations have been highlighted with brief comments in blue text. For example, the professional focus included: the education package for the APs; and the dHMR reports written by APs to provide advice to the GPs; as well as an expectation of the existing HMR service-framework that an agreed management plan is developed following a review.\textsuperscript{110}
Figure 3.3: How the dHMR addressed the specific components of the conceptual framework.

Blue text highlights the aspects of the trial design that were specifically addressing recommendations from the framework. ACS = Acute Coronary Syndrome, dHMR = directed Home Medicines Review, GP = General Practitioner, QOL = Quality of Life.
3.1.2 Setting

Patient enrolment and dHMR referral occurred at the two major tertiary referral hospitals in Tasmania, Australia. The Royal Hobart Hospital (RHH) is a 490-bed public hospital with an 8-bed coronary care unit (CCU), percutaneous coronary intervention (PCI) and coronary artery bypass grafting (CABG) facilities, and accepts patients from across the state for CABG referrals. The Launceston General Hospital (LGH) is a 300-bed public hospital with a 4-bed coronary care unit and PCI facilities. Both hospitals run cardiac rehabilitation (CR) programs that are offered to all ACS patients. Patients admitted to these centres generally receive verbal and written education regarding lifestyle changes following ACS from nurses, and medication counselling from nurses or pharmacists, prior to discharge.

3.1.3 Inclusion/Exclusion Criteria

All adults aged 18 years and over with a primary diagnosis of ACS presenting at the RHH and LGH were considered for enrolment into the trial. The wide age range was chosen to investigate differences in the discharge management of patients, and to examine the suitability of the dHMR intervention across different age groups. Disparities in treatment of ACS among patients of different ages has been previously recognised as an area for further interventional focus by Alexander et al in the CRUSADE trial and other studies have acknowledged the potential for improvement in the prescribing of and adherence to evidence-based medications among older survivors of ACS. Furthermore, suitability of the HMR service among the elderly has been recognised as an area requiring further investigation through a qualitative service review.

Patients were excluded from trial enrolment if they: were not returning to their home following hospital discharge (as this is a requirement of the existing HMR service); were non-Medicare eligible (for example, not a permanent Australian Resident as this is another requirement of the HMR service); had any degree of
cognitive impairment (formally diagnosed or not) such that the process of informed consent was obscured; or had been diagnosed with a malignancy that was expected to be terminal within 12 months.

3.1.4 Randomisation

We used a computer-generated random sequence to provide the randomisation coding. Patients were randomised to the control or intervention groups following computerised recognition that they met the inclusion criteria and provided informed consent. Entry of this information into the central trial database enabled the enrolling researcher to unlock the randomisation status for that participant.

3.1.5 Controls

Following randomisation to the control group, patients were offered the usual care processes involved with post-discharge management of ACS in Australia. Through the public health system, patients were able to attend a CR program at their local hospital as well as a cardiologist follow-up appointment, usually occurring at one month following discharge. The CR programs from the two different hospitals varied slightly in their level of physical activity, but the material covered in their information sessions was similar. CR referral and attendance is known to vary, therefore completion of CR was recorded, such that this could be controlled for in assessing the primary outcome.

3.1.6 Intervention

Patients in the intervention group received a dHMR at approximately two months following discharge as well as usual care. The time of two months post-discharge was selected as previous studies of patients with ACS have demonstrated that this is a time when they are most vulnerable to discontinue one or more medications.6,26,136
Based on pre-existing funding arrangements and recommended reasons for referral, the HMR service was available in Australia for all patients with ACS following hospital discharge.\textsuperscript{108} The uptake of this service, however, may have been limited by the absence of HMR referral systems in this transitional period. Furthermore, the currently available service could be tailored to address the expected needs of patients recently diagnosed with an ACS. It was hypothesised that the existing service could be optimised in several ways, making the proposed dHMR better directed toward the needs of the ACS population.

\subsection*{3.1.7 Changes to optimise the existing HMR service}

Typically, HMRs are ordered by a referral letter generated by the patient’s GP. Referral letters may vary significantly in their level of detail, potentially leaving the AP with little direction prior to the patient interview. This concern was highlighted as a potential downfall of the service in a qualitative review.\textsuperscript{109} To address this issue, the enrolling researchers used a specifically designed database that automatically populated the HMR referral with relevant information obtained through baseline data collection. The referral letter was forwarded to the GP for approval and addition of any further information, such as medications that had changed since discharge. GPs were also contacted by phone to further engage them in the dHMR process. GP approval is a requirement for HMR payment under the existing public service arrangements and having the GP engaged with the intervention early was expected to increase their willingness to actively participate in the process, for example, in response to receiving dHMR reports and in the formulation of medication management plans. This novel approach also relieved the GP from having to complete most of the referral data entry, allowing for simple addition of only useful information. The GP may have also found the information on the referral letter useful, as previous research has demonstrated that standard discharge letters following ACS admissions do not always contain a sufficient level of information and sometimes take too long to reach the GP, reducing their clinical utility.\textsuperscript{26}
In addition to the disease-specific referral letter, the service was further directed by offering APs across Tasmania an online education and assessment package, as outlined in detail in Chapter Two. In order for an AP to complete an interventional dHMR according to the trial protocol, they were required to have a current accreditation status and have successfully completed the education and assessment package. Upon completion of the education and assessment package, APs gained recognition of continuing professional development and an AUD50 reimbursement for their time. Briefly, the education package involved five online lectures focussing on ACS management principles and methods for identifying and resolving adherence barriers. Assessment was through an online quiz. The online learning system included an ACS-specific checklist to aid dHMR-report writing and a selection of exemplary dHMR report findings taken from the first few completed reports. The primary project officer also made themselves available for phone consultation with the APs throughout the trial period.

3.2 Trial outcomes

All outcomes were measured at the endpoint of six months post-discharge. Each outcome included a comparison between the control and the intervention. The Lemmens et al framework guided outcome selection, ensuring measurement of important clinical outcomes as well as the individual steps of the intervention that required monitoring (process outcomes). Monitoring these individual steps, such as pharmacist detection of drug-related problems (DRPs) and GP acceptance of pharmacist recommendations, was important to measure the level of alignment between the theoretical plan and the practical application of the intervention, herein termed ‘intervention fidelity’. It was also believed that using a detailed monitoring and outcome reporting process may elucidate areas of practice worthy of focus in future research.
3.2.1 Primary outcome

The primary outcome was the proportion of patients who were adherent to a guideline-concordant ACS medication regimen at six months. To be considered adherent, the patient had to be discharged on and persistent with all four classes of guideline-recommended medications and record a medication possession ratio (MPR) greater than or equal to 0.8. The approach to only calculate MPRs for medications to which patients were persistent,\(^{137}\) and the use of a dichotomous cut-off for the MPR,\(^{138-141}\) are both previously accepted methods, however, the use of these measures as a composite within this study is a novel approach to defining adherence. While the degree of non-adherence to the regimen relied mostly on patient behaviours, non-persistence may have occurred as a result of either the patient not collecting a prescription or their GP not prescribing the medication. Due to resource and data collection constraints, it was only feasible to assess prescribing at discharge, therefore the direct causes of non-persistence could not be identified. The following sections explain the reasoning behind the approach to split adherence and persistence and section 3.2.1.3 illustrates how each component was calculated.

3.2.1.1 Detection of non-persistence

Patients were identified as non-persistent to any guideline-recommended medication if they were discharged with a guideline-concordant regimen, but did not to collect a supply of one or more medications within the first 60 days post-discharge, or if there was a gap in dispensing equal to twice the number of days supplied on the previous dispensing at any time during follow-up. Non-persistence was further delineated into ‘early non-persistence’ and ‘anytime non-persistence’. Patients demonstrating ‘early non-persistence’ were those who were discharged as guideline-concordant but either had no collections of one or more guideline-recommended medications, or obtained a supply of a guideline-recommended medication within 60 days post-discharge, but collected no further supplies in the following 120 days. Those demonstrating ‘anytime non-persistence’ were those who
collected supplies of medications both before and after the 60-day post-discharge cut-off, but had at least one gap in dispensing equal to twice the number of days supplied on the previous dispensing. The combination of ‘anytime non-persistence’ and ‘early non-persistence’ covers all types of non-persistent medication collection patterns and is termed ‘total non-persistence’ at six months post-discharge. ‘Anytime non-persistence’ is also presented separately among the sample who were persistent beyond two months (those not detected by ‘early non-persistence’). For P2Y12 antagonists, ACEI/ARBs, and statins, the period used to determine non-persistence was effectively a gap of two months in supply based on typical Australian prescribing patterns. This was considered a clinically suitable gap in medication supply to denote non-persistence.142,143

The class of medication, prescribed daily dose, and the quantity supplied were all recorded allowing for patients to remain persistent even if they switched between medications within the same class. This information was also used to determine how long each supply should last and a calculation of any supply gaps. The heterogeneity in prescribing of beta-blockers, whereby some patients may have been discharged with a 200-day supply and others with only a 30-day supply (most commonly dispensed as a 100-tablet unit of supply, but with varying doses prescribed), rendered this definition of persistence less sensitive for this class of medication. However, the algorithm could still detect early non-persistence as a result of only a single supply of a beta-blocker on discharge among the majority – those with a 100-day supply or less – and this was accepted as sufficient reason to not exclude this medication class from the assessment of the primary outcome. The ability to detect early non-persistence across all guideline-recommended medications was considered particularly important to assess the impact of the intervention on the quality of care following ACS. Early discontinuation of guideline-recommended medications has been linked to 12-month mortality and the timing of the
intervention was chosen to allow for specific problems during this time to be addressed promptly, resulting in a need to detect such events.6

Due to the supply arrangements for aspirin in Australia, this medication was typically dispensed by the discharging hospital, but subsequent supplies were commonly purchased without a prescription record. As such, aspirin was excluded from the primary outcome and antiplatelet adherence was measured only through the monitoring of P2Y12 antagonist supply. Although the recommended duration of P2Y12 antagonists had been anecdotally observed to vary across Tasmanian cardiologists, the trial was designed based on acceptance of the most recent guidelines available at the time, citing a recommendation of 12 months DAPT for all patients following ACS.5 Nonetheless, consideration of factors that may affect recommendations surrounding DAPT duration, such as the deployment of drug-eluting stents (DES) versus other management options was identified as an important point to consider during the analysis of the primary outcome.144,145

If non-persistence was detected for a particular medication, it did not contribute toward the average MPR calculated for any medications to which the patient was persistent. Separation of persistence from surrogate measures of adherence, such as the MPR, is important to improve the association between the measure and the behaviour it is intended to describe.9,66

3.2.1.2 Detection of adherence by a modified medication possession ratio algorithm
The MPR for all persistent guideline-recommended medications was calculated and averaged for each patient. A value greater than or equal to 0.8 was considered adherent, which is a commonly accepted cut-off for this measure, including when it is used to determine adherence to cardiovascular medicines.65,138,139 Although this value has often been referred to as arbitrary, a recent observational study has provided some clinical validation of this cut-off with reduced rates of major adverse
cardiovascular events (MACE) among patients suffering recent MI who had MPR>0.8 by comparison to those with MPR<0.8. The calculated MPRs of medications with which the patient had been persistent were averaged and the medians of these results for the control and intervention groups were also reported as a sub-analysis. This accounts for the fact that while dichotomous assessment of MPR is common, the best cut-off to use is unclear and further clarity toward understanding the magnitude of the changes in adherence may be obtained by also comparing group medians.

For this study, a specific adaptation of the MPR was used, which we have termed the ‘modified MPR’ (MMPR). This adaptation was chosen based on the observation that traditional MPR calculations often give an overestimation of adherence over short observation periods, particularly where medication supplies may overlap. Similar efforts to address these problems and improve the MPR have been considered by other authors and this represents the basis of the algorithm presented. The MMPR was determined by subtracting the ‘days without medication’ from the ‘days in observed period’ and dividing the resulting numerator by the ‘days in observed period’ minus 1. For example, at six-month follow-up, the ‘observed period’ ended at 180 days post-discharge; however, the denominator to the MMPR equation was 179, accounting for the common occurrence of within hospital medication dosing on the day of discharge. As such, a continuous supply of 179 days or more resulted in an MMPR value of 1, or perfect adherence. Figure 3.4 shows the equation used to obtain the MMPR for each individual guideline-recommended medication.

Figure 3.4: Equation used to obtain the modified medication possession ratio (MMPR) as calculated for this study

\[
\text{MMPR} = \frac{\text{days in observed period} - \text{days without medication}}{\text{days in observed period} - 1}
\]
The MMPR was capped at a maximum value of 1 as oversupply of cardiovascular medication is expected to be a result of stockpiling rather than genuine overuse.\textsuperscript{65,138,141} To further minimise the potential effect of stockpiling behaviours artificially increasing the MMPR, the quantity of any supplies collected prior to depletion of the current supply was added to the expected medication depletion date. For example, if a supply was collected one day prior to the expected depletion date of the previous supply, the new supply’s expected depletion date had this additional day added to it. If multiple supplies occurred near the end of the 180-day observation period, only the medication that was supplied and required up until 180 days post-discharge was counted.

### 3.2.1.3 Illustration of how the MMPR algorithm detected non-adherence and non-persistence

Figure 3.5 provides an example of how the algorithm dealt with overlapping supplies and supplies near the end of the observed period. In this figure, the second to fifth supplies were all collected early and summed together, giving a period covered according to the total supply. This was followed by a five-day gap in supply and the adjusted supply pattern shows how the supply collected at 155 days post-discharge was only partly counted in the MMPR calculation, being truncated at 25 days’ supply. Effectively, this resulted in a five-day gap and an MMPR of 0.98.

Fixed-interval (FMPR) and variable-interval MPR (VMPR) calculations are provided as a point of reference. While these algorithms have been used by previous researchers, they were considered not suitably specific for the current study.\textsuperscript{148}
Figure 3.5: Conversion of actual to adjusted supply for a continuously early supply pattern, followed by a small gap and a truncated final supply. The modified MPR algorithm and comparison to previously described MPR algorithms are overlayed. FMPR – fixed interval medication possession ratio; VMPR – variable interval medications possession ratio; MMPR – modified medication possession ratio as described within the current study. Each supply refers to a 30-day supply of medication.

![Diagram of supply patterns](image)

- FMPR = 180/180 = 1.00
- VMPR = 180/185 = 0.97
- MMPR = 175/179 = 0.98

Figure 3.6 again highlights how the algorithm dealt with supplies collected near the end of the observed period, particularly resulting in a lower MMPR by comparison to other adaptations. However, this figure also highlights how ‘anytime non-persistence’ was detected and that this resulted in a ‘null’ value for the MMPR, such that non-persistence was reported as a separate finding, rather than artificially lowering the MMPR. The pattern of medication supply presented here is of particular interest for the current study as such a pattern could theoretically occur as a result of a patient restarting a medication following a post-discharge dHMR. However, it was decided that a full month without medication available in this period shortly following ACS conferred a high risk of significantly worse health
outcomes. As such, for the intervention to be considered to have resulted in a genuine benefit, the restarting of guideline-recommended medications would need to occur rapidly following detection of non-persistence by the study pharmacist and the relatively tight gap used to detect non-persistence remains justified.

Figure 3.6: Conversion of actual to adjusted supply. A supply on discharge is followed by a period of ‘anytime non-persistence’, before restarting with continually early supplies. The modified MPR algorithm and previously described MPR algorithms are overlayed.

FMPR – fixed interval medication possession ratio; VMPR – variable interval medications possession ratio; MMPR – modified medication possession ratio as described within the current study. Each supply refers to a 30-day supply of medication.

In Figure 3.7 there are only two continuous supplies collected, with the first being on the day of discharge. As both supplies have been collected in the period prior to two months post-discharge and there are no supplies in the period following, the algorithm detected this as ‘early non-persistence’. The MMPR is again reported as
null and would not count toward the cumulative/average MMPR for this patient. In the primary outcome analysis, any finding of non-persistence would render the patient as non-persistent to a guideline-concordant regimen. However, for secondary analyses, such as analysis of median MMPRs between groups, it was important to be able to average the MMPRs calculated for those medications with which the patient had been persistent.
Figure 3.7: Conversion of actual to adjusted supply. A supply is collected on discharge and a continuation supply is collected early. No further supply denotes early non-persistence. The modified MPR algorithm and previously described MPR algorithms are overlayed.

FMPR – fixed interval medication possession ratio\(^{149}\); VMPR – variable interval medications possession ratio\(^{149}\); MMPR – modified medication possession ratio as described within the current study. Each supply refers to a 30-day supply of medication.
During the baseline interview, the two main pharmacies that a patient attended were recorded, aiming to make the dispensing records as complete as possible. As the MPR is typically applied retrospectively to medication records of managed health organisations with only low rates of medication collection at non-recorded sites, it was recognised that collection of a complete medication history using the Australian system of medication supply may be difficult. However, dispensing records in Australia are rich in data, often allowing for identification of repeated dispensing from an original prescription. These histories were checked and if there were apparent gaps in a dispensing history, the patient was contacted to ask if they had collected medication elsewhere. Those with remaining supply gaps were assessed by the primary project officer. If the dispensing data showed that supplies from the same prescription had been collected before and after a gap of supply that could not be confirmed by a dispensing record (for example when the patient claimed they had collected elsewhere but couldn’t remember the location or name of the pharmacy), the record was further discussed with a second pharmacist researcher not involved with patient recruitment, and the patient was only included if it was deemed most-likely that a repeat supply had been collected elsewhere. Any gaps remaining unexplained or instances whereby the patient could not be contacted resulted in the history being deemed incomplete. These patients were considered lost to follow-up and removed from all outcome assessment, with the incidence of this occurrence reported in the results, see section 4.1.

### 3.2.1.4 Self-report of medication adherence and persistence

To allow for a significant loss of patients due to incomplete dispensing records, self-reported medication adherence was used as an alternative measure. This was also reported and used to triangulate adherence in combination with the MMPR as a further sub-analysis. The four-item Morisky adherence questionnaire was used to measure self-reported adherence. This is a well-validated instrument, having been used previously with good predictive validity in patients at risk of cardiovascular
Patients self-reported their persistence with guideline-recommended medications by recording their current regimens at the six-week and six-month survey follow-up.

3.2.1.5 Assessing contraindications and discharge prescribing of guideline-recommended medications

In the case where a patient had a clearly documented contraindication to one of the four guideline-recommended medication classes, their medication regimen was still considered “complete” provided they were taking all other guideline-recommended medications. For example, a patient with asthma not taking a beta-blocker but still taking clopidogrel, an ACE inhibitor, and a statin, was considered in the same group as someone prescribed all four medications. As it has been shown that the initiation of guideline-recommended medications following ACS is largely driven by hospital-based doctors, only those discharged with a guideline-concordant medication regimen were assessed for the primary outcome. It was considered appropriate for all patients to be considered in the primary outcome assessment as the Australian guidelines published at the time of trial design considered all patients with ACS as eligible for all four medications and this was consistent with previous efforts to improve guideline-concordant prescribing at discharge. However, components of the primary outcome, such as non-persistence, were explored further among only those discharged as guideline-concordant to account for potentially low rates of discharge prescribing. As a follow-up to this, non-persistence was also assessed as a cumulative result whereby patients discharged on four, three, two, or fewer guideline-recommended medications had the persistence algorithm applied and the results summed, allowing for an assessment of this outcome across a greater number of enrolled patients.
3.2.2 Secondary outcomes

Secondary outcomes included hospital readmission rates, length of hospital stays, changes in quality of life (QoL), cardiac rehabilitation (CR) completion rates, smoking cessation rates, and mortality. Hospital readmissions and mortality were further categorised as ACS-related or due to other causes. QoL was measured at six weeks post-discharge as a pre-dHMR baseline measure and again at six months. The Euroqol “EQ-5D 3L”\textsuperscript{150} was used to measure general QoL and the Seattle Angina Questionnaire (SAQ)\textsuperscript{151} was used to measure cardiac-specific QoL. Both instruments have been validated when administered individually\textsuperscript{151-154} and in combination\textsuperscript{155} to assess QoL in patients with coronary heart disease.

The first section of the Eq-5D-3L comprises five questions using a 3-point Likert-scale for the domains of “mobility”, “personal care”, “usual activities”, “pain”, and “anxiety and depression”. For each domain, the patient can report either no problems (coded as 1), some limitations (coded as 2), or severe limitations/extreme problems (coded as 3). The individual domains are combined to give a score ranging from “11111” representing perfect health, to “33333” representing the worst health state imaginable. To provide a quality versus quantity of life analysis, response patterns have been validated using population samples from specific countries, whereby people are asked to rate how long they would prefer to live in full health followed by immediate death as opposed to a longer period of time in the health state presented. This is known as a time-trade-off (TTO) analysis and the algorithm returns a utility score from -0.217 to 1, whereby 1 represents perfect health and scores less than 0 represent situations considered as worse than death. The algorithm used within this study was developed by Viney et al based on an Australian validation of the Eq-5D.\textsuperscript{156} In addition to the five domains, the Eq-5D-3L concludes with a visual analogue scale (VAS) rating for how the patient rates their current quality of life on a scale of 0 to 100.
The SAQ is a series of 19 Likert-scale questions with the length of the Likert-scale varying between sections. The 19 questions are broken down into five domains, with nine questions assessing physical limitations, one question assessing angina stability, two questions assessing angina frequency, four questions assessing treatment satisfaction, and three questions assessing QoL. The answers to the questionnaire are processed according to an algorithm designed by Spertus et al and this results in a score for each of the five domains. Spertus et al also demonstrated that the SAQ can be sensitive to subtle changes in CHD, making it suitable for the purpose of comparing between the control and intervention groups within the present study.

In addition to a self-report of smoking status at baseline and the study endpoints, each smoker’s dependence on cigarette smoking was further categorised using the Fagerstrom Test for Nicotine Dependence (FTND).

3.2.3 Process outcomes

In addition to reporting the important clinical outcomes that may be affected by the intervention, it was also recognised that there are many individual components of such interventions that can be measured and may highlight barriers or enablers to the overall success of the intervention. From the professional aspect of the dHMR, it was considered important to measure GP acceptance of the intervention through approval of dHMR referrals, pharmacists’ recognition of DRPs, the clinical relevance of the DRPs identified, and GP acceptance of pharmacists’ recommendations. Figure 3.8 and Figure 3.9 represent the measurement of the effect of these professional and organisational barriers on trial implementation. Of the components highlighted in blue, all were measured and reported, with the exception of the quality of the verbal and face-to-face components of the intervention. The survey data was intended to provide a surrogate explanation of the quality of the information conveyed at the dHMR interviews, however, capturing and analysing the audio-visual components
of the interactions that APs had with patients and their GPs would have required significantly greater resources than that available.
Figure 3.8: Evaluation of the professional focussed components of the intervention.\textsuperscript{68}

The blue text in this figure highlights where the professional focussed components of the intervention fit into the Lemmens et al framework. dHMR – directed Home Medicines Review; MedReDi – Medication Reviews re-Directed – the title given to the trial.

Evaluation Processes for MedReDi

**Professional Focus**

- Improve/correct knowledge-base
- Offer opportunities to develop skills and expertise – education and assessment package for pharmacists

- Improved attitudes toward provision of appropriate care (behavioural intention) – % of GPs producing agreed management plans following dHMR report

- Professional behaviour/practice changes – partly measured through patient’s dispensing records, but may be obscured by primary non-adherence

Intervention Processes

Patient Focus

Professional Focus

Health System Factors

Organisational Design

Inter-professional Relationships and Coordination

Outcomes
Figure 3.9: Evaluation of the health-system’s impact on the implementation of the intervention.

The blue text in this figure highlights how the local health-system structure may affect the implementation of the intervention described within this trial protocol. Again, the relevant points raised by the Lemmens et al framework have been considered.

dHMR – directed Home Medicines Review; MedReDi – Medication Reviews re-Directed
From the patient’s perspective it was considered important to investigate, firstly, how the dHMR process may have influenced psychological variables that have been previously recognised as relevant to adherence behaviour, as well as how strongly these variables correlated to the outcome of adherence and persistence within this particular trial setting. A full analysis of baseline confounding on the primary outcome from the concepts assessed in each questionnaire was, however, considered beyond the scope of this project due to time and resource limitations. The concepts we chose to consider and the validated instruments that were used to evaluate each construct are detailed in Figure 3.10.
Figure 3.10: Evaluation of the patient-focused component of the intervention. This figure highlights the comprehensive evaluation that was designed for the patient-focused component of the intervention. IPQ – Illness Perception Questionnaire, PHRQ – Perceived Health Risk Questionnaire, BMQ – Beliefs about Medicines Questionnaire, TABS – Tool for Adherence Behaviour Screening, MPR – Medication Possession Ratio. MedReDi – Medication Reviews re-Directed
The concepts of knowledge, illness perception, beliefs about medications, and self-efficacy have all been studied separately in CHD populations. In developing the conceptual framework for the evaluation of chronic disease interventions, however, Lemmens et al recognised the important interrelations between these concepts and how this can affect the ultimate outcome of patient behaviour change. Risk perception and adherence-specific behaviours are two lesser studied concepts that may also affect or predict adherence and, as such, were added to our model of assessment. The following is a brief summary of the questionnaires selected for this purpose:

- For adherence-specific behaviours the Tool for Adherence Behaviour Screening (TABS) was selected.
- To assess medication knowledge “recall of individual medication purpose” was selected, as adapted from Hope et al.
- For self-efficacy seven items from the Cardiac Self-Efficacy Scale were selected.
- For beliefs about medications, eight items from the Beliefs About Medicines Questionnaire (BMQ) were selected and two items were developed to assess the impact of cost “The cost of my medications makes it difficult for me to take them regularly” and “Medications are not good value for money” which were assessed on the same 5-point Likert scale as the BMQ questions.
- For illness perception the eight quantitative items of the Brief Illness Perception Questionnaire (Brief IPQ) were selected.
- For risk perception the Perceived Heart Risk Questionnaire (PHRQ) was selected.

All of these questionnaires have been validated in populations of patients with CHD. The complete questionnaire set chosen for this study can be viewed in
Appendix B – Questionnaire battery.

3.2.4 Sample size

The aim was to detect a change in the primary outcome of 15% between the control and intervention groups. This predicted change was based on the results of the recently conducted Discharge Management of Acute Coronary Syndromes (DMACS) study, whereby a 12% post-intervention improvement was observed on the proportion of patients taking the same four guideline-recommended medications at discharge.\textsuperscript{26} To detect a change of 15%, assuming a control group result of 45%, a power to detect a difference of 80% with alpha = 0.05, a minimum sample size of 186 patients per group was required. To account for an approximate dropout rate of 20%, the enrolment target was 465 patients. Based on Australian guidelines, those discharged with a diagnosis of ACS should be discharged on a guideline-concordant regimen and an omission of guideline-recommended medications on discharge was considered guideline non-concordance, unless a contra-indication or other reason for non-prescription was highlighted.\textsuperscript{1} It was therefore expected that all patients would be included in the analysis of the primary outcome and that patients with clearly documented contraindications to one or more specific medication classes would be included as adherent to that particular medication. Sub-analyses of components of the primary outcome, such as non-persistence among only those discharged with a guideline-concordant regimen were also included to improve the assessment of the intervention if low rates of discharge prescribing were found.

3.2.5 Data collection

Baseline data collection occurred in hospital at the time of enrolment and at six weeks post-discharge – when the participants were sent their first questionnaire set. The in-hospital baseline data collection included the recording of traditional coronary risk factors, such as prior diagnosis of hypertension, diabetes, smoking status, social factors (employment and home setting), and prior history of CHD.
Comorbidities were recorded and counted toward a comorbidity status as classified by the updated Charlson Comorbidity Index (CCI). The scale was age-adjusted and dichotomised in alignment with similar methodologies. The final baseline data collection point of six weeks post-discharge reflected the intention to gauge each patient’s status on each of the questionnaires in the time directly before the dHMR and not while in hospital, as factors, such as adherence behaviour, may be very high in hospital but may significantly decline over time following discharge. Patients in the intervention group were asked to ensure that they completed their questionnaire before their AP visit. Phone-call reminders were scheduled at 10 days post questionnaire mail-out to improve response rates and minimise the risk of questionnaires being filled after the AP visit.

APs’ successful completion of the education and assessment package was required prior to starting any trial dHMR. This was recorded through an online system, specifically designed to guide each pharmacist through to completion of the package, while also monitoring their usage levels of the education website via separate login codes. Although completion of the package was encouraged by an AUD50 honorarium, programme completion could not be enforced beyond this level and those patients receiving a dHMR by a pharmacist who had not successfully finished the education and assessment package prior to the dHMR interview were excluded from the on-treatment analysis, as discussed in section 3.2.6.

Following the dHMR interview, data collection started with the pharmacist’s dHMR report and the agreed patient-GP management plan. Collection of these documents allowed for assessment of pharmacists’ recognition of DRPs, the recommendations made to improve these problems, and the GPs’ acceptance of these recommendations, as described in Figure 3.8 and Figure 3.9. DRPs and recommendations for their resolution were categorised using the “DOCUMENT” system, see Appendix C – DOCUMENT DRP classification system. This allowed for identification of common DRP themes throughout the trial. Telephone follow-up
was scheduled two months after the interview if the reports and management plans had not been received. Recent amendments to the Medicare-funded HMR reimbursement process reinforced the requirement that an agreed management plan be formulated following all HMRs, which was expected to help facilitate this data collection point. Timely access to national records on HMR claiming were not available, such that receipt of a standard or directed HMR by a control patient could be determined. However, discussion with more active APs suggested that such risk was likely low as they did not commonly encounter this patient group in their routine practice. Furthermore, the group of APs involved in the trial was relatively small and most APs were in reasonably frequent contact with the project officers. While no events were reported by APs or the patients involved, it is possible that control patients may have received an HMR or dHMR and this may have gone unreported.

Follow-up at six months post-discharge included requests to community pharmacies for patient dispensing records, hospital register checks for readmissions, lengths of stay, and cardiac rehabilitation referral and completion rates, and a questionnaire mail-out with another ten day phone call reminder. A deaths registry check for mortality was planned, however, this was not performed as all patients’ vital statuses were identified through either medical records or survey contact.

### 3.2.6 Statistical analysis

All baseline variables were compared between the control and intervention groups using independent samples t-tests for continuous, normally distributed variables, the Mann-Whitney U-test for non-normally distributed continuous variables, and Pearson’s chi-squared analysis for categorical variables. Fisher’s exact test was used for chi-square analysis with expected counts lower than the accepted cut-off for 2x2 contingency tables, the Likelihood Ratio was used for contingency tables larger than 2x2 with expected counts lower than the accepted cut-off, and Kappa’s test for
agreement was used to compare self-reported adherence against the MMPR. Where tests were repeated at baseline and follow-up, as with the questionnaires, independent t-tests or U-tests were undertaken at both time points, as well as paired t-tests or the Wilcoxon Signed Ranks Test depending on parametric or non-parametric distribution, to compare for within group changes over time. All outcomes were reported as descriptive comparisons between the control and intervention groups, with significance reported at alpha = 0.05. For baseline assessment of comorbidities using the updated CCI, an age-adjustment was applied as with the original CCI,\textsuperscript{176} and this was stratified into two categories, 0-2 versus 3 or more. Similar stratifications have been applied previously and the dichotomous stratification best suited the current study.\textsuperscript{171,177} As there were several potential barriers that may have prevented a patient who was randomised to the intervention group from receiving a dHMR according to the protocol, both an intention-to-treat analysis and an on-treatment sensitivity analysis were applied. To remain on-treatment, a patient had to have their home-visit before four months post-discharge and the AP performing the visit had to hold a current accreditation status and have completed the education package prior to the visit.

As described in section 4.2.2, while investigating the persistence component of the primary outcome, a statistical trend was noted between “study group allocation” and guideline-concordant persistence to six months by univariate analysis. Binary logistic regression (LR) was undertaken to explore potential confounding from baseline variables on the effect of “study group allocation” on persistence. Only patients who were guideline-concordant at discharge were included due to sample-size limitations for the other groups. For the LR, all variables measured prior to the home-visit were considered baseline variables, including those measured during hospital admission, all items of the six-week questionnaires, and CR completion rates. Questionnaire sub-totals were used in preference to individual items to minimise the risk of identifying individual items as confounders by chance rather
than a true effect. Individual variables were only included if the sub-total resulted in a large number of missing patients due to non-completion of the full questionnaire or if the questionnaire did not have a sub-total. The change in estimate (CE) approach was used to identify variables that had a potential confounding effect.\textsuperscript{178,179}

This involved generating multiple LR models by including “study group allocation” in each model and cycling through all baseline variables, one at a time, with potential confounders identified as those that caused a change in the point estimate of the study group allocation variable by greater than or equal to 10% (CE≥10%). Pearson’s Chi-Square or Spearman’s Rank Correlation tests were used to identify collinearity. Among collinear variables, the variable causing a greater CE was retained. From this set of variables, a final LR model was created by adding and removing variables from the model, one at a time (stepwise), and retaining variables that continued to cause a CE≥10%, without an excessively large increase in the standard error (SE), generally limited by removing variables that resulted in changes of SE≥10%.

By building the LR model with both forward and backward steps, individual variables with the greatest unique confounding effect were identified. Variables showing confounding effects in a similar direction showed a reduced CE when included in a model with a more pronounced confounder, therefore the less prominent confounder was identified and removed. Due to the small sample size, there was a risk of including too many variables and developing a model with excessively large SE.\textsuperscript{180} The method described here controlled for confounding while containing SE and maintaining the statistical validity of the model. An excessive SE would also limit the application of the result in a clinical context.

A wide variety of methods have been previously described for controlling for confounding in observational research,\textsuperscript{179,181-183} however, a gold-standard approach to control for confounding in RCTs has not been established. Despite this, there is an increasingly recognised need to control for confounding in RCTs.\textsuperscript{184} Although
commonly used to demonstrate an absence of confounding, standard significance testing of baseline groups does not rule out confounding bias if there is a non-significant difference between randomised groups for a covariate that shows a strong impact on the outcome measured. Based on the currently available literature the method described here is appropriate to apply in the RCT setting to specifically identify potential confounders rather than predictors of the outcome. It is important to note that the method described here does not involve any significance testing in the initial stages of confounder selection. Although the use of significance testing to develop LR models is widespread, this approach more accurately identifies potential predictors of an outcome rather than confounding covariates. A variable that predicts a certain outcome may not always confound an interaction between another variable and the outcome, whereas the CE method directly assesses this effect.

All statistical analyses were performed using IBM SPSS version 21.0. (Armonk, NY: IBM Corp).

### 3.2.7 Ethical approval

This trial received ethical approval through the Tasmanian Health and Medical Human Research and Ethics Committee. Approval number: H11821. All participating patients provided informed consent.
Chapter Four: Results

4.1 Trial recruitment, baseline demographics and discharge prescribing

Full details of patient recruitment are provided in Figure 4.1. In summary, 359 patients with suspected ACS were screened for enrolment into the study; 26 patients were excluded, 14 were discharged prior to obtaining consent, 54 did not have a final diagnosis of ACS, and 81 declined consent. Of the remaining 184, twelve withdrew consent shortly following discharge, three died soon after discharge, one patient died during the follow-up period, and five were lost to follow-up. Despite extensive efforts to obtain dispensing records from as many pharmacies possible, twelve patients (five controls, seven intervention patients) were excluded based on an incomplete dispensing record (effectively lost to follow-up). Thus, 151 patients were included in the intention-to-treat (ITT) analysis (76 controls, 75 intervention patients). An on-treatment (OT) sensitivity analysis excluded a further 16 patients from the intervention cohort due to non-compliance with the study protocol. Further discussion and assessment of the barriers to on-treatment completion of the intervention are reported under section 4.4 Process outcomes. The number of patients with sufficient information for assessment of the primary outcome was substantially less than the predicted sample size requirements, therefore the following results must be interpreted with caution as further discussed in section 5.7.1.
Baseline demographics are outlined in Table 4.1. There were no significant differences in baseline demographics between the control and intervention groups. The cohort was predominantly white males, with a mean age of 61.8 years old. The primary mode of management was coronary artery stenting, with stents deployed in approximately 75% of patients.
Table 4.1: Baseline demographics and discharge diagnosis

ITT – intention-to-treat; OT – on-treatment; SD – standard deviation; LDL-C – low density lipoprotein-cholesterol; CCSUA – Charlson comorbidity score, updated and age-adjusted; (N)STEMI – (non)-ST-segment-elevation myocardial infarction; Unspec ACS – unspecified acute coronary syndrome; *for drug-eluting stenting, control n=60, ITT n=55, OT n=42.

<table>
<thead>
<tr>
<th>Demographic</th>
<th>Control</th>
<th>ITT</th>
<th>P</th>
<th>OT</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>(N=151)</strong></td>
<td>N/76 (%)</td>
<td>N/75 (%)</td>
<td></td>
<td>N/59 (%)</td>
<td></td>
</tr>
<tr>
<td>Male gender</td>
<td>54 (71.1)</td>
<td>58 (77.3)</td>
<td>0.378</td>
<td>47 (79.7)</td>
<td>0.253</td>
</tr>
<tr>
<td>Mean age (SD)</td>
<td>61.1 (10.4)</td>
<td>62.6 (9.8)</td>
<td>0.376</td>
<td>62.3 (9.6)</td>
<td>0.494</td>
</tr>
<tr>
<td>Body mass index (SD)</td>
<td>29.9 (6.1)</td>
<td>29.9 (6.5)</td>
<td>0.964</td>
<td>29.9 (5.4)</td>
<td>0.962</td>
</tr>
<tr>
<td>LDL-C (mmol/L) Median (IQR)</td>
<td>2.7 (2.2-3.5)</td>
<td>3.0 (2.5-3.6)</td>
<td>0.307</td>
<td>2.9 (2.5-3.6)</td>
<td>0.393</td>
</tr>
<tr>
<td>Maximum troponin (mcg/L) Median (IQR)</td>
<td>10.5 (0.1-52.1)</td>
<td>8.0 (0.6-43.9)</td>
<td>0.929</td>
<td>8.0 (0.5-45.8)</td>
<td>0.875</td>
</tr>
<tr>
<td>Caucasian</td>
<td>73 (96.1)</td>
<td>73 (97.3)</td>
<td>0.660</td>
<td>57 (96.6)</td>
<td>0.865</td>
</tr>
<tr>
<td>Privately insured</td>
<td>27 (35.5)</td>
<td>29 (38.7)</td>
<td>0.690</td>
<td>20 (33.9)</td>
<td>0.844</td>
</tr>
<tr>
<td>Employed</td>
<td>38 (50.0)</td>
<td>26 (34.7)</td>
<td>0.057</td>
<td>22 (37.3)</td>
<td>0.140</td>
</tr>
<tr>
<td>Lived alone</td>
<td>15 (19.7)</td>
<td>14 (18.7)</td>
<td>0.867</td>
<td>12 (20.3)</td>
<td>0.931</td>
</tr>
<tr>
<td>History of hypertension</td>
<td>50 (65.8)</td>
<td>39 (52.0)</td>
<td>0.085</td>
<td>31 (52.5)</td>
<td>0.119</td>
</tr>
<tr>
<td>Diabetes</td>
<td>19 (25.0)</td>
<td>16 (21.3)</td>
<td>0.593</td>
<td>12 (20.3)</td>
<td>0.523</td>
</tr>
<tr>
<td>Demographic</td>
<td>Control (N=76)</td>
<td>ITT (N=75)</td>
<td>P</td>
<td>OT (N=59)</td>
<td>P</td>
</tr>
<tr>
<td>-------------------------------------</td>
<td>----------------</td>
<td>------------</td>
<td>--------</td>
<td>-----------</td>
<td>--------</td>
</tr>
<tr>
<td>Non-smoker</td>
<td>54 (71.1)</td>
<td>51 (68.0)</td>
<td>0.684</td>
<td>37 (62.7)</td>
<td>0.305</td>
</tr>
<tr>
<td>History of coronary heart disease</td>
<td>15 (19.7)</td>
<td>19 (25.3)</td>
<td>0.410</td>
<td>16 (27.1)</td>
<td>0.312</td>
</tr>
<tr>
<td>No prior medical history</td>
<td>9 (11.8)</td>
<td>10 (13.3)</td>
<td>0.782</td>
<td>8 (13.6)</td>
<td>0.765</td>
</tr>
<tr>
<td>CCSUA</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>(0-2)</td>
<td>54 (71.1)</td>
<td>44 (58.7)</td>
<td>0.111</td>
<td>37 (62.7)</td>
<td>0.305</td>
</tr>
<tr>
<td>(3+)</td>
<td>22 (28.9)</td>
<td>31 (41.3)</td>
<td></td>
<td>22 (37.3)</td>
<td></td>
</tr>
<tr>
<td>Location (South)</td>
<td>49 (64.5)</td>
<td>51 (68.0)</td>
<td>0.647</td>
<td>42 (71.2)</td>
<td>0.409</td>
</tr>
<tr>
<td>Discharge Diagnosis</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>STEMI</td>
<td>34 (44.7)</td>
<td>35 (46.7)</td>
<td></td>
<td>27 (45.8)</td>
<td></td>
</tr>
<tr>
<td>NSTEMI</td>
<td>16 (21.1)</td>
<td>26 (34.7)</td>
<td></td>
<td>21 (35.6)</td>
<td></td>
</tr>
<tr>
<td>Unstable angina</td>
<td>15 (19.7)</td>
<td>6 (8.0)</td>
<td>0.081</td>
<td>6 (10.2)</td>
<td>0.137</td>
</tr>
<tr>
<td>Unspec ACS</td>
<td>11 (14.5)</td>
<td>8 (10.7)</td>
<td></td>
<td>5 (8.5)</td>
<td></td>
</tr>
<tr>
<td>Coronary artery stenting</td>
<td>60 (78.9)</td>
<td>55 (73.3)</td>
<td>0.418</td>
<td>42 (71.2)</td>
<td>0.298</td>
</tr>
<tr>
<td>Drug-eluting stent*</td>
<td>38 (63.3)</td>
<td>35 (63.6)</td>
<td>0.973</td>
<td>28 (66.7)</td>
<td>0.729</td>
</tr>
</tbody>
</table>

Discharge prescribing of guideline-recommended medications is outlined in Table 4.2. There were more patients discharged on beta-blockers in the intervention group (p=0.046). There were no significant differences in the rate of prescribing for the
combination of all four guideline-recommended medications (guideline-concordance) at discharge. Guideline-concordant prescribing at discharge occurred in 59.6% of the total cohort.

Table 4.2: Guideline-recommend prescribing at hospital discharge

<table>
<thead>
<tr>
<th>Discharge medications</th>
<th>Control N/76 (%)</th>
<th>ITT N/75 (%)</th>
<th>P</th>
<th>OT N/59 (%)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>P2Y$_{12}$ antagonist</td>
<td>69 (90.8)</td>
<td>70 (93.3)</td>
<td>0.563</td>
<td>55 (93.2)</td>
<td>0.755</td>
</tr>
<tr>
<td>Statin</td>
<td>75 (98.7)</td>
<td>73 (97.3)</td>
<td>0.620</td>
<td>57 (96.6)</td>
<td>0.581</td>
</tr>
<tr>
<td>Beta-blocker</td>
<td>56 (73.7)</td>
<td>65 (86.7)</td>
<td>0.046</td>
<td>52 (88.1)</td>
<td>0.037</td>
</tr>
<tr>
<td>ACEI/ARB</td>
<td>60 (78.9)</td>
<td>59 (78.7)</td>
<td>0.966</td>
<td>45 (76.3)</td>
<td>0.711</td>
</tr>
<tr>
<td>≤2</td>
<td>10 (13.2)</td>
<td>4 (5.3)</td>
<td>3 (5.1)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>3</td>
<td>22 (28.9)</td>
<td>25 (33.3)</td>
<td>21 (35.6)</td>
<td>0.257</td>
<td></td>
</tr>
<tr>
<td>4</td>
<td>44 (57.9)</td>
<td>46 (61.3)</td>
<td>35 (59.3)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>GC at D/C &lt;4 meds</td>
<td>32 (42.1)</td>
<td>29 (38.7)</td>
<td>24 (40.7)</td>
<td>0.667</td>
<td>0.867</td>
</tr>
<tr>
<td>4 meds</td>
<td>44 (57.9)</td>
<td>46 (61.3)</td>
<td>35 (59.3)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
4.2 Primary outcomes

4.2.1 Adherence and persistence by modified medication possession ratio

The primary outcome was a composite of adherence and persistence to a guideline-concordant regimen at six months post-discharge. Using the number of patients who were discharged as guideline-concordant as shown in Table 4.2, there were no significant differences between the control and intervention groups with 26 (59.1%) control patients and 22 (47.8%) intervention patients (p=0.284) maintaining persistence and adherence at six months. On-treatment sensitivity analysis and reassessment of the MMPR as a continuous variable did not reveal any further significant findings. To ensure non-persistence was not mislabelled as non-adherence, an MMPR was only generated for patients who were persistent with their discharge medications as outlined in section 3.2.1.1. Therefore, further exploration of non-persistence as an individual component of the primary outcome was conducted.

4.2.2 Early and anytime non-persistence to six months

Among those who were discharged on a guideline-concordant regimen, non-persistence was reported as ‘early non-persistence’ alone (same as ‘persistence to two months’) and in combination with ‘anytime non-persistence’ (same as ‘persistence to six months’). Further assessment of ‘anytime non-persistence’ as an individual variable (same as ‘persistence from two to six months’) is also presented in the subsequent section. Figure 4.2 shows no significant difference in the proportion of patients with early non-persistence, but there was a trend toward a higher proportion of patients with the combination of early and anytime non-persistence (represented by ‘total non-persistence’) in the intervention group at six months (p=0.065) suggesting that the dHMR may have had a negative impact on persistence. As a trend was identified, the result was re-examined through binary LR, to control for potential confounding from baseline variables; this is presented in section 4.2.6.
Based on the results as presented in Figure 4.2, the dHMR did not affect early non-persistence, but there was a trend toward a difference in the combined non-persistence measure at six months. Combining ‘early non-persistence’ and ‘anytime non-persistence’ reflected ‘total non-persistence’ at 6 months. However, this approach may have diluted the assessment of the anytime non-persistence component of this outcome. To better understand the type of prescription collection patterns affected by the intervention, Figure 4.3 shows anytime non-persistence among those not detected by the early non-persistence algorithm, that is, those who were persistent to two months but not six months. The proportion of persistent patients was significantly higher in the control group at 86.8%, versus 66.7% in the intervention group (p=0.036), again suggesting there may have been a negative effect on persistence as a result of the intervention.
The effect of medication discontinuation was further explored by analysing persistence, regardless of the number of guideline-recommended medications prescribed at discharge. In this analysis, all patients who were prescribed a guideline-recommended medication were included as persistent if they continued with the same combination of guideline-recommended medications at two and six months post-discharge. The purpose of this analysis was to further identify if the intervention had a negative impact on persistence to guideline-recommended medications overall, or if this was generally limited to those discharged as guideline-concordant, as shown in Figure 4.2. Table 4.3 shows a trend toward a lower proportion of persistent patients at six months in the intervention group (p=0.060 for the on-treatment analysis).
Table 4.3: Proportion of patients persistent to guideline-recommended medications, regardless of the combination of medications prescribed on discharge

Results presented are for those who were persistent. ITT – intention-to-treat; OT – on-treatment

<table>
<thead>
<tr>
<th>Time</th>
<th>Control N/76 (%)</th>
<th>ITT N/75 (%)</th>
<th>P</th>
<th>OT N/59 (%)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>2 months</td>
<td>64 (84.2)</td>
<td>62 (82.7)</td>
<td>0.799</td>
<td>49 (83.1)</td>
<td>0.856</td>
</tr>
<tr>
<td>6 months</td>
<td>52 (68.4)</td>
<td>42 (56.0)</td>
<td>0.115</td>
<td>31 (52.5)</td>
<td>0.060</td>
</tr>
</tbody>
</table>

In Table 4.4, patients with early non-persistence were excluded, as with Figure 4.3, to allow for investigation of the specific effect of the intervention on anytime non-persistence. The proportion of anytime non-persistence was again higher in the intervention group for the on-treatment analysis (p=0.032). This suggests that non-persistence was higher in the intervention group, regardless of the number of guideline-recommended medications prescribed at the point of hospital discharge.

Table 4.4: Proportion of patients persistent to guideline-recommended medications, regardless of the combination prescribed on discharge, excluding early non-persistence

Results presented are for those who were persistent. ITT – intention-to-treat; OT – on-treatment

<table>
<thead>
<tr>
<th>Time</th>
<th>Control N/64 (%)</th>
<th>ITT N/62 (%)</th>
<th>P</th>
<th>OT N/49 (%)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>2 - 6 months</td>
<td>52 (81.3)</td>
<td>42 (67.7)</td>
<td>0.082</td>
<td>31 (63.3)</td>
<td>0.032</td>
</tr>
</tbody>
</table>

Non-persistence to each class of guideline-recommended medication was analysed to determine if there was a particular class leading to a lower rate of persistence in the intervention group, as presented in Figure 4.4. The number of patients in each analysis reflects the number of patients discharged with a prescription for the
particular medication class. There were no significant differences between the
groups for beta-blockers and ACEI/ARBs; however, there were more control patients
persistent to P2Y12 antagonists beyond two months, 98.6% versus 89.1% in the on-
treatment analysis (p=0.044). As with Figure 4.3, anytime non-persistence was
separated to include only those who were persistent beyond two months and the
proportion of patients persistent to statins was higher in the control group, 92.6%
versus 79.6% in the on-treatment analysis (p=0.034).
Figure 4.4: Proportion of patients persistent to individual guideline-recommended medications.

“2 months” refers to early non-persistence, “6 months” includes early and anytime non-persistence, and “2 to 6 months” reflects only those with anytime non-persistence. ITT – intention-to-treat; OT – on-treatment; ACEI/ARB – angiotensin converting enzyme inhibitors/angiotensin II receptor blockers. *Fisher’s exact test
Proportion of patients persistent to individual guideline-recommended medications (continued).

“2 months” refers to early non-persistence, “6 months” includes early and anytime non-persistence, and “2 to 6 months” reflects only those with anytime non-persistence. ITT – intention-to-treat; OT – on-treatment; ACEI/ARB – angiotensin converting enzyme inhibitors/angiotensin II receptor blockers.
4.2.3 Mean modified medication possession ratio

As discussed in section 3.2.1 of the methods, no MMPR value was generated for medications to which patients were non-persistent, to avoid medication discontinuation skewing the mean MMPR results. Therefore, each patient who continued at least one guideline-recommended medication, without a two-month supply-gap, had an MMPR calculated and averaged across all persistent medications. This reflected their level of adherence to medication with which they were persistent. As with persistence, MMPR was assessed as part of the primary outcome, but also as a discrete variable, presented in Table 4.5. The number in each group was slightly lower than the overall cohort, reflecting that some patients had discontinued all medications and these were not included in this analysis. There were no significant differences in the MMPR across all groups whether assessed as a continuous variable or by the convention of MMPR≥0.8 to define adherence.

Table 4.5: MMPR at six months post-discharge among those who were persistent with at least one guideline-recommended medication

MMPR – modified medication possession ratio; ITT – intention-to-treat; OT – on-treatment; IQR – interquartile range

<table>
<thead>
<tr>
<th>MMPR</th>
<th>Control N/73 (%)</th>
<th>ITT N/72 (%)</th>
<th>P</th>
<th>OT N/56 (%)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>≥0.8</td>
<td>65 (89.0)</td>
<td>61 (84.7)</td>
<td>0.441</td>
<td>46 (82.1)</td>
<td>0.262</td>
</tr>
<tr>
<td>Median (IQR)</td>
<td>0.95 (0.86-0.98)</td>
<td>0.96 (0.86-0.98)</td>
<td>0.618</td>
<td>0.95 (0.84-0.98)</td>
<td>0.932</td>
</tr>
</tbody>
</table>

4.2.4 Adherence and persistence by self-report

Patients’ self-reported adherence was assessed using the Morisky Adherence Questionnaire (MAQ). Self-reported persistence was assessed via a patient or pharmacy-generated record of their current medication list. This served two purposes; firstly, as a back-up in case of a high number of incomplete medication
histories, and secondly for triangulation of adherence and persistence with the MMPR. The combined response rate for the four-item MAQ at both six-week and six-month time points was 66.7%. Despite the relatively simple format of the MAQ and placement as the first questionnaire directly following the medication list, eleven patients answered only some of the questions from the MAQ and these results were not counted. MAQ scores of 0 denoted adherence and any score greater than 0 reflected sub-optimal adherence. Six-week and six-month scores are presented in Table 4.6 showing no significant differences in the proportion of patients self-reporting as adherent between the groups, pre or post intervention. Further exploration of individual items of the MAQ did not reveal any significant differences between the groups at either time point (data not shown).

Table 4.6: Number of patients self-reporting as adherent by Morisky adherence questionnaire

<table>
<thead>
<tr>
<th>Time</th>
<th>Control N/49 (%)</th>
<th>ITT N/51 (%)</th>
<th>P</th>
<th>OT N/38 (%)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>6 weeks</td>
<td>34 (69.4)</td>
<td>33 (64.7)</td>
<td>0.619</td>
<td>25 (65.8)</td>
<td>0.722</td>
</tr>
<tr>
<td>6 months</td>
<td>34 (69.4)</td>
<td>33 (64.7)</td>
<td>0.619</td>
<td>26 (68.4)</td>
<td>0.923</td>
</tr>
</tbody>
</table>

As with the MMPR, self-reported adherence and persistence were combined to consider the composite outcome of those discharged as guideline-concordant and reporting to be adherent and persistent with this regimen to six months. There was no significant difference in this finding with 13 (40.6%) control patients and 12 (34.3%) intervention patients self-reporting as adherent and persistent to six months (p=0.592).

Among those who were discharged as guideline concordant, there were no significant differences between the groups in the rates of self-reported persistence from six weeks to six months, as in Figure 4.5 (p=0.872).
Figure 4.5: Self-reported persistence with a guideline-concordant regimen over time


Table 4.7 outlines total self-reported persistence over time regardless of the number of guideline-recommended medications being taken at discharge. There were no significant differences in the proportion of patients self-reporting as persistent between the groups at each time point.

Table 4.7: Total self-reported persistence over time

<table>
<thead>
<tr>
<th>Time</th>
<th>Control N/57 (%)</th>
<th>ITT N/54 (%)</th>
<th>P</th>
<th>OT N/41 (%)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>6 weeks</td>
<td>44 (77.2)</td>
<td>43 (79.6)</td>
<td>0.755</td>
<td>31 (75.6)</td>
<td>0.855</td>
</tr>
<tr>
<td>6 months</td>
<td>34 (59.6)</td>
<td>27 (50.0)</td>
<td>0.307</td>
<td>20 (48.8)</td>
<td>0.110</td>
</tr>
</tbody>
</table>
4.2.5 Triangulation of adherence and persistence by MMPR and self-report

Among those discharged as guideline-concordant, there were no significant differences in the rates of persistence or the composite of adherence and persistence when both the MMPR algorithm and self-report measures were combined, as presented in Table 4.8. “Persistence alone” is a composite of those who were persistent to six months by both self-report and the MMPR algorithm. “Adherent and Persistent” includes a positive result for both persistent measures as well as having a consistent score of zero on the MAQ or an improvement on MAQ, and an MMPR greater than or equal to 0.8. When comparing the level of agreement between the two measures for each finding, the kappa statistic for persistence measures demonstrated moderate agreement at 47.4% (p<0.001, standard error 11.1%). For adherence and persistence by both measures the agreement was lower at 23.4% (p=0.05, standard error 11.6%).

Table 4.8: Cumulative adherence and persistence to a guideline-concordant regimen at six months by both medication possession ratio and self-report

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Control N/32 (%)</th>
<th>ITT N/35 (%)</th>
<th>P</th>
<th>OT N/26 (%)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Persistence alone</td>
<td>16 (50.0)</td>
<td>14 (40.0)</td>
<td>0.411</td>
<td>10 (38.5)</td>
<td>0.380</td>
</tr>
<tr>
<td>Adherent and Persistent</td>
<td>8 (25.0)</td>
<td>8 (22.9)</td>
<td>0.837</td>
<td>8 (26.9)</td>
<td>0.868</td>
</tr>
</tbody>
</table>

4.2.6 Multivariate model to predict persistence at six months

As shown in section 4.2.2, there was a statistical trend toward a higher proportion of patients who were persistent among those discharged as guideline-concordant in the control group (p=0.065). This warranted further investigation for potential confounding from baseline variables and an LR model was developed as discussed
in section 3.2.6. The final model is presented in Table 4.9 showing completion of CR, the angina frequency domain of the SAQ, and question three of the BMQ (doctors prescribe too many medications) as confounders for the relationship between study group allocation and persistence to a guideline-concordant regimen at six months. Specifically, these items support the univariate finding that allocation to the control group led to a higher rate of persistence (OR 3.7, CI 1.1-12.3, p=0.035) and suggest that the intervention may have had a negative effect on persistence. The Hosmer and Lemeshow Test for Goodness of Fit suggested a low risk of model overfit (p=0.712) and this was further evidenced by relatively narrow confidence intervals.

Table 4.9: Multivariate analysis of six-month persistence to a guideline-concordant regimen

CI – confidence interval.

<table>
<thead>
<tr>
<th>Variable</th>
<th>Odds ratio (95% CI)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Allocation to control group</td>
<td>3.7 (1.1-12.3)</td>
<td>0.035</td>
</tr>
<tr>
<td>Completed cardiac rehabilitation</td>
<td>2.2 (0.7-6.8)</td>
<td>0.193</td>
</tr>
<tr>
<td>Seattle Angina Questionnaire, angina frequency domain</td>
<td>1.0 (1.0-1.1)</td>
<td>0.047</td>
</tr>
<tr>
<td>&quot;Doctors prescribe too many medications&quot;</td>
<td>0.7 (0.4-1.3)</td>
<td>0.235</td>
</tr>
</tbody>
</table>

4.3 Secondary outcomes

4.3.1 Mortality rates, hospital readmission rates, and lengths of stay

Two intervention patients died in the period shortly following discharge, prior to the dHMR visit. One occurred at 6 weeks post-discharge, with the cause recorded as a major haemorrhagic stroke attributed to warfarin therapy. The other occurred two weeks post-discharge and was of an unknown cause in a private hospital. One control patient died three days post-discharge with an unconfirmed but suspected cardiac cause of death. Another control patient died from CHF during the follow-up
period, approximately 14 weeks post-discharge. There were no significant
differences in the mortality rate between the groups at six months (p=0.681).

There were no statistically significant differences in the proportion of patients with
hospital readmissions between the control and intervention groups (25.0% vs 33.3%,
p=0.260). One patient in the control group had 11 hospital readmissions during the
follow-up period but was noted to have frequent admissions prior to the study. As
such, this patient was considered an outlier and removed from further analysis of
readmission data. After adjustment, there were a total of 30 unplanned and seven
cardiovascular-related unplanned readmissions in the control group. There were 36
unplanned and eleven cardiovascular-related unplanned readmissions in the
intervention. Among those with an unplanned readmission, the median number of
readmissions was one in each group (interquartile range 1.0-2.3 for control and 1.0-
2.0 for the intervention patients). There were no significant differences (p=0.413 for
unplanned readmissions, p=0.706 for cardiovascular-related unplanned
readmissions).

One patient in the control group had a total of 35 days in hospital during follow-up.
This patient was considered an outlier and excluded from the length of stay analysis.
Following adjustment, 17 control patients with unplanned readmissions spent a total
of 70 days in hospital with the median length of stay equal to 1.0 days (interquartile
range 1.0-7.5). Twenty-five intervention patients with unplanned readmissions spent
a total of 85 days in hospital with a median length of stay of 2.0 days (interquartile
range 1.0-5.5). These differences were not significant (p=0.826). Of those with
unplanned readmissions, there were no significant differences between the groups in
the rates of admissions that lasted longer than a day (47.1% control and 52.0%
intervention patients, p=0.753).
4.3.2 Cardiac rehabilitation attendance and completion rates

Nineteen patients (10 control patients, 9 intervention patients) who were geographically isolated from standard CR services and known to have not completed CR at either of the recruiting hospitals were included in the non-attendance group. The remaining patients had clear records to indicate that they either did not attend any CR sessions, they attended some sessions but did not complete CR, or that they attended a full CR program (typically six sessions). These results are presented in Figure 4.6; there were no significant differences in rates of attendance or completion across the study groups (p=0.509).

*Figure 4.6: Degree of engagement with cardiac rehabilitation services*

ITT – intention-to-treat; OT – on-treatment

4.3.3 Smoking cessation rates and nicotine dependence

As seen in Table 4.1, 30.5% patients reported to be cigarette smokers during their index admission. Among the 122 (80.7%) who responded to the smoking and
nicotine dependence section of the six-week questionnaire, the smoking rate was 27.0% and this had fallen to 13.9% by six weeks post-discharge, reflecting a self-reported smoking cessation rate of approximately 50% following ACS. Among the quitters, 1 control patient self-reported that they had restarted smoking by six months and 2 control patients and 1 intervention patient did not respond to the smoking section of the six-month questionnaire, reducing the proportion of self-reported persistent quitters to 36.4%. There were no significant differences between the control and intervention (p=0.170). One further intervention patient who was still smoking at six weeks self-reported to have quit by six months and another who did not respond to the six-week questionnaire reported to have quit by six months.

The FTND was used to classify nicotine-dependence among the cigarette smokers within the trial. The test utilises six questions to give a dependency score ranging from very low to very high. Only twelve patients (eight control patients, four intervention patients) completed this test at both six weeks and six months. All four intervention patients scored very low or low at both time points. Among the control patients at six weeks, one scored each of very low, moderate, and high dependency, with the remaining five scoring low dependency. This increased at six months with four scoring low dependency and two for each of moderate and high dependency. There were no significant differences between the control and intervention group (p=0.105) comparing low versus moderate/high dependency. The small sample size of smokers significantly limited the likelihood of showing any statistical difference.

4.3.4 Quality of life

Patients were surveyed on their QoL at six weeks post-discharge as a pre-intervention measure and again at six months post-discharge to assess the impact of the intervention. The first instrument used to assess QoL was the EuroQol’s Eq-5D-3L. The proportion of patients reporting severe/extreme problems to any of the five domains was low and, as such, the Likert scale was dichotomised to those with no
problems versus those reporting problems. The proportion of patients with problems versus without problems for each domain is presented in Figure 4.7. There were no significant differences between the control and intervention for any of the domains at either time point.
Figure 4.7: Eq-5D responses by domain at six weeks and six months. See overleaf: anxiety and depression.

ITT – intention-to-treat; OT – on-treatment
Eq-5D responses by domain at six weeks and six months: anxiety and depression (continued).

ITT – intention-to-treat; OT – on-treatment

Utility scores were calculated based on a value set for the Eq-5D derived from a validation study of an Australian population. There were no significant differences between control and intervention at both time points as shown in Table 4.10. Similarly, there were no significant differences within each group over time (p=0.656 for the control group and p=0.934 for the intervention group).

Table 4.10: Median six-week and six-month utility scores for the Eq-5D

<table>
<thead>
<tr>
<th>Time</th>
<th>Control N/57 (IQR)</th>
<th>ITT N/54 (IQR)</th>
<th>P</th>
<th>OT N/41 (IQR)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Six weeks</td>
<td>0.774 (0.677-1.000)</td>
<td>0.786 (0.673-1.000)</td>
<td>0.711</td>
<td>0.745 (0.641-1.000)</td>
<td>0.477</td>
</tr>
<tr>
<td>Six months</td>
<td>0.798 (0.614-1.000)</td>
<td>0.798 (0.609-1.000)</td>
<td>0.672</td>
<td>0.798 (0.609-1.000)</td>
<td>0.562</td>
</tr>
</tbody>
</table>
Figure 4.8 represents the median, interquartile range, and minimum/maximum scores for the VAS of the Eq-5D. There were no significant differences between the groups at either time point (p=0.590 at six weeks and p=0.680 at six months). Within group changes over time were also not significant (p=0.583 for the control group and p=0.289 for the intervention group).

Figure 4.8: Box-plot of Eq-5D VAS. Minimum and maximum values represented by error bars, interquartile range is represented by the central box and the median is represented by the central intersect.

Individual responses to the five domains of the SAQ were processed according to the algorithm by Spertus et al and are reported by domain in Table 4.11. There were no significant differences at six weeks, however, there was a trend toward a higher reported angina stability score at six months in the intervention group (p=0.054). This score corresponded to a single question from the SAQ whereby patients were asked to reflect on their angina symptoms when undertaking their most strenuous activity at the time of the questionnaire compared with that from one month prior to the questionnaire. Comparison within the groups over time
using the Wilcoxon Signed Ranks Test showed that the differences in angina stability resulted from a decrease in score over time within the control group, $z = -2.102$ based on positive ranks with $p = 0.036$, whereas the intervention group remained steady, $z = -0.947$ based on positive ranks ($p = 0.344$). Both the control and intervention groups also reported increased cardiac-specific QoL at six months as in Table 4.11, however, the increase was slightly higher and with a greater level of significance in the control group, $z = -2.882$ based on negative ranks ($p = 0.004$) versus $z = -2.160$ based on negative ranks for the intervention group ($p = 0.031$).

Table 4.11: Calculated median scores for the five domains of the Seattle angina questionnaire

<table>
<thead>
<tr>
<th>Time</th>
<th>Domain</th>
<th>Control N/57 (IQR)</th>
<th>ITT N/54 (IQR)</th>
<th>P</th>
<th>OT N/41 (IQR)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>PLS</td>
<td>69.4 (50.0-88.9)</td>
<td>75.0 (50.7-94.4)</td>
<td>0.208</td>
<td>76.4 (52.8-91.7)</td>
<td>0.246</td>
</tr>
<tr>
<td></td>
<td>AS</td>
<td>50.0 (50.0-75.0)</td>
<td>50.0 (50.0-100.0)</td>
<td>0.181</td>
<td>50.0 (50.0-100.0)</td>
<td>0.130</td>
</tr>
<tr>
<td>Six</td>
<td>AF</td>
<td>100.0 (80.0-100.0)</td>
<td>100.0 (75.0-100.0)</td>
<td>0.807</td>
<td>95.0 (70.0-100.0)</td>
<td>0.552</td>
</tr>
<tr>
<td>weeks</td>
<td>TS</td>
<td>100.0 (87.5-100.0)</td>
<td>93.75 (81.3-100.0)</td>
<td>0.183</td>
<td>93.8 (81.3-100.0)</td>
<td>0.176</td>
</tr>
<tr>
<td></td>
<td>QoL</td>
<td>58.3 (41.7-83.3)</td>
<td>58.3 (41.7-83.3)</td>
<td>0.802</td>
<td>58.3 (41.7-83.3)</td>
<td>0.754</td>
</tr>
</tbody>
</table>

IQR – interquartile range; ITT – intention-to-treat; OT – on-treatment; PLS – physical limitation score; AS – angina stability; AF – angina frequency; TS – treatment satisfaction; QoL – quality of life.
### Six months

<table>
<thead>
<tr>
<th></th>
<th>PLS</th>
<th>AS</th>
<th>AF</th>
<th>TS</th>
<th>QoL</th>
</tr>
</thead>
<tbody>
<tr>
<td>PLS</td>
<td>72.2 (54.2-93.1)</td>
<td>77.8 (51.4-97.2)</td>
<td>50.0 (50.0-75.0)</td>
<td>100.0 (80.0-100.0)</td>
<td>75.0 (58.3-91.7)</td>
</tr>
<tr>
<td>AS</td>
<td>50.0 (50.0-50.0)</td>
<td>50.0 (50.0-62.5)</td>
<td>100.0 (50.0-75.0)</td>
<td>90.0 (70.0-100.0)</td>
<td>50.0 (50.0-75.0)</td>
</tr>
<tr>
<td>AF</td>
<td>100.0 (80.0-100.0)</td>
<td>100.0 (80.0-100.0)</td>
<td>93.8 (80.0-100.0)</td>
<td>93.8 (81.3-100.0)</td>
<td>66.7 (50.0-83.3)</td>
</tr>
<tr>
<td>TS</td>
<td>100.0 (81.3-100.0)</td>
<td>100.0 (80.0-100.0)</td>
<td>93.8 (80.0-100.0)</td>
<td>93.8 (81.3-100.0)</td>
<td>66.7 (50.0-83.3)</td>
</tr>
<tr>
<td>QoL</td>
<td>75.0 (58.3-91.7)</td>
<td>77.8 (50.0-93.8)</td>
<td>50.0 (50.0-62.5)</td>
<td>66.7 (50.0-83.3)</td>
<td>75.0 (58.3-91.7)</td>
</tr>
</tbody>
</table>

### 4.4 Process outcomes

#### 4.4.1 Intervention fidelity

From 76 scheduled dHMRs, 17 (22.4%) failed to occur according to protocol. Eight patients scheduled for dHMR did not ever receive one, five dHMRs were not completed until after four months post-discharge, three dHMRs were undertaken by APs who failed to complete the education package, and one dHMR was undertaken after four months post-discharge and by an AP who failed to complete the education package. These incidents were further classified into three categories: patient-related, GP-related, and AP-related, to identify the primary cause of the barrier to a per-protocol intervention. Three patients decided they did not want the service but were still willing to participate in trial follow-up, and in seven cases each, there were GP
and AP-related barriers. Such a high rate of AP-related barriers was particularly surprising, however, the true number of patient-related barriers is diluted in this assessment as there were initially 81 patients who did not consent to participation in the trial and 12 withdrew their consent shortly following hospital discharge. Although there are many reasons for declining consent, and this was often unspecified, not wishing to receive the intervention and/or not feeling they needed any help made up a large proportion of the concern voiced by non-consenters.

Among the 59 patients who received the intervention per-protocol, the “on-treatment” group, the median time from discharge to intervention was 65 days (interquartile range 61 to 75 days). The earliest visit was 37 days post-discharge and the latest visit still within the study protocol time limits was 114 days post-discharge. Therefore, even the on-treatment group had a large variation in timing of follow-up and any further tightening of on-treatment criteria would have made statistical analysis of this group invalid. Although GP follow-up is considered a component of the HMR cycle by the Pharmaceutical Society of Australia (PSA) just 26 (44.1%) of the APs in the on-treatment group submitted GP follow-up. All APs involved with the trial were prompted to submit their documentation showing that the GP had completed the dHMR follow-up by the project pharmacists, however, the response by many APs was that they never received GP follow-up. In contrast, those who attempted to enforce GP follow-up as a part of their routine dHMR process did so reasonably well, with all but one AP receiving GP follow-up in 50% or more of cases. Receipt of GP follow-up was not considered a requirement of the trial protocol as a result of this mixed interpretation of the HMR guidelines and the small sample size resulting from such restriction. Of those who did receive GP follow-up, seven (25%) were without comment and essentially ‘thank you’ notices for the service being completed. Twelve (42.9%) received 100% acceptance of recommendations, while in the remaining nine, between 20 and 80% of recommendations were accepted.
This summary of intervention fidelity highlights quite a significant degree of heterogeneity in the way the intervention was conducted, based on a relatively simple set of compliance measures.

### 4.4.2 Drug-related problem (DRP) analysis

AP recommendations were categorised by the DOCUMENT system, classifying DRPs into recognised categories of clinical importance, see Appendix C – DOCUMENT DRP classification system. Figure 4.9 shows the percentage that each category was raised out of all DRPs recorded. ‘Undertreated conditions’ was the most common DRP raised, accounting for nearly 30% of all DRPs. Drug selection, compliance, education, and toxicity/ADRs each accounted for 10-15% of DRPs. Over/under-dose, monitoring, and unclassifiable DRPs accounted for the remainder.
Figure 4.9: DRPs as classified by the DOCUMENT classification system. Columns correspond to the percentage each category appeared out of all DRPs raised.

DRPs – drug related problems; ADRs – adverse drug reactions
Figure 4.10 highlights how often each DRP category was recognised as a percentage of all DRPs among those who were persistent versus non-persistent according to the anytime non-persistence outcome, as in Figure 4.3. The aim of this analysis was to identify if there were any themes that may explain the lower rates of persistence found in these patients as a result of the intervention. Apparent differences include a higher proportion of compliance-focussed DRPs raised in the non-persistent population, which suggests APs were actually detecting and attempting to address problems with adherence in those who were later found to have such issues by a more objective measure (the MMPR). Persistent patients also appeared to receive more education-based DRPs, however, with such correlations, it remains unclear whether this approach was a driver of persistence or a result of fewer genuine problems identified among these patients; which may have in turn, allowed more time to deliver education.
Figure 4.10: DRPs according to the DOCUMENT classification system, as identified in patients who were either persistent or not during the two to six month follow-up. Columns correspond to the percentage each category appeared out of all DRPs raised.

DRPs – drug related problems; ADRs – adverse drug reactions
Recommendations for resolution of DRPs are presented categorically as a percentage of all recommendations made in Figure 4.11. Several categories were not raised at all and were omitted from the figure, including “prescription not dispensed”, “drug brand change”, “refer to hospital”, and “refer for medication review”. The provision of information category was presented as a cumulative of the sub-categories in this section, which mostly reflected education/counselling sessions and the provision of a written summary of medications. The high proportion of recommendations requiring referral to prescriber reflects the need for prescriber input into any recommendations that would require an adjustment to a prescription; as well as recommendations that suggested more than one option as a possible solution to the DRP raised, with the AP requesting the GP to choose the most appropriate option. The next most common recommendation was for DRPs whereby no recommendation was necessary, typically reflecting comments or observations made that did not require further action, but warranted classification as a DRP. This may have included monitoring or assessment undertaken at the dHMR, rather than a recommendation for ongoing monitoring. The relatively low percentage of education/written information recommendations, in spite of a reasonably high number of DRPs in the education category is most likely explained by most of these DRPs not resulting in further specific recommendations being made.
Figure 4.11: DRP recommendations as classified by the DOCUMENT classification system. Columns correspond to the percentage each category appeared out of all recommendations made.
Recommendations for resolution of DRPs as a percentage of all recommendations made was further divided into those who were persistent or not according to the anytime non-persistence outcome and this is presented in Figure 4.12. Non-persistent patients had a higher proportion of recommendations to increase the dose of a particular medication (p=0.006). This was investigated qualitatively to determine if recommendations to increase doses may have then led to these medications being stopped, potentially as a result of increased dose-related side effects, for example. However, in almost all of these cases, the drug with the recommendation to increase the dose was not one to which the patient was non-persistent. Persistent patients had a visually higher proportion of DRPs not requiring a recommendation and this may align with a greater amount of education being delivered at these dHMR interviews as shown in Figure 4.10. This would support the suggestion from Figure 4.11 that the “no recommendation necessary” category is partly made up by DRPs that are more so a formal documentation of the APs’ actions in delivering education and not requiring further recommendations to be made.
Figure 4.12: DRP recommendations according to the DOCUMENT classification system, as identified in patients who were either persistent or not during the two to six month follow-up. Columns correspond to the percentage each category appeared out of all recommendations made.
To more clearly assess whether or not the intervention was focussed toward the expected ACS-related or adherence-related problems, each DRP was further classified into these two categories or not at all. Table 4.12 shows that 79.9% of all DRPs were relevant to ACS and this was similar across persistent and non-persistent patients. Just 20.5% of DRPs were relevant to adherence and this was higher for those who were non-persistent to at least one guideline-recommended medication (p=0.056).

*Table 4.12: DRPs categorised by relevance to ACS or adherence*

ACS – acute coronary syndrome

<table>
<thead>
<tr>
<th></th>
<th>ACS-related n (%)</th>
<th>Adherence-related n (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Persistent (n/127)</strong></td>
<td>100 (78.7)</td>
<td>19 (15.0)</td>
</tr>
<tr>
<td><strong>Non-persistent (n/112)</strong></td>
<td>91 (81.3)</td>
<td>30 (26.8)</td>
</tr>
<tr>
<td><strong>Total (n/239)</strong></td>
<td>191 (79.9)</td>
<td>49 (20.5)</td>
</tr>
</tbody>
</table>

### 4.5 Patient-focussed process outcomes (survey results)

A written, mail-out survey/questionnaire battery was utilised to measure the impact of the intervention on the patient at both six weeks and six months post-discharge, see
Appendix B – Questionnaire battery. The results from each section of this survey were analysed to explore if any changes in the primary outcome could be further explained by changes in associated adherence behaviours as identified through the conceptual framework. The combined response rate for both six-week and six-month questionnaires was 66.7%.
4.5.1 Tool for Adherence Behaviour Screening (TABS)

At the time of trial design, the TABS had not been extensively studied as a unique surrogate outcome measure for defining whether or not patients were adherent. Instead, the TABS was used separately to further define adherence behaviours within the cohort. For this reason, the results from this questionnaire are presented in this section as opposed to the primary results. The TABS comprises eight, five-point Likert scale questions and is split into an adherence and non-adherence subscale with four questions in each section. Each section is summed to give a total adherence and non-adherence score as well as a differential total score, whereby the non-adherence total is subtracted from the adherence total. Median scores are presented in Table 4.13 showing a wider IQR for the adherence subscale in the intervention group at six months with a trend suggestive of lower adherence (p=0.072). There were no other significant differences at either time point. Similarly, there were no significant differences within the groups over time.

The individual items of each subscale at six months post-discharge were explored to determine if there was one particular item that was different between the groups which may suggest a particular behaviour that was affected by the intervention. There were no significant differences detected in any items from the adherence subscale. However, the results were skewed toward the end of the Likert scale for each question, therefore the TABS was further explored by arbitrarily dichotomising the results around the point of difference on individual questions. Among the non-adherence subscale, the only question with a significant difference was “I put up with my medical problems before taking any actions” with 71.2% of intervention patients recording an answer of “never” compared with just 52.6% of controls (p=0.047). This suggests that the intervention patients may have been more likely to take action when noticing a change in their medical status and again this may have affected their medication collection patterns. This finding remained significant for the on-treatment sub-analysis (p=0.048) which may suggest that there was a genuine
effect of the intervention on encouraging patients to take action when noticing medical problems. The questions remaining unanswered are whether or not these actions involved a consultation with the patient’s GP, and if this did occur, how the patients felt about their medication management after seeking further advice.

Table 4.13: TABS subscales at six weeks and six months post-discharge


<table>
<thead>
<tr>
<th>Time</th>
<th>TABS subscales</th>
<th>Control N/57 (IQR)</th>
<th>ITT N/54 (IQR)</th>
<th>P</th>
<th>OT N/41 (IQR)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>6 weeks</td>
<td>Adherence</td>
<td>20 (19.0-20.0)</td>
<td>20 (18.0-20.0)</td>
<td>0.278</td>
<td>20 (18.0-20.0)</td>
<td>0.417</td>
</tr>
<tr>
<td></td>
<td>Non-adherence</td>
<td>7 (5.0-10.0)</td>
<td>7 (5.0-10.3)</td>
<td>0.665</td>
<td>7 (5.0-9.0)</td>
<td>0.782</td>
</tr>
<tr>
<td></td>
<td>Differential</td>
<td>12 (8.0-15.0)</td>
<td>11 (7.8-14.0)</td>
<td>0.178</td>
<td>11 (8.5-14.0)</td>
<td>0.576</td>
</tr>
<tr>
<td>6 months</td>
<td>Adherence</td>
<td>20 (19.0-20.0)</td>
<td>20 (18.0-20.0)</td>
<td>0.072</td>
<td>20 (18.0-20.0)</td>
<td>0.149</td>
</tr>
<tr>
<td></td>
<td>Non-adherence</td>
<td>7 (4.0-9.0)</td>
<td>7 (5.0-8.0)</td>
<td>0.810</td>
<td>6 (5.0-8.0)</td>
<td>0.964</td>
</tr>
<tr>
<td></td>
<td>Differential</td>
<td>12 (9.0-16.0)</td>
<td>12 (8.0-14.0)</td>
<td>0.488</td>
<td>12 (8.3-14.0)</td>
<td>0.560</td>
</tr>
</tbody>
</table>
4.5.2 Medication knowledge

Knowledge about medications for CHD was assessed by patients correctly reporting the indication for their medications. The indication was requested alongside the self-report of medications, therefore the answers could be classified into a percentage of correct answers. Patients who submitted a survey but did not complete the self-report of medication lists were scored as zero for knowledge. The proportion of patients scoring less than 100% at both time points was low, therefore the outcome was analysed as a dichotomous variable as shown in Table 4.14. There were no significant changes in scores from six weeks to six months, and no significant differences in scores between the groups at either time point.

Table 4.14: Proportion of patients with 100% knowledge scores based on recall of medication indication

<table>
<thead>
<tr>
<th>Time</th>
<th>Control ITT</th>
<th>ITT</th>
<th>P</th>
<th>OT</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>N/57 (%)</td>
<td>N/54 (%)</td>
<td></td>
<td>N/41 (%)</td>
<td></td>
</tr>
<tr>
<td>Six weeks</td>
<td>41 (79.9)</td>
<td>38 (70.4)</td>
<td>0.856</td>
<td>29 (70.7)</td>
<td>0.897</td>
</tr>
<tr>
<td>Six months</td>
<td>37 (64.9)</td>
<td>41 (75.9)</td>
<td>0.204</td>
<td>32 (78.0)</td>
<td>0.160</td>
</tr>
</tbody>
</table>

4.5.3 Self-efficacy

The cardiac self-efficacy questionnaire developed by Sullivan et al is a 13-item, five-point Likert scale questionnaire. The questionnaire is split into two domains with eight questions relating to the patient’s self-efficacy in controlling symptoms and five questions relating to maintaining function. Each question is coded as 1-5 and an average for each domain is generated. For the purpose of this study, an abbreviated set of questions was used, removing a degree of duplication and outdated questions. Four questions relating to controlling symptoms and three to maintaining function
remained. Self-efficacy scores were moderate to high across the cohort and there were no significant differences in the median results for each domain at both time points between the groups, as in Table 4.15. Within group comparisons using the Wilcoxon Signed Rank Test showed no significant differences over time. Similarly, there were no significant differences when individual questionnaire items were analysed (data not shown).

Table 4.15: Self-efficacy subscales of controlling symptoms and maintaining function
IQR – interquartile range; ITT – intention-to-treat; OT – on-treatment; CS – controlling symptoms; MF – maintaining function.

<table>
<thead>
<tr>
<th>Time</th>
<th>Self-efficacy domain</th>
<th>Control N/57 (IQR)</th>
<th>ITT N/54 (IQR)</th>
<th>P</th>
<th>OT N/41 (IQR)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>6 weeks</td>
<td>CS</td>
<td>4.0 (3.4-4.5)</td>
<td>3.8 (3.3-4.3)</td>
<td>0.327</td>
<td>3.5 (3.3-4.3)</td>
<td>0.159</td>
</tr>
<tr>
<td></td>
<td>MF</td>
<td>3.3 (2.3-4.0)</td>
<td>3.0 (2.3-4.0)</td>
<td>0.998</td>
<td>3.0 (2.2-4.0)</td>
<td>0.734</td>
</tr>
<tr>
<td>6 months</td>
<td>CS</td>
<td>4.0 (3.3-4.3)</td>
<td>3.9 (3.3-4.5)</td>
<td>0.903</td>
<td>4.0 (3.3-4.5)</td>
<td>0.620</td>
</tr>
<tr>
<td></td>
<td>MF</td>
<td>3.7 (2.3-4.3)</td>
<td>3.4 (2.3-4.3)</td>
<td>0.819</td>
<td>3.3 (2.3-4.2)</td>
<td>0.698</td>
</tr>
</tbody>
</table>

4.5.4 Beliefs about Medicines

The Beliefs about Medicines Questionnaire (BMQ) is an 18-item questionnaire with five questions relating to each of the patient-specific domains of ‘medication necessity’ and ‘medication concern’, and four questions relating to the non-specific domains of ‘medication overuse’ and ‘medication harm’. Two questions from each domain were selected for this study based on their expected relevance to CHD as
well as two items developed to assess the perceived value of medication following ACS. For the ‘specific necessity’ scale, a higher score represents a higher perception of need for medication, whereas with the remaining scales a higher score represents a more sceptical view toward medication. The individual questions of each domain were summed and median scores are presented in Table 4.16. Patients’ beliefs about medicines were largely unaffected by a dHMR according to this questionnaire, with the exception of the ‘specific concerns’ domain which remained steady among control patients, \( z = -0.242 \) based on negative ranks (\( p=0.809 \)), but decreased over time for intervention patients, \( z = -2.124 \) based on positive ranks (\( p=0.034 \)) (assessed by Wilcoxin Signed Ranks Test, not shown in the table).
Table 4.16: Beliefs about medicines subscales and perceived medicine value

<table>
<thead>
<tr>
<th>Time</th>
<th>Subscale</th>
<th>Control N/57 (IQR)</th>
<th>ITT N/54 (IQR)</th>
<th>P</th>
<th>OT N/41 (IQR)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Six weeks</strong></td>
<td><strong>Necessity</strong></td>
<td>8 (7.0-9.0)</td>
<td>8 (8.0-9.0)</td>
<td>0.458</td>
<td>8 (8.0-9.0)</td>
<td>0.468</td>
</tr>
<tr>
<td></td>
<td><strong>Concern</strong></td>
<td>6 (4.0-7.8)</td>
<td>6 (4.0-6.5)</td>
<td>0.764</td>
<td>6 (4.0-7.0)</td>
<td>0.755</td>
</tr>
<tr>
<td></td>
<td><strong>Overuse</strong></td>
<td>5 (4.0-6.0)</td>
<td>5 (4.0-6.0)</td>
<td>0.312</td>
<td>5 (4.0-6.0)</td>
<td>0.583</td>
</tr>
<tr>
<td></td>
<td><strong>Harm</strong></td>
<td>4 (3.0-6.0)</td>
<td>4 (3.0-5.0)</td>
<td>0.369</td>
<td>4 (3.0-5.0)</td>
<td>0.562</td>
</tr>
<tr>
<td></td>
<td><strong>Value</strong></td>
<td>4 (4.0-6.0)</td>
<td>4 (4.0-6.0)</td>
<td>0.873</td>
<td>4 (4.0-6.0)</td>
<td>0.836</td>
</tr>
<tr>
<td><strong>Six months</strong></td>
<td><strong>Necessity</strong></td>
<td>8 (7.0-9.0)</td>
<td>8 (8.0-9.0)</td>
<td>0.484</td>
<td>8 (8.0-9.0)</td>
<td>0.152</td>
</tr>
<tr>
<td></td>
<td><strong>Concern</strong></td>
<td>6 (4.0-7.0)</td>
<td>5 (4.0-6.0)</td>
<td>0.071</td>
<td>5 (4.0-6.0)</td>
<td>0.170</td>
</tr>
<tr>
<td></td>
<td><strong>Overuse</strong></td>
<td>5 (4.0-6.0)</td>
<td>5 (4.0-6.0)</td>
<td>0.896</td>
<td>5 (4.0-6.0)</td>
<td>0.474</td>
</tr>
<tr>
<td></td>
<td><strong>Harm</strong></td>
<td>4 (3.0-6.0)</td>
<td>4 (3.0-5.0)</td>
<td>0.406</td>
<td>4 (3.0-5.0)</td>
<td>0.420</td>
</tr>
<tr>
<td></td>
<td><strong>Value</strong></td>
<td>4 (3.0-6.0)</td>
<td>4 (4.0-6.0)</td>
<td>0.266</td>
<td>4 (4.0-6.0)</td>
<td>0.261</td>
</tr>
</tbody>
</table>

4.5.5 Brief Illness Perception Questionnaire (Brief IPQ)

The Brief IPQ contains eight questions that require patients to rate the perceived impact of their condition on various aspects of their life using a zero to ten scale, with ten being attributed to the most significant impact. The original questionnaire
also included a ninth question which is open-ended, but this was omitted for the purpose of assessing the impact of an intervention. Figure 4.13 shows the proportion of responses to each rating for each question at six weeks post-discharge. Questions are reported in the order they were asked, as in
Appendix B – Questionnaire battery. The six-month follow-up responses are presented in Figure 4.14. Responses to questions two “How long do you think your heart condition will continue?” and four “How much do you think your treatment can help your heart condition?” were consistently high at both time points. There were no significant differences between the groups at either time point.

Using the Wilcoxon Signed Ranks Test to explore within group differences over time, there was a significant increase found among intervention patients for the median rating of question three “How much control do you feel you have over your heart condition?”, $z=-2.521$ based on negative ranks ($p=0.012$), but the control group remained steady, $z=-0.592$ based on positive ranks ($p=0.554$). This could be expected as a result of the intervention with disease self-management discussions occurring during the dHMR home-visits. This finding remained true for the on-treatment sensitivity analysis, $z=-2.323$ based on negative ranks ($p=0.020$). The on-treatment analysis also revealed a higher level of concern (question six) over time among intervention patients, $z=-2.087$ based on negative ranks ($p=0.037$).
Figure 4.13: Proportion of ratings to each question of the Brief Illness Perception Questionnaire at six weeks post-discharge

ITT – intention-to-treat

How much does your heart condition affect your life?

- **Control**
- **ITT**

How long do you think your heart condition will continue?

- **p=0.714**

How much control do you feel you have over your heart condition?

- **p=0.216**

How much do you think your treatment can help your heart condition?

- **p=0.448**
Proportion of ratings to each question of the Brief Illness Perception Questionnaire at six weeks post-discharge (continued)

ITT – intention-to-treat.

How much do you experience symptoms from your heart condition?

How concerned are you about your heart condition?

How well do you feel you understand your heart condition?

How much does your heart condition affect you emotionally?

![Graphs showing responses to questions on the Brief Illness Perception Questionnaire at six weeks post-discharge.](image-url)
Figure 4.14: Proportion of ratings to each question of the Brief Illness Perception Questionnaire at six months post-discharge

ITT – intention-to-treat.
Proportion of ratings to each question of the Brief Illness Perception Questionnaire at six months post-discharge (continued)

ITT – intention-to-treat.

How much do you experience symptoms from your heart condition?

\[ p = 0.725 \]

How concerned are you about your heart condition?

\[ p = 0.221 \]

How well do you feel you understand your heart condition?

\[ p = 0.876 \]

How much does your heart condition affect you emotionally?

\[ p = 0.372 \]
4.5.6 Perceived Heart Risk Questionnaire (PHRQ)

The PHRQ was designed to assess patients' perceptions of their risk for having a heart event of similar or worse nature in future. The questionnaire follows a similar zero to ten rating scale as with the Brief IPQ. The proportion of responses to each rating for each question at six weeks is shown in Figure 4.15 and the six-month follow-up results are shown in Figure 4.16. For questions one to three, the majority of responses were five or higher at both time points, suggesting a relatively high perceived risk of future heart events. For question four “How bad would it be for you if you were to have the same heart problem again?” the responses were more consistently toward the upper end of the scale at both time points, suggesting that most patients recognised the potentially fatal outcome of a future event. There were no significant differences between the groups at each time point, nor within the groups over time.
Figure 4.15: Proportion of ratings to each question of the Perceived Heart Risk Questionnaire at six weeks post-discharge

ITT – intention-to-treat

1. How serious do you think your heart condition is?

2. How do you rate your chance of having the same heart problem again in your lifetime?

3. Compared to other people of your age and gender, how would you rate your chance of having the same condition again?

4. How bad would it be for you if you were to have the same heart problem again?

Respondents were randomized to a Control group and an ITT group. The p-values for each question are as follows:

- How serious do you think your heart condition is? p=0.701
- How do you rate your chance of having the same heart problem again in your lifetime? p=0.944
- Compared to other people of your age and gender, how would you rate your chance of having the same condition again? p=0.742
- How bad would it be for you if you were to have the same heart problem again? p=0.352
Figure 4.16: Proportion of ratings to each question of the Perceived Heart Risk Questionnaire at six months post-discharge

ITT – intention-to-treat

How serious do you think your heart condition is?

How do you rate your chance of having the same heart problem again in your lifetime?

Compared to other people of your age and gender, how would you rate your chance of having the same condition again?

How bad would it be for you if you were to have the same heart problem again?

Responses (%)

Rating scale

p = 0.730

p = 0.337

p = 0.547

p = 0.681
Chapter Five: Discussion

5.1 Primary outcomes

In this randomised controlled trial of a dHMR at two months post-discharge versus usual care following ACS, there was no significant difference in the primary outcome of adherence and persistence to a guideline-concordant regimen at six-months (p=0.284). This composite outcome encompassed two behavioural processes; medication adherence, and persistence, and further examination of the persistence component of this outcome showed a trend toward a lower proportion of persistent patients in the intervention group at six months (p=0.065). This trend was supported through multivariate analysis, which showed the control group were more likely to be persistent after controlling for confounding (OR 3.7, CI 1.1-12.3, p=0.035). There was some variance in execution of the trial protocol and an on-treatment analysis was conducted, which primarily excluded patients who received dHMRS close to the six-month follow-up. This showed lower rates of persistence to P2Y$_{12}$ antagonists at two months, and statins between two and six months. Similarly, for all patients who were discharged on at least one guideline-recommended medication, persistence between two and six months was significantly lower in the on-treatment group. Possible reasons for these somewhat unexpected outcomes were explored utilising the process outcomes and survey data collected, as well as through comparison to similar previous studies. However, the findings must also be considered in light of several study limitations, such as the small sample size and variable intervention fidelity.

This study utilised a conceptual framework for the evaluation of chronic disease interventions to guide the development and evaluation of the intervention. A benefit of this approach was that changes occurring in the primary outcome could be further explored through assessment of interrelated variables. For example, the primary outcome was assessed objectively through pharmacy refill records, but also subjectively through a validated adherence questionnaire, the MAQ, and be self-report of persistence. These methods showed only moderate statistical agreement, with the self-reported adherence and persistence results suggesting an overall null effect from the intervention. While a combination of self-report and MPR has been recommended...
by the WHO, it is important to recognise that there are subtle differences in the constructs assessed with a brief adherence questionnaire, by comparison to collection of pharmacy refill records. Each method reflects a unique aspect of the overall behaviour of medication adherence, such that the two surrogate measures may only be slightly related. Nonetheless, the majority of the other 76 questionnaire items similarly showed no significant differences from between group analyses. There were, however, a few subtle changes in questionnaire outcomes, particular through analysis of within group changes over time, and these tended to add support to the finding of lower persistence in the intervention group. The following sections will expand on the analysis of the questionnaires and other process outcomes, aiming to identify possible explanations for the lack of improvement in the primary outcome and the decline in persistence among patients in the intervention group.

5.2 Patient-focussed process outcomes and persistence

A battery of validated surveys was compiled to assess several adherence-behaviour concepts at six weeks as a baseline, with a follow-up comparison at six months. If there were changes in the primary outcome it was expected that changes in adherence behaviours and beliefs would help to explain why the intervention had either a positive or negative effect. Two-thirds of the cohort responded at both time-points and this was accepted as a good response rate given the time required to complete the lengthy questionnaire. The TABS questionnaire was summed into two subscales to identify behavioural preferences particularly associated with adherence versus preferences particularly associated with non-adherence. There were no significant differences observed between the groups, nor within group changes over time. The ability to detect differences in these scales was most-likely limited by ceiling effects as a result of most patients answering strongly for or against each of the Likert-scale questions. However, when the questions were dichotomised around the point of difference, the intervention group were more likely to record an answer of “never” versus all other options for the non-adherence item “I put up with my medical problems before taking any actions” compared with the control group (p=0.047). This may have reflected an effect of the intervention in encouraging patients to take
action if they noticed problems and this may have also affected medication dispensing records. However, there was no correlation between this item and persistence at six months. This item stimulated further interest into the types of actions patients were more willing to take, and if related to medications, whether or not they chose to involve their GP in the decision-making process around these actions.

Beliefs about medications were assessed using the BMQ and there were no significant differences between the groups at either time point for the BMQ or the additional perceived medicine value questions. However, within group analysis for the question “I sometimes worry about the long-term side effects of my heart medication” showed no significant change in the control group, but a significant decrease over time for the intervention (p=0.034). It is of interest that Horne et al found a strong relationship between a higher level of concern and a desire to change the medication regimen in their validation study of the BMQ. Several other studies have confirmed a link between higher scores for the specific concerns scale of the BMQ and poorer medication adherence. It is possible that those in the intervention group who held a high level of concern at six weeks adjusted their medications in some way, possibly through guidance from the intervention, and this somewhat relieved their concern such that it was lower when reassessed at six months. To further support this theory, a higher level of concern over side effects at six weeks was significantly correlated with non-persistence at six months (p=0.045, data not shown).

Ideally, a component of the pharmacist home visit would be a discussion of the benefits from continuing medication and/or providing education on the generally low incidence of serious side effects among the medications typically prescribed following ACS; as well as advice on how to appropriately manage side effects, should they occur. While this should, in part, reinforce education initially provided by hospital and community pharmacists, the two-month home visit should also provide an opportunity to tailor the information provided based on a review of the individual’s tolerance of their new medications to that point. The education package focussed on both of these concepts of the benefits from guideline-recommended medications and management of side effects, and 25% of all DRPs were either for ‘education’ or ‘toxicity/ADRs’,
as shown in Figure 4.9. Therefore, it would seem that both of these issues were addressed during some dHMRs. However, it is not clear whether the concerns decreased particularly among those who received the intervention and remained persistent, which would suggest a lower concern mediated by education; versus those who became non-persistent, potentially showing a lower concern as a result of no longer taking the medication. A better understanding through further behavioural research about how concerns over medication side effects can be effectively managed to improve adherence and persistence would be beneficial.

Illness perception according to the eight Likert-scale items of the Brief IPQ showed no significant differences between the groups at either time point. However, the intervention group reported an increase over time in the ‘perception of control’ over their condition (p=0.012) while the control group remained steady. It was also found that higher perceived control at six weeks correlated with higher rates of persistence (p=0.043, data not shown). It is possible that the intervention improved perceived control at some stage prior to the six-month follow-up. If such effects were conveyed sooner, they may have led to a different outcome on persistence. Further behavioural research looking to improve the understanding of changing a patient’s perception of control over time and the effect this has on persistence would be valuable in guiding the design of future interventions.

Medication knowledge, self-efficacy, perceived heart risk, and QoL did not appear to significantly differ between groups nor were there significant changes noted over time within the groups. However, components of all of these questionnaires, other than medication knowledge, were identified as potential confounders causing a CE≥10%. Due to the small sample size and strict LR methodology, only a single domain of the SAQ and a single-item from the BMQ remained as confounders in the final LR model. Nonetheless, this shows that at least some of the domains and/or individual items of these questionnaires interacted with medication persistence as assessed by pharmacy refill records. Although the power to detect significant differences in the majority of the questionnaire items was limited by the sample size, the approach to gather this wide variety of data proved useful. The assessment of medication knowledge was particularly brief due to a lack of validated questionnaires available within the
ACS setting and this most-likely added further limitations to the assessment of this outcome. It is possible that knowledge-related changes, such as an increased awareness of medication side effects may have led to patients stopping medications within the intervention group; however, as such an effect was not monitored, it can only be recommended to be further considered as an outcome of future studies.

By controlling for confounding from perceptions and beliefs, the univariate finding of lower persistence among intervention patients was supported and the statistical power of the study was improved.\textsuperscript{189} Furthermore, use of appropriate analysis to compare within group changes provided several links to support the finding of lower persistence in the intervention as a potentially true effect rather than a statistical error. Future research into adherence-focussed interventions would benefit from assessing a wide variety of adherence and persistence related concepts, as studied here, particularly to control for potential confounding from baseline differences in patients’ beliefs and perceptions.

### 5.3 Drug-related problems and persistence

The categorisation of DRPs and recommendations to resolve them were explored by comparing persistent against non-persistent patients to determine if there were any differences, particularly in adherence/persistence-related categories. Although the most frequently cited DRP classification was “undertreated conditions” for both persistent and non-persistent patients, there was a visibly higher proportion of “compliance”-related DRPs and a lower proportion of “education”-related DRPs among non-persistent patients, as presented in Figure 4.10. This suggests that for at least some non-persistent patients, there were problems identified with medication adherence or persistence (the ‘compliance’ DRP category) during the home visit. For a variety of possible reasons, such as the intervention not being consistently delivered in a timely fashion, the recognition of adherence problems did not lead to improved adherence or persistence at six months. These potential design-related barriers are explored further in sections 5.5 and 5.6.
The categorisation process saw a disproportionately large number of “refer to prescriber” recommendations across both persistent and non-persistent patients and this limited the utility of this tool as a means to clarify how the intervention may have led to lower rates of persistence. The ‘increase dose’ category, however, showed a significant difference with 16.7% of all recommendations for non-persistent patients being to increase the dose of a medication, versus just 2.5% for persistent patients (p=0.006), as presented in Figure 4.12. These patients were explored further to determine if the recommendations to increase the dose of a medication may have led to non-persistence of that medication or a medication with similar side effects, such as beta blockers and ACEI/ARBs sharing a similar dose-limiting effect of lowering systolic blood pressure. In all of these cases, the medication(s) that were discontinued did not appear to be related to recommendations to increase the dose of other medications. This individual case review also confirmed that this category had been labelled correctly and it was found that most of these recommendations were for ACEI/ARBs or beta blocker dose escalation. A possible explanation for the higher proportion of ‘increase dose’ recommendations among non-persistent patients could be that persistence problems appeared too complex to attempt to resolve by comparison to making subtle adjustments in the dosing of medications that the patient was tolerating. This is supported somewhat by Table 4.12 showing ‘ACS-focussed’ DRPs were four times more likely to be identified than ‘adherence-focussed’ DRPs. Allocating a lower priority to adherence-related problems by comparison to other identified issues appears surprising. However, this is supported by previous research involving a community pharmacist-led risk factor modification intervention, whereby pharmacists consistently developed goals for multiple cardiovascular risk factors, with the exception of medication adherence. Although this finding only provides justification for a null effect rather than significantly lower rates of persistence in the intervention group, it is important to consider that medication management may have been optimised in other ways, not necessarily related to persistence. Similarly, a greater degree of understanding and confidence in managing non-adherence or non-persistence may be required.

The clinical significance of alternative outcomes, such as dose titration, warrants further exploration in light of this finding. Upward dose titration of both ACEIs/ARBs and beta-blockers
was briefly cited as an appropriate medication management recommendation within the educational material and this target has been used previously in transition-of-care interventions among patients with ACS.\textsuperscript{191,192} Although there is evidence to suggest that treatment with beta blockers,\textsuperscript{36,37} and ACEI/ARBs,\textsuperscript{34} may decrease the rate of mortality following ACS, there is a lack of clinical evidence to support dose escalation among this population.\textsuperscript{36,37} Importantly, the major research supporting dose titration comes from improvements in mortality for patients with CHF rather than ACS.\textsuperscript{193,194} Therefore, this outcome was not used to assess the intervention within the current study as the long-term benefits from dose titration following ACS, although likely to be beneficial, have not been clearly defined. In contrast, non-adherence and non-persistence to guideline-recommended medications has been consistently correlated with worse clinical outcomes.\textsuperscript{6,44} As the effect of the intervention in the current study appeared to result in fewer patients persisting with guideline-recommended therapy, it would seem pertinent for future research to continue to focus on developing interventions that can improve medication persistence. The following sections explore further possible explanations for this unexpected finding within the current study.

5.4 Individual dHMR report review and further case-based discussion

The planned assessment of DRPs and recommendations using the DOCUMENT categorisation system did not show a particularly strong reason for lower persistence in the intervention. Therefore, the reports of all patients who were guideline-concordant at discharge and non-persistent at six months (26 patients, per Figure 4.2) were re-analysed to determine if there were written recommendations within the dHMR reports to cease or pause guideline-recommended therapies. Similarly, case examples of clinically significant interventions in medication management were identified and will be discussed as a comparison. To reduce the risk of individual bias, summaries of all non-persistent patients were distributed among the research team and cases of interest were discussed to determine if the identified management paradigms could be fairly attributed as a likely result of the intervention.
Of the 26 patients in the intervention group who were non-persistent, there were no dHMR reports whereby recommendations to overtly cease guideline-recommended therapies were recorded and this reflected positively on the education and performance of the APs involved. There were four cases ‘of interest’ identified, three of which may have missed an opportunity to minimise non-persistence based on the content recorded in the report, and one whereby there were recommendations made which may have inadvertently led to a gap in medication use. Although four out of 26 cases appears insignificant, having four more persistent cases in the intervention group may have led to a non-significant difference between groups due to the relatively small number of patients enrolled. Therefore, these cases require further exploration to identify possible themes.

Case one dealt with a suspected statin-induced side effect of muscle pain. This patient had a gap in supply of their statin therapy and this may be expected when managing such issues. Importantly, they restarted on a lower dose of a potent statin and appeared to continue this, with anecdotal follow-up showing persistence with this medicine in the period between six and twelve months post-discharge. Although this isolated case contributed to non-persistence in the intervention group, the patient arguably gained a long-term benefit from the intervention. This potentially shows a limitation of the two-month permissible gap in the algorithm used to detect non-persistence.

Among the three other cases, there was a theme of premature cessation of DAPT. Case two was a patient who presented with a STEMI and received PCI with DES as a primary treatment strategy. They were discharged with a recommendation of DAPT for twelve months and triple therapy with warfarin for three months due to the risk of apical thrombus following their large initial infarction. At the home visit, the AP noted cessation of both warfarin and clopidogrel and this was recorded in the report; however, there were no comments about why these medications were stopped, nor reference to education conveyed to the patient or GP about the potential benefit gained from continuing DAPT to 12 months. Arguably, it may have been appropriate for the project officer to intervene further in this case to ascertain if there was some form of bleeding incident or other explanation for not continuing DAPT in a patient with recently deployed DES.
due to the high risk of restenosis. However, this did not occur and there was no further explanation for this anomaly. In cases three and four, the patients had received PCI with BMS as a primary treatment strategy and both were found to be non-persistent to DAPT during dHMR follow-up. With further investigation it was noted that both of these cases had been recommended very short, three-month durations of DAPT by the interventional cardiologist at hospital discharge. Such cases were previously discussed among the trial committee during the recruitment phase and it was determined that they were appropriate to include in the trial, given the guideline recommendations to continue DAPT to twelve months in all patients with confirmed ACS. Although the cardiologist’s practice may have been a potential barrier to improving persistence by way of pharmacist-led intervention, it does not explain the lower rates of persistence as a result of the intervention. While a primary treatment strategy of DES correlated with persistence to a guideline-concordant regimen (data not shown), it was not identified as a confounder of the relationship between study group allocation and persistence. Therefore, it is likely that the impact from cardiologist recommendations for shorter DAPT durations in those not receiving DES was similar across the control and intervention groups. Nonetheless, in neither case did the AP record recommendations to continue DAPT for twelve months. Although all three cases represent potentially missed opportunities to recommend continuation of treatments in accordance with national guideline recommendations, it would seem unlikely that the pharmacist could have prevented non-persistence given the prescriber recommendations to discontinue medications in at least two of these cases. Therefore, individual case review did not help to clarify a mechanism for the lower proportion of persistent patients within the intervention group.

Whether using validated methods, such as the DOCUMENT categorisation system, or by simple case-based assessment, the dHMR reports provided little explanation for the lower rates of persistence among intervention patients. However, the dHMR intervention hinged largely on face-to-face interactions, telephone interactions, and rapport building between the AP and their patients/GPs. Furthermore, Carter et al showed that an AP’s ability to listen to their patient may affect the patient’s willingness to participate in future HMRs. Assessing these interactions in
some way was recognised as important during the adaptation of the conceptual framework to this study, as shown in Figure 3.9. However, specifically assessing the quality of these interactions would have required at least audio recordings of the home interviews and possibly of any further interactions between APs and patients/GPs. This would have been expensive and more invasive and, as such, it was considered beyond the scope of the current study. Such detailed understanding may be an appropriate point of investigation for future studies of similar interventions. If audio recordings are deemed overly invasive or expensive, surveys of patient’s perceptions, as with Carter et al may at least capture a basic level of understanding in this area.¹⁹⁵ Not having any part of the survey directed at understanding patients’ satisfaction or perceptions toward the quality of the intervention was a downfall of the current study.

While the above three cases described potentially missed opportunities among patients who were at risk of non-persistence and had a potential to benefit from a successful intervention, there were also cases identified that showed the ability of the intervention to detect interventions of high clinical significance. By the time of two months post-discharge, patients were likely to have visited their GP and community pharmacist at least once each. Therefore, it should be assumed that without a scheduled dHMR, these examples of medication misadventure would have continued and put the patient at risk of serious harm. The first case had received PCI with DES following a diagnosis of in-stent restenosis following an MI eight months earlier. They had been diagnosed with AF following their previous infarction and were discharged on triple therapy involving warfarin, aspirin, and prasugrel. Specifically, prasugrel had been prescribed as a substitute for clopidogrel due to the assessment that the patient was now at a higher risk of re-infarction. At the two-month home visit, the AP noted that the patient was persistent with triple therapy, however, he had also been advised by his ex-wife, who was one of his primary carers, to continue taking the clopidogrel. The patient attended different community pharmacies and the collection of four concomitant antithrombotic medications was not detected until the home visit. The AP liaised with the patient’s GP accordingly and ensured clopidogrel was not to be continued, as well as recommending that all of the patient’s 14 prescription items be
reconciled to the same collection date. This case represented significant medication misadventure, with the potential for harm minimised by way of dHMR intervention.

A second case example involved a patient who had a cerebrovascular accident (CVA) two months prior to their index admission of a NSTEMI. They were discharged from hospital on a combination product of aspirin and dipyridamole, which had been initiated following the CVA, as well as a new prescription for clopidogrel. Such combination therapy was unintentional and is inappropriate, not only for the added risk of bleeding, but also because dipyridamole has wide variation in its pharmacodynamics effects and has been associated with an increased risk of ischaemic coronary events in unstable IHD.\textsuperscript{196,197} Given the time-course association of when dipyridamole was initiated, it is possible it was even implicated as a contributor to the recent NSTEMI. However, in this instance, the event was detected by the project officer while aiming to follow-up on the scheduling of the patient’s home visit. The patient was using a community pharmacy-prepared dose administration aid and they were in the process of switching the packing of this device to a new community pharmacy, closer to their current place of residence. During this time, the interventional cardiologist, hospital pharmacist, GP, and two different community pharmacists had either not detected this unusual combination or chose not to query it. Therefore, it is unlikely this event would have otherwise been detected. While the aim of this study was not to improve medication management through involvement of any of the project officer’s clinical judgement, this incident was briefly discussed among the trial committee and determined too serious to avoid. The patient’s GP was contacted to begin resolving the issue and the medications listed on the administration aid submitted with the six-week survey from the patient confirmed that dipyridamole had been ceased. This particular event is of interest because large meta-analyses have been used in attempt to demonstrate the relative safety of dipyridamole in the IHD population.\textsuperscript{198} In such studies, however, the variability of effect can be lost as a result of a small number of patients with worsening disease being diluted by a slightly larger number of patients showing improvements.\textsuperscript{197} Somewhat similarly, the effects observed in the current study are limited by the small sample size and a larger study is required before a more definitive assessment of the intervention can be considered. However, the poor
intervention fidelity, as discussed in section 5.6, would require a significant degree of attention if such larger studies were to be conducted.

Another case highlighting a unique attempt to manage a complex patient who stopped all medications, has also been reported elsewhere. In this particular case, the AP had suggested to re-introduce guideline-recommended medication slowly over time. Such an approach, while patient-centred, would not have achieved a positive outcome by the MMPR, emphasising the need for flexibility in the assessment of such interventions. Overall, the individual case analysis added little further in explaining the finding of lower persistence among the intervention group, other than a minor trend of missed opportunities among a few cases. There were, however, cases of serious medication misadventure identified, which highlighted the potential for improvements in outcomes resulting from optimised medication management. Although this was only a small proportion of the overall cohort, these cases had gone unnoticed by other health professionals and were likely to have resulted in serious negative outcomes if they remained unresolved. Furthermore, the analysis of DRPs as a process outcome did not highlight the significance of these cases and they would not have been reported based on investigation of pre-planned trial outcomes alone. Future research involving patients at risk of medication misadventure should aim to include assessments of a variety of surrogate markers of clinical outcomes following pharmacist intervention, for example, the prevention of potentially serious ADRs.

Similar recent studies of HMRs further emphasise this point. A retrospective analysis of international normalised ratio (INR) control among war-veterans or war-widows who were treated with warfarin found no difference in the time in therapeutic range (TTR – an assessment of INR control over time) in the six months following receipt of an HMR by comparison to both the control group TTRs and to the same patients’ TTRs from the six months prior to their HMR. The secondary outcome was a composite of thrombotic and haemorrhagic events, which also saw no difference following HMR intervention, and the study concluded that HMRs appeared to have no impact on INR control. In contrast, Stafford et al utilised a similar model of directed pharmacist home visits offering intensive follow-up of patients recently discharged
from hospital, who were either starting or continuing warfarin therapy. This study also found no change in TTR between the intervention and control groups; however, the composite of thrombotic and haemorrhagic events was lower in the intervention group at the 90-day follow-up. Furthermore, persistence with warfarin was significantly higher in the intervention group, and the primary outcome, which was a composite of minor and major haemorrhagic events occurred less frequently among intervention patients. Collectively, the wide variety of improvements suggested that the intervention resulted in important clinical benefits and these effects were probably not solely mediated by INR control. The comparison of these two studies highlights the importance of obtaining a variety of outcomes to adequately assess the impact of pharmacist interventions among patients at risk of medication misadventure.

5.5 Comparisons with similar adherence-focussed interventions

The process outcomes and individual case analysis offered some plausible explanations for the lower persistence observed among intervention patients as well as highlighting a need to consider other outcomes not related to adherence when assessing such interventions. Comparison against other interventional studies may help to draw out key differences that could lead to improvements in the design of future interventions aiming to improve adherence and persistence.

5.5.1 Intervention design differences

The main element of the intervention within the current study, was a one-off, semi-structured home visit at two months post-discharge. By comparison Ho et al designed a multi-faceted pharmacist-led intervention following ACS, which achieved a pre-specified improvement in adherence of 15% at twelve months. The intervention was relatively complex involving the delivery of education from a pharmacist on discharge, with repeated follow-up at one week and one month post-discharge. Intervention patients received a dose administration aid (DAA), information on how to use it, their refill dates were synchronised, and multiple reminders to refill their medications were sent by way of an automated voice messaging system. While the
semi-structured nature of the dHMR intervention meant that certain features, such as DAAs, could be implemented if necessary, Ho et al more consistently ensured all components of the intervention would be delivered to each patient and this may have more consistently covered a wider variety of adherence barriers. Interestingly, the estimated costs of this intervention were similar to that of the intervention described in the current study, perhaps reflecting a shorter amount of time spent with patients at each interaction, less funding provided to GPs, and the use of technology-based adherence aids, which can be relatively inexpensive.

Another important factor may be the repeated follow-ups both before and soon after discharge. Patients’ information needs change over time post-ACS, as does their desire to be involved in treatment decisions, therefore interventions engaging early with this process may help to tailor the later opportunities for follow-up. Xavier et al also showed the potential for repeated follow-ups to improve adherence following ACS and saved costs, in this instance, by utilising a less expensive workforce of community health workers to deliver a case-management style of intervention. The timing of both Xavier et al and Ho et al with follow-up occurring soon after discharge may also be relevant as cardiologist follow-up has been correlated to improved medication adherence, only if completed within six weeks post-discharge. Future research into adherence-focussed interventions following ACS should aim to utilise both a variety of technological advances and an adapting workforce, including skilled professional-support workers where appropriate. This should aim to ensure a wide variety of adherence barriers are consistently addressed, the patients are engaged early with the service, and costs of the intervention are contained. Such research should explore the impact of variations in service delivery, such as allowing APs to recommend an appropriate duration of follow-up. This could potentially be with the same AP but not necessarily requiring travel to the patient’s home, for example, a clinic-based follow-up prior to a GP appointment or when collecting a medication refill at their community pharmacy. The study by Ho et al allowed this type of directed follow-up beyond thirty days at the pharmacist’s discretion. Such amendments to the HMR service may improve its ability to be patient-centred and this should be explored, with future research models pushing the barriers of the current HMR model. Although there is some potential for
follow-up within the Australian healthcare system by way of a medication use review (MURs), known as a “Medscheck” within a community pharmacy, the current funding arrangements do not allow these to occur within the twelve months following an HMR. It is not clear if any evidence has guided the decision for such a long time between formal follow-up opportunities and the impact from this cost-containment approach may affect the opportunity of the services to be better integrated to serve the needs of the patient. It seems likely that a much shorter timeframe would be appropriate if such services were to be utilised as useful follow-up to a complex dHMR, although further research is required to confirm this notion. Further barriers associated with limitations of the current HMR service model are explored in section 5.6

5.5.2 The impact of sample size and different approaches to assessing adherence and persistence

The current study saw significantly lower rates of persistence at six months among intervention patients. However, the assessment of changes in the primary outcome, including both adherence and persistence, was somewhat limited by the small sample size. Ho et al recruited a relatively larger sample than the current study with 241 patients followed to twelve months, allowing for greater statistical power. The study by Xavier et al also had the advantage of a larger sample with 806 patients followed to twelve months. While both studies achieved statistically significant improvements in adherence, the clinical significance was unclear and the study by Ho et al was scrutinised; being labelled as a potentially massive added cost-burden to the healthcare system if it was to be funded across all patients with ACS.Interestingly, the results of an insurance claims database study observing 4,015 patients post-MI saw reduced rates of major adverse cardiovascular events (MACE) by comparing those with MPR≥80% versus those with lower rates of adherence post-ACS. This was a relatively similar improvement in adherence to that achieved by Ho et al and it is likely that the larger sample size and twice the duration of follow-up improved the statistical power to detect follow-on differences in clinical outcomes resulting from the different levels of adherence. The results of a sub-study of the MI-FREE trial were somewhat similar to this large database study, suggesting that achieving a high level of adherence may be more important than making larger gains in patients with poorer baseline
non-adherence. This new data suggests a particularly high level of adherence is required to improve clinical outcomes. This is, however, in conflict with previous research, whereby it was shown that those who continued just one guideline-recommended medication survived longer than those who stopped all medications. It may be that those with small gaps in adherence and those with large gaps in persistence all stand to gain benefit from targeted intervention, however, the intervention may need to be appropriately tailored to the individual in order to address these vast differences in adherence behaviour.

This raises some questions requiring further exploration in future research. For example, can we identify those in the greatest need of intervention and thus avoid attempts to intervene with patients who did not require it in the first place? Algorithms to highlight patients at risk of medication misadventure are being developed, such as the PADR-EC score, however, there is little useful guidance on selecting patients at risk of medication non-adherence or non-persistence within the literature. Current guidance suggests there is a wide variety of patient variables that may be implicated in non-adherence and it is not clear which variables are most important. The survey results from the current study suggest that development of a brief tailored questionnaire may be useful in identifying those likely to be at risk of non-persistence, however, it was not within the scope of this project to explore predictors of non-persistence.

Another question raised is whether or not one intervention can appropriately deal with such contrasting behaviours from minor non-adherence to complete non-persistence. Ho et al has shown that those with moderate adherence can be effectively targeted to achieve higher levels of adherence, however, little is known about the success rates of interventions delivered to those who stop multiple medications. It is likely that these patients may require a significantly greater amount of time during follow-up by comparison to those already achieving moderate levels of adherence. The current study highlighted that aiming to improve adherence and persistence by targeting the entire population of patients with ACS through a one-off intervention is unlikely to be successful and may even be deleterious.
The combination of simple and complex interventions within a healthcare system may allow for a greater variety of adherence barriers to be targeted over time. For example, a hospital pharmacist or ‘transition of care’ liaison pharmacist could be instated as the gatekeeper of interventions, utilising validated systems to aid in determining who is likely to benefit, enabling the process to occur in a timely manner, tailoring the intervention components to the needs of the individual, and monitoring for a variety of clinical improvements. Such methods appear practical with only minor adaptations to existing intervention frameworks, however, further research of such models is required to determine if they could be effective in improving patient outcomes.

5.6 Intervention fidelity

Guidance from the conceptual framework ensured a variety of patient-focussed process outcomes were considered in the explanation of the intervention’s effect on the primary outcome. Similarly, several processes were considered as essential components of the intervention design, such that a dHMR could be considered to have occurred per protocol or not, as an assessment of ‘intervention fidelity’. Based largely on timing of the dHMR visit and completion of the education package prior to undertaking a dHMR, fidelity appeared to be reasonably good with 77.6% of scheduled dHMRs occurring per-protocol. However, the requirement of GP follow-up was not considered a component of the trial protocol and the home visit timing was relaxed to anywhere between discharge and four months post-discharge. Both these factors were considered important components of the intervention, but were completed to such low levels that statistical analysis of an on-treatment group would not have been possible if they were mandated. The low rate of GP follow-up at 44.1% is a potentially significant limitation of the service and suggests poor integration within the healthcare system. A tighter timing around the point of two months post-discharge may have been appropriate as the aim was to ensure continuation of medication therapy and a gap in supply of less than a month was used to define non-persistence. The effect of timing alone was explored through ad-hoc analysis, excluding all dHMRs that occurred later than eleven weeks post-discharge (three weeks after the
expected home visit) and while the numbers were small, the trend appeared to remain consistent with the on-treatment findings as in Figure 4.2 (data not shown). Therefore, delayed timing of the home visit as a single factor in isolation could not be considered as the sole reason for lower persistence among intervention patients.

When barriers to on-time completion and GP follow-up were investigated, it was interesting to note that this appeared to be somewhat provider specific. There were some APs who were more consistently punctual on both these aspects and although this did not show a change in outcome by sub-grouping, the sample was likely too small to power such analysis. This showed, however, that the current format of dHMR intervention could be delivered closely against the designed protocol. Unfortunately, there was no clear theme of attributes among those who more consistently achieved these components of the service, such that enablers to on-time completion could be identified. Further exploration through focus groups with APs may help to identify barriers and enablers to timely and complete delivery of the intervention. Research into GPs’ perceptions about the HMR service suggests that there may be some aspects of the existing HMR structure that limit its delivery in a timely and complete manner, such as the processes and paperwork involved and that inconsistency with the quality of reports received. The GPs interviewed suggested that a standard reporting format would be desirable. This may partly explain the lack of GP follow-up for some patients in the current study. Investigation of patients’ perceptions suggests that both these points of timely visits and GP follow-up are key to keeping the patient engaged. Those experiencing delays and/or failure to receive a specific GP appointment to discuss the review expressed a lack of faith in the health system as a result. The combined effects of delayed visits and low GP follow-up within the current study could clearly relate to disengagement with the health system and help to explain the potentially deleterious outcome on medication persistence. It may be appropriate to consider a co-designed approach, whereby stakeholders, such as GPs, community pharmacists, APs, and patients are interviewed to help develop the design of the intervention as has been previously suggested.

Within the current study the tailoring of the intervention was deliberately limited to ensure the standard HMR funding mechanisms could be followed. Not only did this allow the trial to be
undertaken with a small budget, it was thought this would also improve the translation of any observed outcome into practice, which has been previously identified as an area of unmet need.\textsuperscript{100,210} This approach, however, may have limited the success of the intervention, possibly even contributing to the negative outcome on persistence. Other studies have shown similarly negative outcomes from relatively brief post-discharge follow-up interventions.\textsuperscript{115,116,211} Conversely, Ho et al and Xavier et al both showed improvements in adherence when the intervention was initiated at the point of discharge and continued during the transitional period.\textsuperscript{84,202} While the current study was coordinated centrally by two researchers (both registered pharmacists) who would consult with patients, APs, and GPs; the aim of these interactions was largely to facilitate the intervention to occur under the standard funding arrangements – effectively ensuring completion of paperwork and arranging home visits. These interactions with the patient could have sought to obtain further useful information while they were in hospital. Transfer of such information to the GP and AP may have better integrated the service within the existing healthcare system and allowed for tailoring toward the needs of the individual.\textsuperscript{201,212} The period post-discharge following ACS is typically busy with cardiac rehabilitation, GP, and specialist appointments and this was one reason for selecting a slightly delayed follow-up at two months. In theory, the home visit has an advantage over these other follow-up opportunities of being able to observe the patient’s medicine storage and administration routine. However, such detailed level of insight may not be required for all patients and greater involvement from the project officers could have further served to identify those needing more detailed follow-up based on early contact with the patient by phone, or through interrogation of their first month’s medication refill record. If a more engaged approach involving specialist referral pharmacists were to be successful, it would have required an additional component of funding in order to translate the service into practice. However, this would be much smaller and more achievable than the funding required to deliver an entirely new service.

This study is not the first to demonstrate difficulties in achieving an accurately implemented intervention by adaptation of an existing service.\textsuperscript{210,213-215} There is, however, a lack of information
on ways to improve the translation of outcomes from successful clinical trials into routine clinical practice.\textsuperscript{216} The current study provides insight into the conduct of the existing HMR service within Australia, suggesting that a significant proportion of reviews are not conducted in a timely manner and to completion with GP follow-up. Future research should consider ways of delivering interventions in a consistently timely and complete manner. The current study noted that some providers were able to more consistently provide a timely and complete service, showing that the intervention can be implement as intended. However, there was not sufficient exploration into the barriers or enablers of this higher level of intervention fidelity. The existing body of research highlights that GPs require interventions to be reported succinctly and patients need to be engaged throughout the process.\textsuperscript{109,206,207,217,218} Broad stakeholder engagement during the design phases of interventions may help to enable successful implementation.\textsuperscript{208,209} If small add-ons to existing formats are required in order to facilitate this and to improve the integration of the service within the healthcare system, this may be more desirable than to risk an existing intervention leading to a deleterious outcome.

### 5.7 Limitations

#### 5.7.1 Sample size

The final sample size was approximately half that intended based on power calculations using the decline in persistence observed from the DMACS study as a guide.\textsuperscript{26} The small sample recruited was further reduced by a slightly lower than expected rate of guideline-concordant discharge prescribing.\textsuperscript{26,81} Despite these limitations, the trial demonstrated a statistical trend in the persistence component of the primary outcome and by controlling for confounding, LR analysis supported this univariate finding. Therefore, a potential strength of the study was the comprehensive measurement of baseline variables to allow for development of the LR model and improved statistical power.\textsuperscript{189} However, inclusion of variables into the LR model was also limited by a large increase in standard error if more than four variables were included, suggestive of model overfit. While the careful selection of variables saw that the most important
confounders were included, it is possible that a larger sample size may have led to tolerance of inclusion of more variables in the model, and this may have led to a different outcome. However, a sample of 50 consecutive clinical trial reports from major journals showed that this would be an unlikely event as controlling for confounding most commonly led to a similar outcome as that from univariate analysis. While LR somewhat improved the confidence lost from a lower than expected sample recruited, the small sample size limits the generalisability of the results. The lack of a trend toward an improvement and poor intervention fidelity suggest refinement of the model of intervention is required prior to conducting further studies of pharmacist-led interventions aiming to improve medication adherence or persistence.

5.7.2 Collection of patient dispensing records for the MMPR

As there was no central database or mechanism accessible that contained information on patient dispensing records, these data needed to be collected from individual pharmacies. This created a potential limitation of missing data due to patients collecting medication at one or more pharmacies that they could not remember by name. As described in the methods, however, there were multiple steps to improve the quality of these records and any remaining uncertainties were adjudicated by a third researcher not involved with data collection or recruitment. This resulted in only 12 patients (7.4%) (five control patients and seven intervention patients) who were excluded as a result of uncertainties in their medication records. This is comparable to the 1-8% of missing data commonly observed through the use of automated records to generate MPRs, and although this was a relative strength of the study given the need for manual submission of the dispensing records, it is possible that the excluded patients may have had significant benefits from the intervention or were significantly worse-off in the control group, but either possibility went unnoticed and is a limitation to the generalisability of the results. Consent to access of a patient’s electronic health record containing data, such as medication refill histories may overcome data collection problems for the MMPR. Such records exist in Australia but are yet to be widely adopted by patients.
5.7.3 Inability to assess improvements in guideline-concordant prescribing

Ideally the study would have investigated the effect of the intervention on improving guideline-concordant prescribing, assessing for example, how many patients were started on new, guideline-recommended medications following the intervention, despite not being prescribed them at discharge. Failure to initiate and up-titrate therapy after hospital discharge is a known problem and it has been shown that GPs are reluctant to initiate new medications without further review from the cardiologist, yet specialist review rarely occurs on a regular basis. Others have argued that this problem should be effectively ignored and all focus put onto perfecting medication management within the hospital. However, there is clearly a communication and responsibility misunderstanding that should be rectified. When patients are in hospital following ACS, their stays are usually short and their health status is dynamic. Therefore, there may be relative contraindications to initiating ACE-inhibitors or beta-blockers, such as low heart rate or blood pressure recordings. Once stable, however, these patients may stand to gain cardio-protective benefits from late/delayed initiation of these agents and further work is required to break down these barriers to guideline-recommended medication initiation post-discharge.

5.7.4 Use of the dHMR report as the primary record of the dHMR content

Although there were multiple components to the assessment of intervention fidelity, the dHMR report was the central pillar used to assess the APs’ activity and the potential impact the intervention. While this report should reflect the most important points covered during the dHMR, the detail contained within the report varied significantly between APs and this may have been an unfair assessment of their overall contribution during the home-visit. For example, previous research has highlighted that there are valuable education and counselling sessions delivered throughout a home-visit that are rarely mentioned in reports. Carter et al have further highlighted that an AP’s attentiveness and listening skills affect patients’ beliefs that the HMR would have a positive outcome and their willingness to have further such interventions in future.
A strength of the current study was the collection of further information, such as recording the timing of the HMR in relation to the patient’s most-recent medical event (ACS), further education of the APs involved with specific information relevant to ACS and adherence management, and collection of GP follow-up of AP recommendations. However, further information could have been collected to assess the quality of such intervention. For example, interviews and qualitative analysis of the beliefs of patients and GPs involved with the HMR service may add further granularity to the assessment of the quality of the service and how it was received by those involved. Further to this, audio-recording to understand what further information is conveyed and potentially even video-recording to ascertain an understanding of non-verbal communication used may offer a significant opportunity to understand the strengths and weaknesses of particular APs’ approaches to the dHMR.

5.7.5 dHMR quality control

As the intervention was based around an existing service, the ability to impact the quality of the intervention was limited by the existing governance framework for HMRs. Following registration as a pharmacist, AACP require completion of a one-day course, a multiple choice questionnaire, and four hypothetical cases (2xHMRs and 2xRMMRs (residential medication management reviews)) before a pharmacist becomes accredited and can undertake HMRs as a freelancer. After this point, the only feedback given to the AP regarding the quality of their reviews is that from the patient, GP, or if they actively seek peer review. While it is in the AP’s best professional interest to aim to conduct the best quality review possible such that the GP will continue to refer patients to their service, there is no guarantee of this. Previously recognised problems with timing and completion of the HMR service were identified within this study. Although some APs more consistently delivered complete and on time interventions, the incentive to do so may not be sufficient and this could be investigated further.

Anecdotally, the fixed level of reimbursement for HMRs has been known to further impact the quality of the service delivered. APs may, somewhat rightfully, aim to ensure their service remains financially lucrative, or at least on par with their other pharmacy-based activities and
this may curtail the time available for the home visit, report write-up, or verbal communication with the GP. Alternative approaches to reimbursement, such as a fee-for-service model based on the type of DRPs addressed, or payment on an hourly rate, managed by a service director, could be explored to allow those in need of a more thorough intervention to receive it. This could be balanced by those in lesser need of intervention receiving the full process in an appropriately shorter timeframe. Co-locating the AP within the GP’s clinic may overcome the travel barrier to delivery of a shorter intervention for those identified as unlikely to require a home visit.

5.8 Future directions

This study provided a detailed assessment of a dHMR delivered two months post-discharge following ACS and there are several recommendations for future research based on the results and comparison to the existing literature.

5.8.1 Development of an algorithm to reliably predict non-adherence and/or non-persistence

Large observational studies initially demonstrated that the population of patients with recent ACS may be at risk of stopping potentially life-saving medication and present a suitable target for adherence-focussed interventions.4,44,75 In addition to this, a clinical benefit from a very high level of adherence has been shown in comparison to lower levels of adherence to guideline-recommended medications following ACS.146,203 Importantly, these studies highlight that although there is a need to improve adherence and persistence following ACS, there is also a reasonably large proportion of patients who are adhering and persisting with therapy to an acceptable standard. Intervening in these patients will waste resources and could be deleterious.85 Developing algorithms to identify those at the greatest risk of non-persistence and non-adherence could help to minimise this potential problem. Although further testing is required, the PADR-EC tool has been developed to predict elderly patients at risk of adverse drug reaction-related admission to hospital, such that these patients could be targeted with medication management intervention.204 Although there is a wealth of research investigating
predictors of medication non-adherence and non-persistence following ACS,\textsuperscript{144,205,220-222} a similar formula to that of the PADR-EC that could predict patients at risk of non-adherence or non-persistence has yet to be shown to be effective in a prospective cohort. The ability to detect patients most likely to be at risk of medication non-adherence or non-persistence could see only those needing intervention to receive it. This could minimise the sample required to observe a clinically significant benefit and the waste of resource associated with delivering an intervention to patients who did not require it.

5.8.2 Explore the effect of tailoring interventions to the needs of individuals while fitting within the existing healthcare system

Within the problem of medication non-adherence following ACS, there may be two quite distinct behaviours leading to sub-optimal clinical outcomes. There are a group of patients who are non-persistent and stop medications altogether,\textsuperscript{6} and a seemingly different group of non-adherent patients who appear to continue medication but take it somewhat haphazardly.\textsuperscript{203} Both these subgroups of the ACS population are likely to benefit from appropriately tailored intervention, however, it would seem unlikely that both would benefit from the same intervention unless such intervention could be dramatically tailored toward the needs of the individual. The literature shows that those whom appear to be persistent but are in need of guidance to improve their rate of adherence are amenable to intervention when it is initiated prior to discharge and involves multiple follow-ups.\textsuperscript{84,202} The current study builds on this by highlighting that a one-off intervention delivered at two months post-discharge or later is unlikely to improve persistence among those struggling with this component of long-term medication adherence. Within the Australian healthcare system, various methods of follow-up to improve pharmaceutical care exist, such as HMRs and MURs. However, the interventions could be better integrated, potentially through oversight from specialist pharmacist administrators or liaisons who could utilise evidence-based algorithms to determine which patients would benefit from particular types of intervention. The AP would be competent in conducting a variety of services of differing intensity and, if they could provide reasoning behind a recommendation for more intense follow-up in certain settings, the liaison pharmacist may be able to approve the funding to do so.
This could allow for services to be not only integrated with each other, but to be wrapped around the patient, which may be particularly appropriate for those presenting with multiple adherence barriers, potentially not taking any of their prescribed medication. Such an approach also remains appealing from a perspective of being rapidly translatable into routine practice as it would only require minimal adjustment to current funding arrangements. The addition of an administrator or manager to oversee the allocation of funding would be the main added cost. These recommendations only require minimal adjustments to the protocol of the current study, specifically, further involvement from the recruiting pharmacists. Such alternative options should be explored with further research into pharmacist-led interventions targeted at patients with ACS.

5.8.3 Ensure a variety of clinically relevant outcomes are explored and assessed during follow-up

The education package delivered to APs contained an equally balanced component of adherence-focussed and medication management-focussed material. The intention was that a solid understanding of medication management principles following ACS would help to empower APs to provide education on the benefits of individual medications and develop methods for managing common side effects. However, it is likely that this training, as well as the APs’ general knowledge base, led to resolution of a variety of DRPs not solely related to medication adherence. Table 4.12 supports this theory, highlighting a much larger proportion of ACS-focussed versus adherence-focussed DRPs were identified. The case analysis similarly showed that some patients experienced quite significant medication misadventure following ACS and some of this was resolved through the intervention. However, there could be several other reasons for APs focussing more on medication management rather than adherence, such as a lack of time to properly delve into adherence barriers, insufficient training for managing adherence barriers, and that the medication management issues appeared as more obvious problems to manage. Furthermore, other research has shown medication adherence can be identified by pharmacists, but is not always given a high priority. Future research should aim
to identify medication management principles that can lead to positive clinical outcomes following ACS and measure these as a component of the intervention outcomes.

5.8.4 Explore the effects of giving further support to the practitioners involved, using a high level of training and ongoing peer review

During the trial, APs could contact the primary project officer for advice regarding patient issues and while this occurred it was relatively infrequent. These conversations were documented in the patient’s file but not formally analysed. In addition to advice from the primary project officer, one of the APs involved was a highly experienced pharmacist, who also lectured in therapeutics and could have been considered a suitable mentor for more junior APs involved. Similarly, a small company of APs undertook several dHMRs and they usually utilised a system of mentorship for their junior APs. However, the remainder of the APs practised independently and although it was not assessed, it is thought they did not seek detailed peer advice regarding their reviews. While it is not particularly well documented within the literature, formal systems for professional review exist, such as ‘360-degree review’ and ‘ClinCAT’ (based on the mini-PAT) clinical peer review systems. Some institutions use these tools widely as methods to assess and provide ongoing support for staff regularly involved in patient care. Such oversight may also be a suitable approach to overcome the need for audio-visual monitoring of the dHMR home visit. If APs could be further engaged with peer-review, they may consider it appropriate to invite a peer-reviewer to attend some of their visits with them. While the current arrangements for HMR funding would not support this approach, this could be considered as an aspect of future research into these types of intervention, allowing a specialist and experienced AP or clinical pharmacist to attend a couple of home visits with the AP prior to their involvement in a trial setting.
5.8.5 Intervention development and evaluation may benefit from guidance involving conceptual frameworks and the principles of co-design utilising stakeholder engagement

The conceptual framework by Lemmens et al provided important guidance in determining a variety of process outcomes to measure throughout the trial. The questionnaire items were carefully selected, as shown in Figure 3.10, and only included if there was previous evidence showing that the constructs assessed were related to adherence or persistence. The education package was developed with input from multiple expert clinicians and extensively peer-reviewed. And feedback on the trial protocol was sought from experienced APs. However, GPs and patients were not consulted in the design of the intervention protocol, nor were their perceptions of the intervention assessed during trial follow-up. Similarly, the AP’s acceptance and perceptions of the intervention were not sought, largely due to resource limitations. Existing research suggests wider engagement during both the design and evaluation stages is important for future research of pharmacist-led interventions.

The conceptual framework also ensured a thorough assessment of intervention fidelity. The low rate of GP follow-up and significantly varied timing of the intervention were two important outcomes that highlighted frequent variation from the trial protocol. This finding is not unique to this study, with translational studies often showing poor implementation due to unforeseen barriers. There were, however, pockets of excellence in this regard with some providers more consistently providing on time and complete reviews. However, barriers and enablers to effective execution of the trial protocol were not explored and such follow-up should be considered a component of future translational research.
Chapter Six: Conclusion

This study aimed to tailor the existing HMR service to the needs of patients with recent ACS and demonstrated no benefit in terms of adherence and persistence to a guideline-concordant regimen at six months post-discharge. Persistence to a guideline-concordant regimen was lower among intervention patients at six months and this univariate finding was supported by controlling for confounding. Furthermore, support was given to this finding through survey analysis involving assessment of patients’ adherence behaviours, beliefs about medicines, and illness perception. A major problem identified was poor intervention fidelity with a large proportion of dHMRs occurring well after the intended two months post-discharge and a low rate of dHMRs completed to the point of GP follow-up. Nonetheless, this study alongside a review of relevant literature can provide guidance for future research aiming to improve outcomes for patients with ACS. In particular, there were several case examples of positive outcomes from the intervention and some providers were able to demonstrate consistently higher intervention fidelity. The findings from this study and the existing literature suggests that future research of pharmacist-led interventions may benefit from exploring factors such as, targeting the intervention to those at risk of non-adherence or non-persistence, broad stakeholder engagement throughout development and evaluation of the intervention, and further flexibility in the model of intervention delivered.

This research was not without limitations including a smaller than intended sample size, risks associated with the completeness of the refill records used for the primary outcome, an inability to assess for improvements in guideline-concordant prescribing post-discharge, a lack of understanding over the quality of the verbal information delivered during the intervention, and a lack of processes for coaching or mentoring APs to improve the quality of this information. These limitations created a variety of challenges in explaining the impact of the finding of lower persistence among intervention patients. In particular, the poor intervention fidelity suggests that further research is required to understand whether or not the result stems from a poorly designed or poorly implemented intervention. It is important that such research into adherence and persistence following ACS continues. On the basis of the findings from the current study, a
dHMR service delivered at two months following ACS could be deleterious. Further research exploring alternative approaches to modifying this service for a better chance of improving outcomes is required.
Chapter Seven: References


30. Murphy SA, Cannon CP, Wiviott SD, McCabe CH, Braunwald E. Reduction in recurrent cardiovascular events with intensive lipid-lowering statin therapy


43. Gunnell AS, Einarsdóttir K, Sanfilippo F, Liew D, Holman CDAJ, Briffa T. Improved long-term survival in patients on combination therapies following an


57. Pungrassami P, Johnsen S P, Chongsuvivatwong V, Olsen J, Sørensen H T. Practice of directly observed treatment (DOT) for tuberculosis in southern


# 8.1 Appendix A – dHMR checklist

<table>
<thead>
<tr>
<th>Question</th>
<th>Yes</th>
<th>No</th>
<th>Further details if required:</th>
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<tr>
<td>Was the patient taking guideline meds at hospital discharge according to the dHMR referral?</td>
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<td>ACE Inhibitor</td>
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<td>Beta Blocker</td>
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<td>Aspirin + clopidogrel/prasugrel/ticagrelor</td>
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<td>Statin</td>
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<td><strong>Currently</strong> taking guideline meds?</td>
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<tr>
<td>ACE inhibitor/ARB</td>
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<td>Is ACE inhibitor/ARB being titrated toward maximum tolerable dose?</td>
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<td>Beta blocker</td>
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<td>Is beta blocker titrated to maintain resting heart rate close to 60 bpm?</td>
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<td>Is the beta blocker dosing regimen appropriate? (e.g. metoprolol tartrate should be twice daily post-ACS)</td>
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<td>Antiplatelet therapy</td>
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<td>What is the patient’s expected treatment time for dual antiplatelet therapy? Are they aware of this?</td>
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<td>Has the patient had any bleeding issues?</td>
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<td>Consider PPI if risk factor is present</td>
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<td>Is the patient at increased risk of bleeding? (e.g. history of bleeding, age &gt; 65 years, etc)</td>
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<td>If aspirin + clopidogrel – would it be worth considering the combination tablet?</td>
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<td>Statin/cholesterol-lowering therapy</td>
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<td>Any new muscle aches or pains noted?</td>
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<td>Is LDL-C moving towards target levels if known?</td>
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<td><strong>Medication Side Effects</strong></td>
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<td>Any new side effects or medication-related concerns?</td>
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<td>Are you able to reassure patient or is a medication change potentially required?</td>
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<td><strong>Medication Adherence</strong></td>
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<td>Direct questioning</td>
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<td>Indirect questioning, eg. adherence barriers:</td>
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<td>Condition-related, eg. duration of condition</td>
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<td>Treatment-related, eg. side effects, regimen complexity</td>
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<td>Health-system, eg. costs, continuity of care</td>
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<td>Social barriers, eg. friends and families influence</td>
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<td>Patient-related, eg. too busy for medications</td>
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<td>N.B. many more possible examples</td>
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<td><strong>Cardiac Rehab</strong></td>
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<td>Currently attending?</td>
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<td>Completed?</td>
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<td>Not started? Consider reinforcing benefits</td>
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<td><strong>Smoking Cessation (where relevant)</strong></td>
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<td><strong>Dietary advice required?</strong></td>
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<td><strong>Exercise advice?</strong></td>
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<tr>
<td><strong>Chest Pain Action Plan?</strong></td>
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8.2 Appendix B – Questionnaire battery

Home Medicines Review Following Heart Events

Participant Questionnaire Set

Questionnaire 1: Medication List and Medication Adherence

Patient Study Number: ____________________________

Completed by? Patient / Carer

Please collect together all your current medicines and list them below. Take a moment to notice the layout of the table – there is a separate section for the name, strength, dosing time, and number of tablets that you take. The final column is a short test of your medicine knowledge. You should try to answer this yourself, without any aids. Do your best, there is no penalty for any incorrect information. There is a second page if required.

<table>
<thead>
<tr>
<th>Current Medication (brand or drug name)</th>
<th>Strength</th>
<th>Time when you take it?</th>
<th>How many you take?</th>
<th>What is it for?</th>
</tr>
</thead>
<tbody>
<tr>
<td>Example: Prednisolone</td>
<td>5mg</td>
<td>Morning</td>
<td>½</td>
<td>Arthritis</td>
</tr>
</tbody>
</table>

<p>| | | | | |
|                                |          |                        |                    |                |
|                                |          |                        |                    |                |
|                                |          |                        |                    |                |
|                                |          |                        |                    |                |
|                                |          |                        |                    |                |</p>
<table>
<thead>
<tr>
<th>Current Medication (brand or drug name)</th>
<th>Strength</th>
<th>Time when you take it?</th>
<th>How many you take?</th>
<th>What is it for?</th>
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</tbody>
</table>
We are interested in how you take your medication. Please place a cross (X) in ONE box that best applies to you. There is no right or wrong answer, we are looking for an honest answer.

<table>
<thead>
<tr>
<th></th>
<th>Yes</th>
<th>No</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Do you ever forget to take your medication?</td>
<td></td>
<td></td>
</tr>
<tr>
<td>2. Are you careless at times about taking your medication?</td>
<td></td>
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<tr>
<td>3. When you feel better, do you sometimes stop taking your medication?</td>
<td></td>
<td></td>
</tr>
<tr>
<td>4. Sometimes, if you feel worse when you take your medication, do you stop taking it?</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**People’s view of their medications (Questionnaire 2)**

Many people find a way of using their medicines that suits them. This may differ from the instructions on the label or from what their doctor had said. Here are some ways in which people have said they use their medicines. For each statement, please place a cross (X) in ONE box that best applies to you.

<table>
<thead>
<tr>
<th></th>
<th>Never</th>
<th>Rarely</th>
<th>Sometimes</th>
<th>Often</th>
<th>Always</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. I get confused about my medication</td>
<td></td>
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<tr>
<td>2. I have strict routines for using my regular medication</td>
<td></td>
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</tr>
<tr>
<td>3. I keep my medications close to where I need to use them</td>
<td></td>
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<tr>
<td>4. I ensure I have enough medication so that I don’t run out</td>
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<tr>
<td>5. I strive to follow the instructions of my doctors</td>
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<tr>
<td>6. I make changes in the recommended management to suit my lifestyle</td>
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<tr>
<td>7. I vary my recommended management based on how I am feeling</td>
<td></td>
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<tr>
<td>8. I put up with my medical problems before taking any actions</td>
<td></td>
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</tr>
</tbody>
</table>
How confident do you feel about taking your medication? (Questionnaire 3)

We are interested in finding out how confident you are in using your medication and your belief in its effect. For each statement, please place a cross (X) in **ONE** box that best applies to you.

<table>
<thead>
<tr>
<th></th>
<th></th>
<th>Not at all confident</th>
<th>Somewhat confident</th>
<th>Moderately confident</th>
<th>Very confident</th>
<th>Completely confident</th>
</tr>
</thead>
<tbody>
<tr>
<td>1.</td>
<td>How confident are you that you can control your chest pain by changing your activity levels</td>
<td></td>
<td></td>
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</tr>
<tr>
<td>2.</td>
<td>How confident are you that you can control your chest pain by taking your heart medication</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>3.</td>
<td>How confident are you that you know when you should call or visit your doctor about your heart disease</td>
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<tr>
<td>4.</td>
<td>How confident are you that you know how to take your heart medication correctly</td>
<td></td>
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<tr>
<td>5.</td>
<td>How confident are you that you can maintain your usual activities at home with your family</td>
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<tr>
<td>6.</td>
<td>How confident are you that you can maintain your usual activities at work</td>
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<tr>
<td>7.</td>
<td>How confident are you that you can get regular aerobic exercise (work up a sweat and increase your heart rate)</td>
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</tbody>
</table>
How you feel about your medications? (Questionnaire 4)

We recognise that not everyone feels the same way about medicines and everyone’s view and perspectives are important. This questionnaire will help us understand your thoughts about taking medicine. Please indicate your thoughts or beliefs about medicines by placing a cross (X) in ONE box per statement that best indicates the way you feel about taking medicines.

<table>
<thead>
<tr>
<th></th>
<th>Strongly disagree</th>
<th>Disagree</th>
<th>Neither agree nor disagree</th>
<th>Agree</th>
<th>Strongly agree</th>
</tr>
</thead>
<tbody>
<tr>
<td>1.</td>
<td>Without my heart medication I would be very sick</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>2.</td>
<td>Having to take my heart medication worries me</td>
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<td></td>
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</tr>
<tr>
<td>3.</td>
<td>Doctors prescribe too many medications</td>
<td></td>
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</tr>
<tr>
<td>4.</td>
<td>Most medications are addictive</td>
<td></td>
<td></td>
<td></td>
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</tr>
<tr>
<td>5.</td>
<td>My heart health in the future will depend on my heart medication that I am taking currently</td>
<td></td>
<td></td>
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</tr>
<tr>
<td>6.</td>
<td>I sometimes worry about the long-term side effects of my heart medication</td>
<td></td>
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<td></td>
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<tr>
<td>7.</td>
<td>Natural remedies are safer than medications</td>
<td></td>
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<tr>
<td>8.</td>
<td>Medications do more harm than good</td>
<td></td>
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<tr>
<td>9.</td>
<td>The cost of my medications makes it difficult for me to take them regularly</td>
<td></td>
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<tr>
<td>10.</td>
<td>Medications are not good value for money</td>
<td></td>
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</tr>
</tbody>
</table>
How does your heart condition affect you? (Questionnaire 5)

In order to gain an idea of how much you believe that your heart condition affects you, please circle ONE number per question that best indicates how you feel about your heart condition. This questionnaire extends over two pages.

<table>
<thead>
<tr>
<th>Question</th>
<th>Responses</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. How much does your heart condition affect your life?</td>
<td>no affect at all 0 1 2 3 4 5 6 7 8 9 10 severely affects my life</td>
</tr>
<tr>
<td>2. How long do you think your heart condition will continue?</td>
<td>a very short time 0 1 2 3 4 5 6 7 8 9 10 forever</td>
</tr>
<tr>
<td>3. How much control do you feel you have over your heart condition?</td>
<td>absolutely no control 0 1 2 3 4 5 6 7 8 9 10 almost total control</td>
</tr>
<tr>
<td>4. How much do you think your treatment can help your heart condition?</td>
<td>not at all 0 1 2 3 4 5 6 7 8 9 10 extremely helpful</td>
</tr>
<tr>
<td>5. How much do you experience symptoms from your heart condition?</td>
<td>no symptoms 0 1 2 3 4 5 6 7 8 9 10 many severe symptoms</td>
</tr>
<tr>
<td>6. How concerned are you about your heart condition?</td>
<td>not at all concerned 0 1 2 3 4 5 6 7 8 9 10 extremely concerned</td>
</tr>
<tr>
<td>7. How well do you feel you understand your heart condition?</td>
<td>don’t understand at all 0 1 2 3 4 5 6 7 8 9 10 understand very clearly</td>
</tr>
</tbody>
</table>
8. How much does your heart condition affect you emotionally? (For example, does it make you angry, scared, upset, or depressed?)

<table>
<thead>
<tr>
<th>not at all</th>
<th>0</th>
<th>1</th>
<th>2</th>
<th>3</th>
<th>4</th>
<th>5</th>
<th>6</th>
<th>7</th>
<th>8</th>
<th>9</th>
<th>10</th>
<th>extremely affected</th>
</tr>
</thead>
</table>

9. How serious do you think your current heart condition is?

<table>
<thead>
<tr>
<th>not at all serious</th>
<th>0</th>
<th>1</th>
<th>2</th>
<th>3</th>
<th>4</th>
<th>5</th>
<th>6</th>
<th>7</th>
<th>8</th>
<th>9</th>
<th>10</th>
<th>very serious</th>
</tr>
</thead>
</table>

10. How do you rate your chance of having the same, or developing the same heart problem again in your lifetime?

<table>
<thead>
<tr>
<th>unlikely to happen again</th>
<th>0</th>
<th>1</th>
<th>2</th>
<th>3</th>
<th>4</th>
<th>5</th>
<th>6</th>
<th>7</th>
<th>8</th>
<th>9</th>
<th>10</th>
<th>almost certain to happen again</th>
</tr>
</thead>
</table>

11. Compared to other people of your same age and gender, how would you rate your chance of having the same heart condition again?

<table>
<thead>
<tr>
<th>unlikely to happen again</th>
<th>0</th>
<th>1</th>
<th>2</th>
<th>3</th>
<th>4</th>
<th>5</th>
<th>6</th>
<th>7</th>
<th>8</th>
<th>9</th>
<th>10</th>
<th>almost certain to happen again</th>
</tr>
</thead>
</table>

12. How bad would it be for you if you were to have the same heart problem again?

<table>
<thead>
<tr>
<th>not very bad at all</th>
<th>0</th>
<th>1</th>
<th>2</th>
<th>3</th>
<th>4</th>
<th>5</th>
<th>6</th>
<th>7</th>
<th>8</th>
<th>9</th>
<th>10</th>
<th>very bad</th>
</tr>
</thead>
</table>

**Smoking Status**

| Do you smoke cigarettes? | [ ] Yes | [ ] No |

If you answered “Yes”, please complete the short questionnaire on the following page. If you answered “No”, please skip the following page and proceed to the questionnaire marked “EQ-5D” on the front cover.
Questionnaire 6 (Cigarette Smokers Only)

This questionnaire will tell us important information about your cigarette habits. Please place a cross (X) in ONE box per statement that best indicates your normal smoking habits.

1. How soon after you wake up do you smoke your first cigarette?
   - [ ] Within 5 minutes
   - [ ] 6 – 30 minutes
   - [ ] 31 – 60 minutes
   - [ ] After 60 minutes

2. How many cigarettes a day do you smoke?
   - [ ] 10 or less
   - [ ] 11 – 20
   - [ ] 21 – 30
   - [ ] 31 or more

3. Do you find it is difficult to refrain from smoking in places where it is forbidden (eg. In church, at the library, in cinemas, etc.)?
   - [ ] Yes
   - [ ] No

4. Which cigarette would you hate most to give up?
   - [ ] The first one in the morning
   - [ ] All others

5. Do you smoke more frequently during the first hours after awakening than during the rest of the day?
   - [ ] Yes
   - [ ] No

6. Do you smoke if you are so ill that you are in bed most of the day?
   - [ ] Yes
   - [ ] No

Thank you for completing this survey. Please continue to the next survey marked “EQ-5D” on the front cover.
Health Questionnaire

(English version for Australia)

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