UTS UNIVERSITY OF TECHNOLOGY SYDNEY

Economic impact of medication non-adherence

Thesis

Rachelle Louise Cutler

2019

Doctor of Philosophy

Graduate School of Health, Discipline of Pharmacy:
University of Technology Sydney

CERTIFICATE OF ORIGINAL AUTHORSHIP

I Rachelle Louise Cutler declare that this thesis, is submitted in fulfilment of the requirements for the award of Doctor of Philosophy, in the Graduate School of Health at the University of Technology Sydney.

This thesis is wholly my own work unless otherwise referenced or acknowledged. In addition, I certify that all information sources and literature used are indicated in the thesis.

This document has not been submitted for qualifications at any other academic institution.

This research is supported by an Australian Government Research Training Program Scholarship.

Signature of Student:

Production Note:
Signature removed prior to publication.

Date: 02/07/19

Abstract

Background: Medication non-adherence is a global issue of major public health concern highlighted by the causal link between non-adherence, increased disease prevalence and health care resource use. Cost assessment of the economic burden lacks uniformity and consistency in determination. The use of a standardised methodology to determine the cost associated with medication non-adherence is required to facilitate international comparisons and demonstrate a reliable estimate of the magnitude of the problem on a global scale.

Objectives: To explore, analyse and estimate the economic impact of medication non-adherence. The research aimed to conceptualise and define a cost estimation framework to streamline the cost outcome indicators that are employed to evaluate the monetary burden linked to non-adherence. Additionally, a monetary estimate of the medication non-adherence burden in Australia was quantified whilst simultaneously exploring the potential role community pharmacists play in reducing the associated burden.

Methodology: A series of discrete studies were undertaken: (1) a systematic review of studies assessing the economic impact of medication non-adherence across disease groups; (2) development of a medication adherence cost estimation (MACE) framework through secondary analysis of the systematic review data; and (3) analysis of a large database of patient dispensing records appraising the cost of medication non-adherence in Australia and the cost saving effect community pharmacist led intervention had on adherence.

Results: The systematic review identified wide scoping cost variations reported across 79 studies, with lower levels of adherence associated with higher health care costs. Annual adjusted disease specific economic cost of non-adherence per person ranged from USD2015 $949- $44190 (chapter 3). Collation of outcomes resulted in the development of the MACE framework through identification of two core cost outcome indicators (direct and indirect costs), seven subcategories (hospital, primary

care, medical test, pharmacy, direct non-medical, societal and productivity costs) and 35 cost outcome indicator examples. The most utilised cost categories were hospital (68%, n=54), primary care (18%, n=15) and pharmacy costs (72%, n=57) (chapter 4). The national cost of medication non-adherence in Australia across hypertension, dyslipidaemia and depression was AUD2018 $10.4 billion. Community pharmacist led intervention was estimated to save the Australian health care system AUD2018 $1.9 billion annually. Application of the MACE framework post pharmacist intervention highlighted the greatest cost contributors to be associated with direct costs, particularly, outpatient expenses $2.1 billion, inpatient admissions $1.9 billion, prescription medications $1.8 billion and medical related expenses $1.6 billion (chapter 5).

Conclusion: Medication non-adherence is a costly burden placing financial drain on health care systems that has failed to be adequately prioritised by governments and health care organisations within national policy. The incorporated framework has been proposed to homogenise international measures and applied to the Australian landscape to demonstrate the scope of the problem and highlight the potential role of community pharmacists moving forward to counteract the rising economic encumbrance. The MACE framework facilitates the strengthening of adherence research and provides a strong foundation for evidence based costing studies to be incorporated into economic evaluations to aid decision making. Decision makers should seek to utilise pharmacists as an integrated member of the health care team to help curb the rising burden of medication non-adherence and generate cost savings to the health care system.

Dissemination of Research

Peer reviewed publications

1. **Cutler, R.L.**, Fernandez-Llimos, F., Frommer, M., Benrimoj, S.I. & Garcia-Cardenas, V. 2018, 'Economic impact of medication non-adherence by disease groups: a systematic review', *BMJ Open*, vol. 8, no. 1
2. **Cutler, R.L.**, Van der Linden, N., Benrimoj, S.I., Fernandez-Llimos, F. & Garcia-Cardenas, V. 2019, 'An evidence based model to consolidate Medication Adherence Cost Estimation: the MACE framework', *Journal of Comparative Effectiveness Research,* vol, 8, no. 8, pp. 555-567.
3. **Cutler, R.L.**, Torres-Robles, A., Wiecek, E., Drake, B., Van der Linden, N., Benrimoj, S.I. & Garcia-Cardenas, V. 2019, 'Pharmacist led medication non-adherence intervention: reducing the economic burden placed on the Australian health care system', *Patient Preference and Adherence,* vol. 13, pp. 853
4. Torres-Robles, A., Wiecek, E., **Cutler, R.L.,** Drake, B., Benrimoj, S.I., Fernandez-Llimos, F. & Garcia-Cardenas, V. 2019, 'Using dispensing data to evaluate adherence implementation rates from a community pharmacy program', *Frontiers in Pharmacology,* vol. 10, pp. 130

Conference proceedings

1. **Cutler, R.L.,** Garcia-Cardenas, V. and Benrimoj, S.I. 2015, 'A poor state of affairs- Overview of the current worldwide non-adherence crisis', International Pharmaceutical Federation 75th International congress, Dusseldorf, Germany, 2015
2. Garcia-Cardenas, V., Zeater, S., **Cutler, R.L.** and Benrimoj, S.I. 2015, 'Implementation of an adherence service in a community pharmacy setting- The Aim High project', International Pharmaceutical Federation 75th International congress, Dusseldorf, Germany, 2015

Acknowledgements

This research was supported by an Australian Government Research Training Program (AGRTP) stipend funded by the Commonwealth Government Department of Education and Training, plus a “Top-up” funded by the University of Technology Sydney (UTS).

The research outlined in this thesis would not have been possible without the ongoing guidance, encouragement and support of my supervisors, Professor Charlie (Shalom) Benrimoj; Emeritus Professor, University of Sydney, Dr Victoria Garcia-Cardenas; Senior Lecturer, Graduate School of Health, School of Pharmacy, UTS and Professor Kylie Williams; Head of Discipline, Pharmacy, Graduate School of Health, School of Pharmacy, UTS.

In addition to my supervisors I would like to acknowledge and thank the other wonderful colleagues with whom I have collaborated. Their knowledge and experience has allowed me to develop a body of research far beyond my expectations when I commenced this journey.

I would like to thank all academics and staff at the Graduate School of Health for their kindness, encouragement and support. Lasting memories have been made throughout this time. Thank you for being there through all the highs and lows with incredible levels of support and endless confidence boosts.

Lastly to my friends and family, thank you for your undying support and unconditional love. Even when you didn’t understand a word of what I was talking about in regard to my research you remained my number one cheer squad. To Helen, thank you for spurring me on and being a constant sounding board, offering inspiration and reassurance. Thank you to my parents for their love, praise and ongoing support of my educational endeavours. Most importantly thank you to Frankie, for always being there, enduring the full journey with unwavering adoration. Thank you!

Preface

This thesis is presented in fulfilment of the doctoral degree (Doctor of Philosophy) requirements of the University of Technology Sydney, Australia.

The thesis is structured as a PhD by compilation. Chapter 1 contains a research overview and general disposition of the thesis. An outline of the overall rationale, objectives and organisation of the thesis is included. Chapter 2 provides the background and reasoning for the topic. Chapters 3-5 comprise the sequential results including a systematic review outlining the economic impact of medication non-adherence across disease groups, development of the medication adherence cost estimation framework and a national estimate of the cost of medication non-adherence in Australia. The chapters have been structured as research articles containing all corresponding references, figures, tables and appendices related to the research activity. This is followed by Chapter 6, which discusses the results, summarises the contribution of work and provides recommendations for future research.

Rachelle L. Cutler is the primary author of each publication. Additionally, co-authors contributed to the conception or design of the work, data collection, data analysis and interpretation, or revision of the manuscripts.

This page is intentionally left blank

Table of Contents

List of Figures

List of Tables

Abbreviations

A	adherent
AbC	absenteeism costs
AC	ancillary costs
ACC	acute care costs
AGRTP	Australian Government Research Training Program
ArC	arrest costs
BHIC	behavioural health inpatient costs
CAD	Canadian dollar
CHF	chronic heart failure
Com	commercial patients
DKK	Danish krone
EDC	emergency department visit costs
ESC	external services costs
EUR	Euro
FC	fracture costs
GBP	Great British Pound
HC	hospitalisation costs
IC	inpatient costs
InC	incarceration costs
InstC	institutional costs
IntC	interdisciplinary costs

IQR	interquartile range
KRW	South Korean won
LA	low adherence
LC	laboratory costs
MA	moderate adherence
MACE	medication adherence cost estimation
MBS	Medicare Benefits Schedule
MC	medical costs
Med	Medicare supplemental patients
MPR	medication possession ratio
MSC	medical services costs
MTC	medical test costs
NA	non-adherent
NC	non-compliance
NE	no exposure
NEHI	the New England Healthcare Institute
NP	non-persistent
NPC	non-pharmacy costs
OC	outpatient costs
OECD	Organisation for Economic Cooperation and Development
OtC	other costs
OtPC	other pharmacy costs
P	persistent

PAC	psychiatric assessment costs
PBS	Pharmaceutical Benefits Scheme
PC	pharmacy costs
PCC	primary care costs
PDC	proportion of days covered
POC	physician office visit costs
PPP	purchasing power parities
PrC	presenteeism costs
PRISMA	preferred reporting items for systematic reviews and meta-analyses
PTOC	paid time off costs
RC	radiology costs
SC	services costs
STDC	short term disability costs
T	turbulent
TC	total costs
TCMC	targeted case management costs
THC	total healthcare costs
TPC	total productivity costs
US	United States
USD	United States dollar
UTS	University of Technology Sydney
WCC	workers compensation costs
WHO	World Health Organisation

Chapter 1

Synopsis

This page is intentionally left blank

Research Overview

This thesis presents a series of discrete but interconnected studies, to address the overarching aim of determining the economic impact of medication non-adherence. Six chapters are presented throughout the thesis, with chapters 3-5 in the form of peer reviewed journal articles (published) to enhance readability. To meet journal requirements for manuscript submission spelling may vary between US English and British English for these chapters.

The specific objectives of this thesis were achieved through development of a theoretical framework to address the heterogeneity in methodological approaches used to quantify the economic burden of medication non-adherence internationally. Thus, facilitating the application of quantitative methodologies to determine the impact community pharmacist led intervention has on the national cost of medication non-adherence in Australia. Chapter 1 provides an overview of the dissertation, followed by chapter 2 presenting the contextual background information, including the purpose of this thesis. The subsequent chapters present a series of work, each chapter addressing specific objectives.

- Chapter 3 uses systematic review methodology to study the economic impact of medication non-adherence across multiple disease groups and determine the range of costs reported within the literature and varying methodologies employed.
- Chapter 4 is a theoretical paper using secondary data from the systematic review in chapter 3 to develop a medication adherence cost estimation framework.
- Chapter 5 utilises quantitative methodologies to retrospectively analyse de-identified patient dispensing data, to extrapolate the national cost of medication non-adherence in hypertension, dyslipidaemia and depression pre and post community pharmacist led intervention.

Chapter 6 details the implications for practice, policy and research. The chapter includes the implications of the body of research and the effect the findings will have

moving forward on a national and international level. Conclusions drawn from the research are also examined.

Appendices including copies of Research Ethics Committee clearance, copies of published works and copyright permissions are included at the end of this thesis. A summary of acronyms and abbreviations used throughout this thesis are included at the beginning.

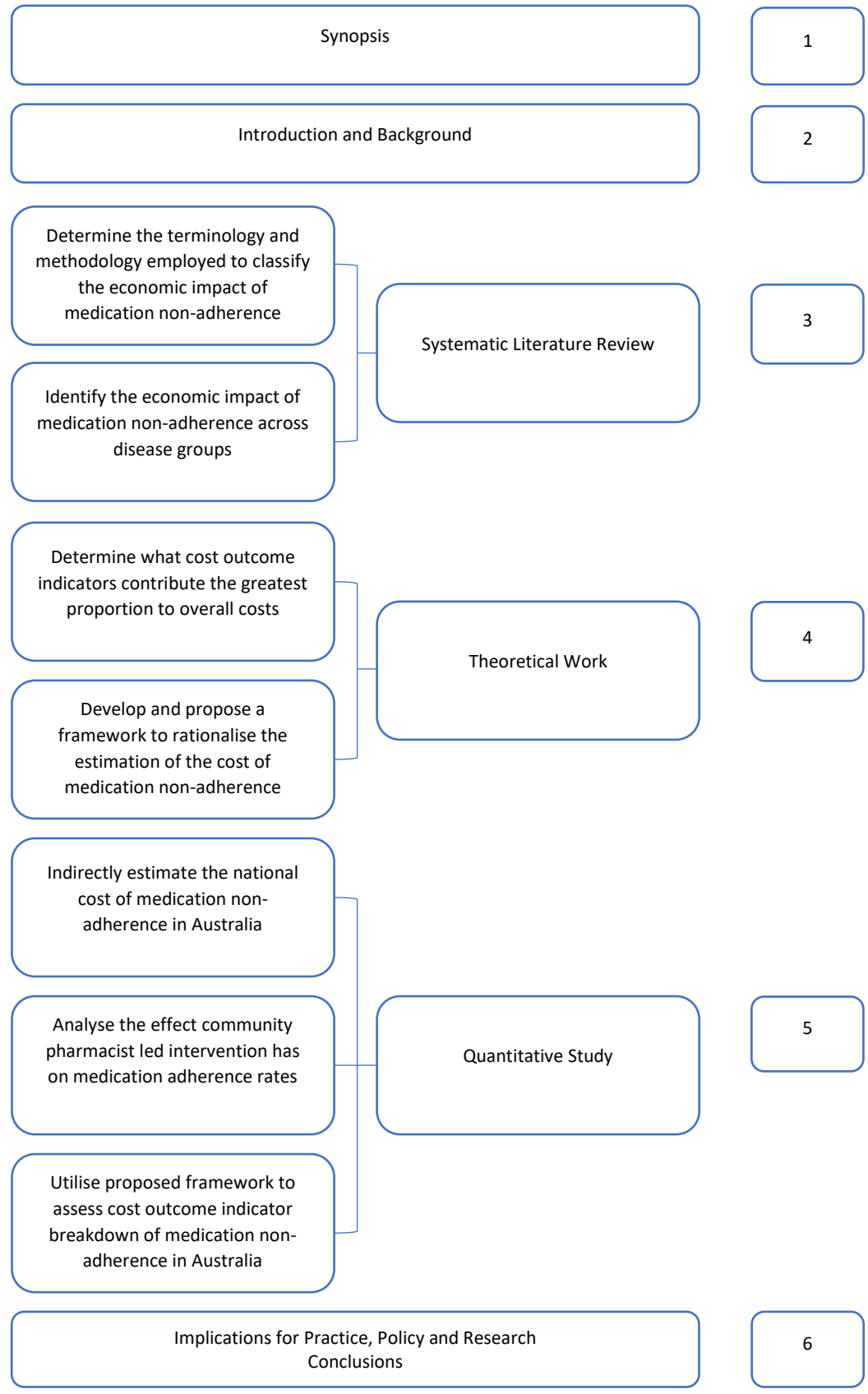

Figure 1: Thesis Structure

Rationale

Medication adherence has been identified as a major health concern impacting society, governments, patients and health care systems on a global scale (Sabaté 2003). The magnitude of the problem continues to expand with ageing populations and the growing disparity between developed and developing countries access to health care. While there is an abundance of evidence surrounding adherence research, the utilisation of such knowledge remains limited and of varying quality (Marie-Schneider & Aslani 2010; Nieuwlaat et al. 2014).

Consensus exists within the literature that medication non-adherence places a significant cost burden on health care systems and leads to wastage and inefficient utilisation of health care resources (Elliott 2013; Roebuck et al. 2011). However, the methodological approaches employed to determine these outcomes exhibit tremendous heterogeneity rendering the comparison of studies challenging and futile. Heterogeneity across studies and countries impedes the inclusion of adherence enhancing measures to be incorporated in national health policy. Loeppke et al estimated that health related productivity loss costs are 2.3 times higher than direct health care costs, nonetheless the majority of existing adherence literature only considers direct health care costs (Loeppke et al. 2009). Furthermore, some studies may consider costs associated with increased health care utilisation such as hospitalisations, ED visits, outpatient appointments while others only examine the effect on prescription medication or purely workplace productivity (Bagalman et al. 2010; Buysman et al. 2017; Joshi et al. 2006). A uniform framework, incorporating direct and indirect cost categories, including cost category examples involved in determining the economic burden of medication non-adherence is required to streamline the current disarray of costing methodologies to facilitate evidence based research to inform policy decisions.

In Australia, there is no estimate of the economic impact medication non-adherence places on the health care system. In order for a sustainable system to remain, review of the current levels of funding are required and removal of inefficiencies and waste

within the system needed (Taylor 2013). Application of a uniform framework will enable a systematic and evidence based methodology to determine the cost burden of non-adherence in Australia. Extrapolation of the cost burden medication non-adherence places on the Australian health care system, will highlight to policy makers the potential savings obtainable and encourage future research within the Australian context.

Numerous stakeholders across the health care system play a pivotal role in improving medication adherence. Community pharmacists are just one of the involved stakeholders who are ideally placed to provide patient centred medication adherence interventions (Pringle & Coley 2015). Reviewing the impact pharmacist led medication adherence interventions have on health care utilisation and costs, demonstrates the underutilisation of pharmacists and one of many solutions as to how inefficiencies and cost wastage within the system can be decreased moving forward. Determining the economic benefit community pharmacists contribute through provision of professional services within the Australian landscape will provide supportive evidence to explore expansion of their role moving forward.

Objectives

This thesis covers the exploration, analysis and estimation of the economic impact of medication non-adherence.

Specific Objectives

- Synthesise the literature to determine the economic impact of medication non-adherence across multiple disease groups, identifying the extent to which methodological approaches contribute to the variation in reported outcomes, cost calculation and adherence classification.
- Explore the methodological approaches used to determine the economic impact of medication non-adherence, in order to develop a framework to standardise the terminology of cost outcome indicators and rationalise the estimation of the cost of medication non-adherence utilising the identified cost outcome indicators.
- Estimate the national cost of medication non-adherence in Australia through utilisation of population based and pharmacy claims data.
- Examine the impact community pharmacist led intervention has on adherence rates and economic burden attributed to non-adherence.

The remainder of this chapter will provide an overview of the body of work encapsulated in this thesis, with the main research findings highlighted.

Economic impact of medication non-adherence by disease groups (chapter 3)

Annual costings of medication non-adherence range from US$100-$290 billion in the United States (New England Healthcare Institute 2009), €1.25 billion in Europe (Pharmaceutical Group of the European Union 2008) and approximately $7 billion in Australia (Australian Institute of Health and Welfare 2016; Institute for Healthcare Informatics 2012). These costs place a strain on health care systems and compromise the effective use of medicines, decrease quality of life, increase the risk of medication misadventures, lead to poor health outcomes, result in preventable hospitalisations and substantially increase health care costs (Sabaté 2003). In order to comprehensively assess the economic impact of medication non-adherence across multiple disease groups at an international level a review of the literature was undertaken.

Wide scoping cost variations in the reported onus medication non-adherence places on health care systems, patients and society at large makes the international comparison of the associated burden challenging (Hiligsmann et al. 2012; Hughes et al. 2001; Roebuck et al. 2011). For example in addiction studies Ruetsch et al reports the total cost of non-adherence as $16,555 (US2013) per patient per annum while Tkacz et al reports the burden as $47,868 in US2010, while in parkinsons disease Davis et al reports $18,511 (US2001) while Delea et al reports $19,686 (US2005) and Wei et al reports $45,867 (US2007) (Davis, Edin & Allen 2010; Delea, Thomas & Hagiwara 2011; Ruetsch et al. 2017; Tkacz et al. 2014; Wei et al. 2014). This disparity is demonstrated across multiple disease states. To aid in understanding the variations amongst studies the methodological approaches that were applied to determine the cost calculation and classification of non-adherence were appraised.

For this purpose, a systematic search was undertaken in PubMed and Scopus in September 2017. Studies quantifying the cost of medication non-adherence in relation to economic impact were included. Costs were defined as any indicator associated with medication non-adherence that was quantified with a monetary value in the original study. All costs were converted to US$2015 to facilitate

meaningful comparisons between data. The Drummond checklist for economic evaluations was utilised to analyse applied methodologies.

Database search retrieved 2909 potential articles, with manual review identifying a further 27 studies. From the 2768 articles screened by title and abstract, 2479 studies were excluded with 289 proceeding to full text review. Seventy nine studies were included in the review with the majority of papers excluded as no monetary value was provided for non-adherence.

Fourteen disease groups across the 79 studies were evaluated, with lower levels of adherence associated with higher total costs. The annual adjusted disease specific economic cost of non-adherence per person ranged from US$949-$44,190. Costs attributed to "all causes" non-adherence ranged from US$5,271 to $52,341. The developed framework aimed to address and minimise such variations (chapter 4). Medication possession ratio was the metric most utilised to calculate patient adherence, with varying cut-off points defining non-adherence. The main indicators used to measure the cost of non-adherence were total cost or total healthcare cost (83% of studies), pharmacy costs (70%), inpatient costs (46%), outpatient costs (50%), emergency department visit costs (27%), medical costs (29%) and hospitalisation costs (18%). Drummond quality assessment yielded 10 studies of high quality with all studies performing partial economic evaluations to varying extents.

Key findings from the systematic review highlighted that medication non-adherence places a significant cost burden on health care systems. Current research assessing the economic impact of medication non-adherence is limited and of varying quality due to the wide variations in methodologies and resultant costs attributed to non-adherence, often failing to provide adaptable data to influence health policy and change due to significant variations in costs and their economic implications. Differences in methods make the comparison amongst studies challenging and makes an accurate estimation of true magnitude of the cost impossible. Standardisation of the metric measures used to estimate medication non-adherence and development of a streamlined approach to quantify costs is required.

An evidence based model to consolidate Medication Adherence Cost Estimation: the MACE framework (chapter 4)

The successive part of the research addressed the methodological limitations of the original studies included in the systematic review and utilised the results to develop a theoretical framework to standardise the approach in determining the economic impact of medication non-adherence.

Identification of medication non-adherence as a major clinical and economic concern has accelerated significant growth of research in the field. Despite this growth, inconsistency remains in the outcomes of research findings, with only some interventions aimed at improving adherence resulting in better health outcomes and overall adherence (Agency for Healthcare Research and Quality 2014). Standard approaches in guidelines for reporting adherence terminology and minimum reporting criteria exist to help minimise this variability (De Geest et al. 2018; Fraser 2010; Vrijens et al. 2012). However, it appears methodological approaches to homogenise the way medication non-adherence costs are measured and reported in economic evaluations have been overlooked. This study developed a theoretical framework to rationalise the estimation of the cost of medication non-adherence, through utilisation of identified cost outcome indicators from the systematic review.

The methodology employed to design the medication adherence cost estimation (MACE) framework consisted of three phases:

- Phase 1- extraction and classification of costs
- Phase 2- comparison and aggregation of cost outcome indicators
- Phase 3- weighted average analysis

From this analysis, thirty five different cost outcome indicators were used to report the economic impact of medication non-adherence. Costs were classified as direct or indirect. Direct costs refer to transactions and expenditures for medical and/or non-medical products and services, including hospitalisations, prescription medications, physician fees, laboratory tests, radiological procedures as well as expenditures such as transportation, lodging, family care and home aides. Indirect costs were defined

as those that occur because of loss of life or livelihood and may result from morbidity or mortality. The majority of studies reported direct costs only (n=73).

To determine which cost outcome indicators contributed the greatest proportion to total cost a weighted average analysis was performed. Across both adjusted and unadjusted cost analysis studies, medical costs associated with hospital costs, primary care costs and pharmacy costs contributed the greatest.

As a result of this analysis the MACE framework was developed around the core cost outcome indicators that emerged from the data. The two core categories in the framework, direct and indirect costs can be further subcategorised into seven classes (hospital, primary care, medical test, pharmacy, direct non-medical, societal and productivity) and 35 cost outcome indicator examples. The indicator examples are not exhaustive to the categories outlined in the framework but serve as a guide for potential expenses that fall within each category. The framework provides a guide to cost estimation and can be applied in its entirety or utilising only those categories that are relevant to the study objectives.

The development of the MACE framework provides the foundations to ensure the generation of quality costing studies that can be used to inform economic evaluations. Economic evaluation can be used to assess the effectiveness of interventions and inform health policy. In order to guide policy makers on how to best allocate limited health care resources in the most efficient and effective manner, it is imperative that a comparable method be developed to accurately estimate the economic impact of medication non-adherence. The MACE framework streamlines the current disarray of cost outcomes that exists in the literature and provides structure via building on existing foundations to create a classification system taking into account direct and indirect costs. The adoption of this framework will help to standardise the cost outcome indicators utilised, hereby facilitating health policy decisions based on consistent evidence, terminology and reporting standards.

Pharmacist led medication non-adherence intervention: reducing the economic burden placed on the Australian health care system (chapter 5)

Medication non-adherence remains a neglected element of patient therapeutic management despite the mounting evidence of its association with increased morbidity and mortality, disease progression and increased utilisation of health care resources and accompanying expenditure (DiMatteo et al. 2002; Sokol et al. 2005). In Australia, inappropriate use of medicines represents 2-3% of all hospital admissions annually (Roughead, Semple & Rosenfeld 2013). Internationally, medication non-adherence has been estimated to cost US$100-$290 billion annually (NewEngland Health Institute 2009), however absence of a directly measured estimate of medication non-adherence for the Australian population remains. This study aimed to indirectly estimate the national cost of medication non-adherence in Australia, through utilisation of a large prescription data set.

Knowing the burden medication non-adherence places on health care systems, it begs to reason what can be done to reduce this burden? Community pharmacists are a key stakeholder who could contribute to trying to solve this problem. Examination into the effect community pharmacists are having on improving medication non-adherence is required. Therefore, this study further investigated the effect community pharmacist led intervention had on patient adherence rates and applied the MACE framework to assess the breakdown of cost outcome indicators contributing to the extrapolated annual cost of medication non-adherence.

In Australia, most illnesses and deaths are caused by chronic conditions, with an estimated 50% of Australians suffering from at least one chronic condition (Australian Institute of Health and Welfare 2018). Mental health and cardiovascular disease are two of the most prevalent conditions with 1 in 5 Australians experiencing one of these (Australian Institute of Health and Welfare 2018). Suboptimal adherence to medications within these conditions leads to disease progression and mortality (Chowdhury et al. 2013; Ford et al. 2007; Krivoy et al. 2015; Shoval et al. 2017). As such three prevalent chronic conditions hypertension, dyslipidaemia and

depression were chosen to extrapolate the annual cost of medication non-adherence in Australia.

Retrospective analysis of de-identified patient pharmacy dispensing data was conducted. The database was used to identify non-adherent patients who received an educational community pharmacist led intervention across Australia. One year of dispensing history was analysed for each patient to determine adherence rates as determined by proportion of days covered (PDC), six months prior to the intervention and six months following the intervention. Patients with a PDC of 80% or greater were classified as adherent. The national cost of medication non-adherence in Australia was extrapolated through adaption of the methods proposed by Nasseh et al (Nasseh et al. 2012). Utilisation of disease prevalence and comorbidity, non-adherence rates and per patient disease specific adherence related costs were applied. All costs were converted to 2018 Australian dollars using the Cochrane Economics Methods Group- Evidence for Policy and Practice Information and Coordinating- Centre Cost Converter tool (Shemilt, Thomas & Morciano 2010).

The community pharmacist led adherence intervention increased PDC across hypertension, dyslipidaemia and depression. On average PDC increased by 9.3% from baseline to six months post intervention. Generally, medication adherence decreased from baseline to intervention time point, peaked in the three months following the intervention before slowly decreasing and plateauing (rosuvastatin 62.4%, irbesartan 62.9%, desvenlafaxine 59.5%). Similar results were demonstrated across all three conditions. The total national cost of medication non-adherence across three prevalent disease states was $10.4 billion per annum. Pharmacist led intervention resulted in a $1.9 billion saving annually. Depression exhibited the greatest saving as a proportion of original expenditure (22%), while dyslipidaemia displayed the greatest dollar value saving ($1.1 billion).

Applying the MACE framework to extrapolated costing data revealed 85% ($7.2 billion) of the $8.5 billion cost attributed to medication non-adherence post pharmacist led intervention was attributable to medical related expenses. The largest cost burden stemmed from hospitalisations in both the outpatient ($2.1

billion) and inpatient ($1.9 billion) setting. This highlights that the reported $1.2 billion cost associated with inappropriate use of medicines within the Australian public hospital system is substantially underestimated.

In order for a viable and cost effective health care system to remain in Australia, changes need to be made to streamline health policy decisions and better allocate limited funding. Removal of wastage and inefficient usage of the current system is imperative. Medication non-adherence is one component where substantial cost savings are available and community pharmacists are ideally placed to coordinate and implement interventions to address this issue.

This page is intentionally left blank

Chapter 2

Introduction and background

This page is intentionally left blank

"Drugs don't work in patients who don't take them"

C. Everett Koop, US Surgeon General

Appropriate use of medications remains sub-optimal despite their proven effectiveness in preventing and managing chronic conditions. In an outpatient setting this is one of the principal obstacles in successful pharmacotherapy, yet often fails to be clinically recognised (Sabaté 2003). While highly prevalent, medication non-adherence is associated with increased morbidity and mortality, disease progression and increased utilisation of health care resources and accompanying expenditure (DiMatteo 2004; Sokol et al. 2005). Nevertheless, medication non-adherence remains a neglected element of patient therapeutic management.

Defining medication adherence

The World Health Organisation (WHO) defines adherence as "the extent to which a person's behaviour- taking medication, following a diet, and/or executing lifestyle changes, corresponds with agreed recommendations from a health care provider" (Sabaté 2003). Medication adherence is composed of initiation, implementation and discontinuation. Initiation occurs when the patient takes the first dose of a prescribed medication. Discontinuation occurs when the patient stops taking the prescribed medication, without the prescriber's recommendation. Implementation is the extent to which the patient's actual dosing corresponds to the prescribed dosing regimen, from initiation until the last dose. While persistence refers to the length of time between initiation and the last dose, which immediately precedes discontinuation (Vrijens et al. 2012).

Medication non-adherence further manifests in two distinct behaviours; unintentional and intentional adherence. Unintentional non-adherence occurs when the patient wants to adhere but is unable to because they lack capacity resources (e.g. difficulty remembering, unable to afford co-payments). Intentional non-

adherence occurs when the patient decides not to follow the recommendations and is closely associated with a patient's perceptual factors such as beliefs and preferences influencing their motivation to start or continue treatment (Horne et al. 2013). Additionally, there can be situations in which there is overlapping between both unintentional and intentional adherence. Motivation may overcome resource barriers and resource barriers may reduce motivation (Heaney 2013). These classifications are used in addition to subjective and objective determinations of adherence.

Measuring medication adherence

Despite semantic variation in adherence terminology, current estimates indicate that between 20-30% of medication prescriptions are never filled (Fischer et al. 2010). In developed countries it is estimated that among patients suffering from chronic conditions 50% do not take their medications as prescribed (Brown & Bussell 2011; Haynes et al. 2002; Sackett et al. 1978) with the magnitude of the problem assumed to be even higher in developing countries. Such large fluctuation in adherence rates is dependent upon the context of the study and the measure used to estimate adherence (Haynes et al. 2008).

Multiple methods and tools are available for measuring adherence but guidance for the most suitable measure for health care professionals and researchers is still lacking (Whalley Buono et al. 2017). Moreover, measures of adherence must also take into consideration the different components of the medication taking process defined by the ABC taxonomy (initiation, implementation, discontinuation and persistence). Each of these components both individually and jointly carry insight into patient medication use behaviour (Vrijens et al. 2012).

Measuring the improvement in medication adherence associated with particular intervention studies remains challenging, as there is no 'gold standard' approach to determine rates of adherence. Ratings of medication adherence are classified as subjective or objective (Williams et al. 2013). Subjective measures require the

assessment of the patient's medication taking behaviour by the provider or patient. Utilisation of self-report or health care professional assessment tools generally results in the drawback of patient under reporting (Velligan et al. 2007; Vik, Maxwell & Hogan 2004). Objective measures do not rely on the patient or provider's opinion and instead assess adherence through examination of measures such as pill counts, secondary database analysis such as health care claims data or prescription dispensing data and biochemical measures (Sabaté 2003).

Increased accessibility of health system data and advancements in electronic information of medication use has facilitated insights into patients' medication taking behaviour or at least the dispensing of those medications. The ease of use and scalability of these big data sets has resulted in pharmacy dispensing databases becoming the mainstay in both evaluation of adherence interventions and design of adherence programs across a multitude of settings (Whalley Buono et al. 2017). A limitation with use of this data is that it is impossible to determine whether the patient actually takes the medication as prescribed (Haynes et al. 2008; Osterberg & Blaschke 2005; Peterson 2003).

The two most common validated measures to calculate medication adherence from dispensing data are the Medication Possession Ratio (MPR) and Proportion of Days Covered (PDC) (Pednekar et al. 2017). The most commonly used method for claims based adherence is MPR, however there tends to be significant variation in the operational definition across studies in addition to the likelihood measure to overestimate the true rate of adherence (Nau 2011). Overestimation predominately results from duplication, since the average MPR does not account for the number of medications, the frequency of medication switching and overlapping days' supply due to early refills (Arnet et al. 2014). It is generally defined as the sum of day's supply for all fills of a given medication, in a particular time period divided by the number of days in the period (Sperber, Samarasinghe & Lomax 2017). Depending on the definition used will determine if discontinuation is taken into consideration.

$$MPR = \frac{Sum\ of\ days\ supply\ for\ all\ fills\ in\ period}{Number\ of\ days\ in\ period}$$

The PDC calculation is based on the fill dates and days' supply for each fill of a prescription, it differs from MPR in that it is not a simple summation of the days' supply, accounting for discontinuation and non-persistence (Nau 2011). PDC examines each day in the period to determine if the patient has the drug on hand, it provides a more conservative estimate of adherence compared to MPR when patients are switching drugs or using dual therapy in class, additionally it is more complex to calculate than MPR (Nau 2011).

$$PDC = \frac{Number\ of\ days\ in\ period\ "covered"\ by\ medication}{Number\ of\ days\ in\ period}$$

Successful strategies to improve medication adherence on a large scale are dependent upon the improved efficiency and effectiveness of interventions and the measures of adherence. The benefits to patients, practitioners, payers and policy makers needs to be taken into consideration in addition to the perspective of the study to determine the most appropriate medication adherence measures to inform decision making about design, implementation and evaluation of adherence interventions (Lam & Fresco 2015). Consideration of the intended pharmacological effect of a medication is also required, with further investigation into the economic impact discontinuation versus suboptimal use has on the health care system. As stakeholders in the health care market contemplate solutions for non-adherence, success at both patient and population level will depend upon an educated understanding of adherence measures and interventions (Whalley Buono et al. 2017).

Clinical impact of medication non-adherence

It has been suggested that the magnitude of medication non-adherence is much larger than perceived, with non-adherent patients more likely to experience poor health outcomes, health complications, premature death, increased hospitalisations and increased use of health care services (Khan & Socha-Dietrich 2018).

Medication non-adherence is said to contribute to nearly 200,000 premature deaths annually in Europe (Pharmaceutical Group of the Eurpoean Union 2018), 125,000 avoidable hospitalisations in the United States (US) (McCarthy 1998), 2-3% of all hospital admissions in Australia (Roughead, Semple & Rosenfeld 2013) and 23% of nursing home admissions (National Pharmaceutical Council 1992).

Across prevalent chronic conditions medication non-adherence results in significant increases in hospitalisation rates, with adherent patients experiencing 1.18-5.72 fewer inpatient hospital days compared to non-adherent patients (Roebuck et al. 2011). Among diabetes patients the one year risk of hospitalisation was more than double for patients with low adherence compared with high (Jimmy & Jose 2011). Non-adherent hypertensive patients have 1.5 times greater hospitalisation risk compared to adherent patients (Khan & Socha-Dietrich 2018), while in dyslipidaemia patients, the risk of emergency department visits was 30% higher among non-adherent patients relative to adherent ones (Gatwood & Bailey 2014; Li & Huang 2015). Additionally, the mortality rate for non-adherent patients with diabetes and heart disease is twice as high as adherent patients (Brown & Bussell 2011; Cramer 2004). Hypertensive patients who fail to adhere to their beta blocker medication to manage blood pressure are 4.5 times more likely to suffer complications from coronary heart disease (Psaty et al. 1990). Poor adherence to asthma medication among elderly patients with moderate to severe asthma has been associated with a 5% increase in annual physician office visits (Balkrishnan & Christensen 2000). Depression has been associated with a two-fold increase in non-adherence rates in coronary artery disease patients (Gehi et al. 2005) with patients suffering depression more likely to miss medical appointments resulting in decreased continuity of care and increased likelihood of relapse and rehospitalisation (Gonzalez et al. 2008).

Medications represent the cornerstone of chronic disease management; medication non-adherence increases the burden of illness on patients and health care systems through worsening clinical conditions and outcomes and ultimately results in the avertable use of health system resources leading to significant economic strain. Addressing non-adherence as a serious health concern will facilitate greater

allocation and access to health care across populations in addition to cost savings for the health care system.

Barriers to improving medication adherence

Medication non-adherence is a complex process, highlighted by a lack of consistency across adherence intervention study design, resulting outcomes in varying degrees of adherence rate changes, clinical outcome modification and costing analysis utilised. A Cochrane review analysing randomised control trial (RCT) adherence interventions determined that only a minority of lowest risk bias RCTs improved both adherence and clinical outcomes, concluding that non-effectiveness may be attributable to a lack of thorough understanding of adherence problems (Nieuwlaat et al. 2014).

Multiple dimensions affect an individual's adherence, with each interplaying on one another to contribute to the potential sources of medication non-adherence. Evidence suggests a combination of five interacting dimensions (social and economic, health care team and system related, condition related, therapy related and patient related) determine adherence (Sabaté 2003). In the majority of cases medication non-adherence results from the culmination of factors rather than one isolated barrier. The most commonly identified barriers are those associated with patient related factors. A patient's level of education has been closely linked with their beliefs about the condition or treatment, particularly a lack of knowledge about the condition, has exhibited a positive correlation with poor adherence due to a lack of motivation from the patient (Jaam et al. 2018). A systematic review of systematic reviews across 19 disease categories identified 771 individual factor items that potentially impacted adherence. Determinants of adherence to medication were further classified into treatment duration, components of adherence to medication (implementation vs. persistence), dimensions of adherence and direction of effect (Kardas, Lewek & Matyjaszczyk 2013). Elimination of a single barrier in the voyage to overcome the challenge of medication non-adherence will prove futile in the large

scheme of the overarching problem. Future interventions require the targeting of multiple themes of barriers to improve patient outcomes. Bearing in mind the number of identified determinants and their inconsistent effect on adherence, prediction of non-adherence of individual patients remains difficult. While not an absolute solution, adherence enhancing interventions are worth considering given their ability to help minimise the clinical, economic and humanistic burden associated with medication non-adherence.

In addition to the preceding barriers there also exists a value misalignment in the adherence landscape further impeding development. The question of whose responsibility it is to improve adherence comes to light. Improving patient outcomes while reducing or managing costs is a problem that must be tackled from multiple angles, in part by focusing on specific areas of health care to identify sustainable solutions both in delivery and long term impact (Brown & Bussell 2011). While the costs of non-adherence are significant, activity to address this is comparatively small, with limited initiatives despite the identified need. The patient is not well equipped to undertake adherence initiatives in isolation, but rather requires an interplay of all stakeholders within the health care system to forge the path forward. Until the mismatch between individual, providers, health care systems and social values of adherence activities become aligned, improvements in medication adherence will remain unlikely. Stakeholders need to identify appropriate and innovative funding mechanisms across the entire health ecosystem and take steps to holistically implement them. Community pharmacist led intervention provides one option moving forward (Centre for Business Innovation Medical Adherence Consortium 2018).

Interventions targeting medication non-adherence

Medication adherence problems persist despite a number of interventions available to address the problem. This results as there is no single or dominant approach to measuring and improving adherence in addition to the vast array of intervention

design methodologies that have been employed (Nieuwlaat et al. 2014). To date intervention studies have been fragmented with a tendency to focus on unidimensional factors (primarily patient related factors). Single factored interventions display limited effectiveness when compared with multi-level interventions (Tonin et al. 2018). Increased understanding of the barriers influencing adherence has resulted in development of refined frameworks and methodologies targeted at improving patient adherence.

To improve medication adherence there must be an intervention to effect a change. Interventions to promote adherence require several components aimed at targeting barriers associated with one or more of the contributing factors. Current methods of improving adherence for chronic health problems are mostly complex and not very effective, such that the full benefits of treatment cannot be realised. Nieuwlaat et al recommend advances in the improved design of feasible long-term interventions, objective adherence measures, and sufficient study power to detect improvements in patient important clinical outcomes (Nieuwlaat et al. 2014).

A recent network meta-analysis conducted by Wiecek et al in 2019 identified that multicomponent interventions displayed the most promising results in maintenance of long-term medication adherence. Technical and reward components enhanced adherence on a short-term basis, while educational and attitudinal interventions evolved over time to be more effective where follow up was greater than seven months. All intervention types proved more effective than standard care (Wiecek et al. 2019). Analysis within clinical conditions revealed the most effective interventions were educational plus technical in circulatory system and metabolic diseases, and infectious diseases. Attitudinal intervention had the greatest effect in musculoskeletal disease and finally educational plus attitudinal interventions proved highest results for mental, behavioural and neurodevelopmental disorders (Torres-Robles et al. 2018). This highlights that to ensure the effectiveness of interventions one may need to take into consideration the clinical condition the intervention is targeting.

A growing body of evidence highlights the positive contribution community pharmacist led intervention can have on improving patient's medication adherence and health outcomes (Aguiar et al. 2012; Blenkinsopp et al. 2000; Mes et al. 2018; Milosavljevic, Aspden & Harrison 2018; Sturgess et al. 2003; Svarstad et al. 2013; Tommelein et al. 2014). Community pharmacists are one of the most accessible health care providers and have regular contact with patient's experiencing chronic health conditions. A systematic review conducted in 2018 demonstrated that community pharmacist led intervention was effective in improving blood pressure control, cholesterol management, chronic obstructive pulmonary disease (COPD) and asthma control, however did not report statistically significant effects of interventions on diabetes or depression control (Milosavljevic, Aspden & Harrison 2018). Additionally, a pharmacist led intervention in the United Kingdom targeted at patients receiving the first prescription for a newly prescribed medication for a chronic condition has been described as both effective and cost-effective. Self-reported non-adherence was significantly lower in the intervention group (9% vs. 16%, p=0.032) at four week follow up (Clifford et al. 2006; Elliott et al. 2008). This intervention was subsequently adopted to form the New Medicines Service delivered through community pharmacies across England and Wales. A 31% increase in adherence rates over a 24 month period was also observed with a pharmacist led educational intervention targeted at COPD patients (Abdulsalim et al. 2018). Pharmacists are well placed within the health care system to provide a range of medication adherence interventions targeted across a wide scope of clinical conditions.

Interventions targeted at enhancing medication adherence provide a cost effective treatment modality to improve the health outcomes of patients with chronic conditions whose adherence is suboptimal (Congressional Budget Office 2012; Viswanathan et al. 2012). At a time when new pharmacological entities are scarce and highly expensive, improving adherence to appropriate and efficacious treatment options represents the best investment for improving the self-management of long-term medical conditions.

Economic impact of medication non-adherence

The association between medication non-adherence and health care costs demonstrates an increasingly unnecessary burden being placed on health care systems (Cutler et al. 2018). Waste in health care is estimated to consume up to 30% of total health care budgets (McGinnis, Grossmann & Olsen 2011). Exposing patients to ineffective health care not only causes harm but wastes scarce taxpayer dollars which could be used towards improving the health of all Australians (Carpenter et al. 2014). It is estimated that spending on health care by the Australian government as a percentage of gross domestic product will nearly double by 2050 (Australian Treasury & Swan 2010). Subsidisation of the Pharmaceutical Benefits Scheme (PBS) represents 30% of funds administered by the Department of Health and the Medical Benefits Scheme (MBS) 52% (Australian Government Department of Health 2017). Approximately 41% of Australian's are reported to having stopped taking their prescribed medication before they were meant to, on at least one occasion (The Pharmacy Guild of Australia 2010). Australia has the second highest amount of self-report non-adherence out of 11 Organisation for Economic Cooperation and Development (OECD) countries (Morgan & Lee 2017) thus, improving medication adherence presents an opportunity to ease the rising burden and allows the better allocation of budgetary resources.

International grey literature reports reveal that health care costs attributed to the improper use of medications can result in costly consequences that are often more expensive than the initial medication expense. In 2009 the New England Healthcare Institute (NEHI) noted that medication non-adherence in addition to suboptimal prescribing, drug administration and diagnosis could result in as much as US$290 billion per year in avoidable medical spending (New England Healthcare Institute 2009). In 2013 the IMS Institute for Healthcare Informatics estimated the annual cost attributed to medication non-adherence in the US to total $105.4 billion (Aitken & Valkova 2013). While in Europe non-adherence is estimated to cost the European Union €125 billion annually (Pharmaceutical Group of the European Union 2018). These reports provide an overview of the magnitude of the non-adherence problem

on a global scale. However, and critically the grey literature estimates of non-adherence provide limited transparency in the approaches utilised to quantify the cost of non-adherence.

Nationally, the Australian non-adherence landscape does not have a directly estimated cost of non-adherence but rather projects that 4.7% of total Australian health expenditure is avoidable due to suboptimal medicines use, extrapolating to approximately AUD$8 billion annually (Aitken & Valkova 2013; Australian Institute of Health and Welfare 2017). Inappropriate use of medicines costs the Australian public hospital system AUD$1.2 billion per year representing 2-3% of all hospital admissions (Roughead, Semple & Rosenfeld 2013). These costs and projections take into consideration additional variables in conjunction with adherence making the true estimation of medication non-adherence difficult nationally.

Patient non-adherence is among the largest factors associated with wasteful and avoidable health care spending. Projections estimate that globally non-adherence results in US$900 billion annually, based on the US accounting for approximately a third of health expenditure (DiMatteo 2004). Chronic conditions represent the largest contributor to medication non-adherence cost burden, with lower adherence rates among individuals' with chronic conditions compared to acute conditions (New England Healthcare Institute 2009). Chronic conditions refer to a broad range of complex and multiple cause health conditions across the spectrum of illness; they are generally long-term and persistent and often lead to gradual deterioration of health and loss of independence. They are the most common and leading cause of premature mortality (Australian Government Department of Health 2017). With changing lifestyles and ageing populations, chronic conditions have become increasingly common and now cause majority of the burden of health illness (Australian Institute of Health and Welfare 2014).

Individual disease state studies highlight the opportunity cost associated with addressing the non-adherence problem. The three most prevalent chronic conditions- diabetes, hypertension and dyslipidaemia provide the greatest prospect for cost avoidance. For every extra dollar spent on medications for adherent patients

a cost saving between US$3-13 in avoidable emergency department visits and inpatient hospitalisations is achievable (Roebuck et al. 2011). Among diabetes patients, those with low levels of adherence have double the health care costs compared with adherent patients (US$16,498 vs. $8,886) (Sokol et al. 2005). Annual per person savings attributable to adherence levels greater than 80% amounted to US$7,823 for congestive heart failure, US$3,908 for hypertension, US$3,756 for diabetes and US$1,258 for dyslipidaemia (Roebuck et al. 2011). Additionally, in COPD patients who were non-adherent had higher health care spending than those who were adherent (US$2,185) and those who discontinued therapy had even higher Medicare spending (US$3,764) (Simoni-Wastila et al. 2012). Non-adherent depressive patients were more likely to cease treatment early exhibiting greater mean ER visits, hospital visits and total number of hospital days compared with adherent patients, resulting in higher mean medical charges than non-adherent patients (US$10,692 vs. $9,411) (White 2003). Thus, highlighting the lost opportunity and contributing to the inefficiencies across health care systems.

Costs of non-adherence go beyond simple measurable components, including elements such as reputational damage and frustration of drug and therapy discovery processes thus hindering the capacity to precisely quantify the economic impact of medication non-adherence (Centre for Business Innovation Medical Adherence Consortium 2018). Moreover, many estimates do not include avoidable costs of long term care, diagnostic testing, broader societal costs of increased disability, reduced productivity and sick leave suggesting that the proposed economic impact of medication non-adherence may be severely underestimated (Khan & Socha-Dietrich 2018).

Substantial variations in the reported economic impact medication non-adherence has on populations, health care systems and governments exist in the literature. Majority of studies have focused on single disease state investigations to estimate the cost of non-adherence. Additionally, the methodologies employed to determine the economic impact contrast substantially. Further investigation is required to streamline the methodological approaches used to assess the economic impact of

medication non-adherence in order to determine the true economic magnitude of the problem.

Implications of medication non-adherence moving forward

Lack of medication non-adherence leads to unnecessary disease progression, disease complications, reduced functional abilities, lower quality of life and premature death with the end result of overall increasing health care expenditures. The current unacceptable levels of non-adherence will continue to be compounded by an ageing society and correlation between ageing and increased chronic disease prevalence. The combined threat of poor adherence and higher rates of multiple chronic conditions requires immediate attention and action (National Council on Patient Information and Education 2013).

Medication non-adherence remains a global problem of striking magnitude, despite the growing body of research examining all aspects of adherence. Moving forward there are a number of areas within the adherence landscape that require further investigation.

1. *What is the true economic magnitude of medication non-adherence?*
2. *How has the economic magnitude of non-adherence been determined?*
3. *What is the economic impact of medication non-adherence in Australia?*

These identified gaps constitute the foundations of the presented thesis.

This page is intentionally left blank

Chapter 3

Economic impact of medication non-adherence by disease groups: a systematic review

Cutler, R.L., Fernandez-Llimos, F., Frommer, M., Benrimoj, S.I. and Garcia-Cardenas, V., 2018. 'Economic impact of medication non-adherence by disease groups: a systematic review'. *BMJ open*, vol. 8, no. 1, p.e016982. http://bmjopen.bmj.com/content/8/1/e016982

This page is intentionally left blank

Abstract

Objective: To determine the economic impact of medication non-adherence across multiple disease groups.

Design: Systematic review.

Evidence Review: A comprehensive literature search was conducted in PubMed and Scopus in September 2017. Studies quantifying the cost of medication non-adherence in relation to economic impact were included. Relevant information was extracted and quality assessed using the Drummond checklist.

Results: Seventy nine individual studies assessing the cost of medication non-adherence across fourteen disease groups were included. Wide scoping cost variations were reported, with lower levels of adherence generally associated with higher total costs. The annual adjusted disease specific economic cost of non-adherence per person ranged from $949-$44,190 (in 2015 US dollars). Costs attributed to "all causes" non-adherence ranged from $5,271 to $52,341. Medication possession ratio was the metric used to calculate patient adherence, with varying cut-off points defining non-adherence. The main indicators used to measure the cost of non-adherence were total cost or total healthcare cost (83% of studies), pharmacy costs (70%), inpatient costs (46%), outpatient costs (50%), emergency department visit costs (27%), medical costs (29%) and hospitalization costs (18%). Drummond quality assessment yielded 10 studies of high quality with all studies performing partial economic evaluations to varying extents.

Conclusion: Medication non-adherence places a significant cost burden on healthcare systems. Current research assessing the economic impact of medication non-adherence is limited and of varying quality, failing to provide adaptable data to influence health policy. The correlation between increased non-adherence and higher disease prevalence should be used to inform policy makers to help circumvent avoidable costs to the healthcare system. Differences in methods make the comparison amongst studies challenging and an accurate estimation of true magnitude of the cost impossible. Standardisation of the metric measures used to

estimate medication non-adherence and development of a streamlined approach to quantify costs is required.

Registration: CRD42015027338

Strengths and Limitations of this study:

- This is a novel attempt to use existing studies to broaden the scope of knowledge associated with the economic impact of medication non-adherence via quantifying the cost of medication non-adherence across different disease groups.
- A large comprehensive review – 2,768 citations identified, 79 studies included.
- Inability to perform a meaningful meta-analysis- insufficient statistical data and considerable heterogeneity according to outcome/indicators.
- Robust application of adapted Drummond checklist to evaluate the quality of economic evaluations.

Introduction

Nearly half of all adults and approximately 8% of children (aged 5-17 years) worldwide have a chronic condition[1]. This, together with ageing populations, is increasing the demand on healthcare resources[2]. Medications represent a cost-effective treatment modality[3], but with estimates of 50% non-adherence to long term therapy for chronic illnesses[4], intentional and unintentional medication non-adherence signifies a prevalent and persistent healthcare problem. Medication adherence is defined as 'the extent to which the patients' behavior matches agreed recommendations from the prescriber', emphasising the importance on the patients' decisions and highlighting the modifiable aspect of non-adherence[5].

Given the proportion of the population who do not adhere to their medication efforts to improve medication adherence represent an opportunity to enhance health outcomes and health system efficiency. Annual costings of medication non-adherence range from US$100-$290 billion[6] in the United States, €1.25 billion[7] in Europe and approximately A$7 billion[8 9] in Australia. Additionally ten percent of hospitalisations in older adults are attributed to medication non-adherence [10 11] with the typical non-adherent patient requiring three extra medical visits per year leading to $2000 increased treatment costs per annum[12]. In diabetes the estimated costs savings associated with improving medication non-adherence range from $661 million to $1.16 billion [13]. Non-adherence is thus a critical clinical and economic problem[4].

Healthcare reformers and payers have repeatedly relied on cost effectiveness analysis to help healthcare systems deal with the rising costs of care[14]. However there is still a budgetary problem that needs to be considered, especially given the widespread policy debate over how to best bend the healthcare cost curve downward[15] and the proportion of healthcare budgets spent on prescription medication[16]. Quantifying the cost of medication non-adherence will help demonstrate the causal effect between medication non-adherence, increased disease prevalence and healthcare resource use. Justification of the associated financial benefit may incentivise health policy discussion about the value of

medication adherence and promote the adoption of medication adherence intervention programs [15].

The objective of this systematic review was, first, to determine the economic impact of medication non-adherence across multiple disease groups, and second, to review and critically appraise the literature to identify the main methodological issues that may explain the differences among reports in the cost calculation and classification of non-adherence.

Methods

The protocol for this systematic review was registered on the PROSPERO: International prospective register of systematic reviews database (CRD42015027338) and can be accessed at http://www.crd.york.ac.uk/PROSPERO/display_record.asp?ID=CRD42015027338. The systematic review was undertaken in accordance with PRISMA guidelines[17].

Search strategy and selection criteria

A literature search was conducted in September 2017. Studies reporting the cost of medication non-adherence for any disease state were included. Searches were conducted in PubMed and Scopus. Neither publication date nor language restriction filters were used. The search used in PubMed was: (non-adherence[TIAB]) OR ("Patient Compliance"[MH] AND ("Drug Therapy"[MH]) OR medication[TIAB])) OR "Medication adherence"[MH] AND (costs[TIAB] OR "Costs and Cost Analysis"[MH] OR burden[TIAB]). This was adapted for other databases (eTable 1). Duplicate records were removed.

To identify relevant articles, an initial title and abstract screening was conducted by the lead reviewer (RLC) to identify studies appropriate to the study question. This process was over-inclusive. In the second phase appraisal, potentially relevant full text papers were read and excluded based on the following criteria: i) papers not reporting the cost of medication non-adherence as a monetary value, ii) systematic

reviews, iii) papers not reporting a baseline cost of medication non-adherence prior to the provision of an intervention and iv) papers not reporting original data. Any uncertainty was discussed amongst two adherence experts (RLC and VGC) and resolved via consensus.

Extracted information

A data extraction form was developed based on the Cochrane Handbook for systematic reviews[18] and piloted on a sample of included studies. The extracted information included the source (study identification, citation and title), eligibility (confirmation of inclusion criteria), objective, methods (study design, study groups, year data extracted, follow up period, comparison, adherence measure, adherence data source and adherence definition), population (sample size, setting, country, disease state/drug studied, inclusion/exclusion criteria and perspective), impact/outcome indicators (indicators measured, indicator data source, indicator definitions and characteristics of the method of assessment), results (costs reported, standardised costs, type of costs, non-cost findings, sub-group analysis and statistical significance), conclusions and miscellaneous (funding source, references to other relevant studies, limitations and reviewers comments).

Costs were defined as any indicator associated with medication non-adherence that was quantified with a monetary value in the original study. This included direct costs (those costs borne by the healthcare system, community and patients' families in addressing the illness), indirect costs (mainly productivity losses to society caused by the health problem or disease) and avoidable costs (those costs incurred for patients suffering complications, resulting from suboptimal medicines use, and patients with the same disease who experienced no complications). The indicators were grouped for analysis based on the original studies classification of the cost. All costs were converted to US dollars (2015 values) using the Cochrane Economics Methods Group - Evidence for Policy and Practice Information and Coordinating -Centre Cost Converter tool [19], allowing meaningful comparisons between non-adherence cost data. This online tool uses a two stage computation process to adjust estimates of costs for currency and/or price year using a Gross Domestic Product deflator index

and Purchasing Power Parities for Gross Domestic Product[19]. The PPP values given by the International Monetary Fund were chosen. If details of the original price year could not be ascertained from a study the mid-point year of the study period was used for calculations. The mean cost was calculated and reported where studies separated out costs for different confounding factors within the one outcome measure in a disease state. Annual costs were extrapolated from the original study data if results were not presented in this manner.

The definition of medication non-adherence was derived from the included studies; with non-adherence referring to differing degrees of adherence based on the studies metric of estimation. Multiple non-adherence costs from individual studies may have been included where further sub-classification of non-adherence levels was defined. The analysis assessed non-adherence costs within disease groups, with disease group and cost classification derived from the study. Total healthcare costs included direct costs to the healthcare system while total costs incorporated direct and indirect costs.

Quality criteria and economic evaluation classification

Economic evaluation requires a comparison of two or more alternative courses of action, while considering both the inputs and outputs associated with each [20]. All studies were classified in accordance with Drummond's distinguishing characteristics of healthcare evaluations as either partial evaluations (outcome description, cost description, cost-outcome description, efficacy or effectiveness evaluation, cost analysis) or full economic evaluations (cost benefit analysis, cost utility analysis, cost effectiveness analysis, cost minimization analysis) by team consensus (RLC and VGC).

The Drummond checklist [21] for economic evaluation was used to assess the quality of studies. The original checklist was modified to remove inapplicable items (4, 5, 12, 14, 15, 30 and 31) as no full economic evaluation met all inclusion criteria. A score of 1 was assigned if the study included the required item and zero if it did not with a maximum potential score of 28. The study was classified as high quality if at least

75% of Drummond's criteria were satisfied, medium quality if 51-74% were satisfied and low quality if 50% of the criteria or less were satisfied.

Meta-Analysis

Outcome/indicator costs were independently extracted using predesigned data extraction forms (total healthcare costs, total costs, inpatient costs, outpatient costs, pharmacy costs, medical costs, emergency department costs, and hospitalisation costs) for the purpose of integrating the findings on the cost of medication non-adherence to pool data and increase the power of analysis.

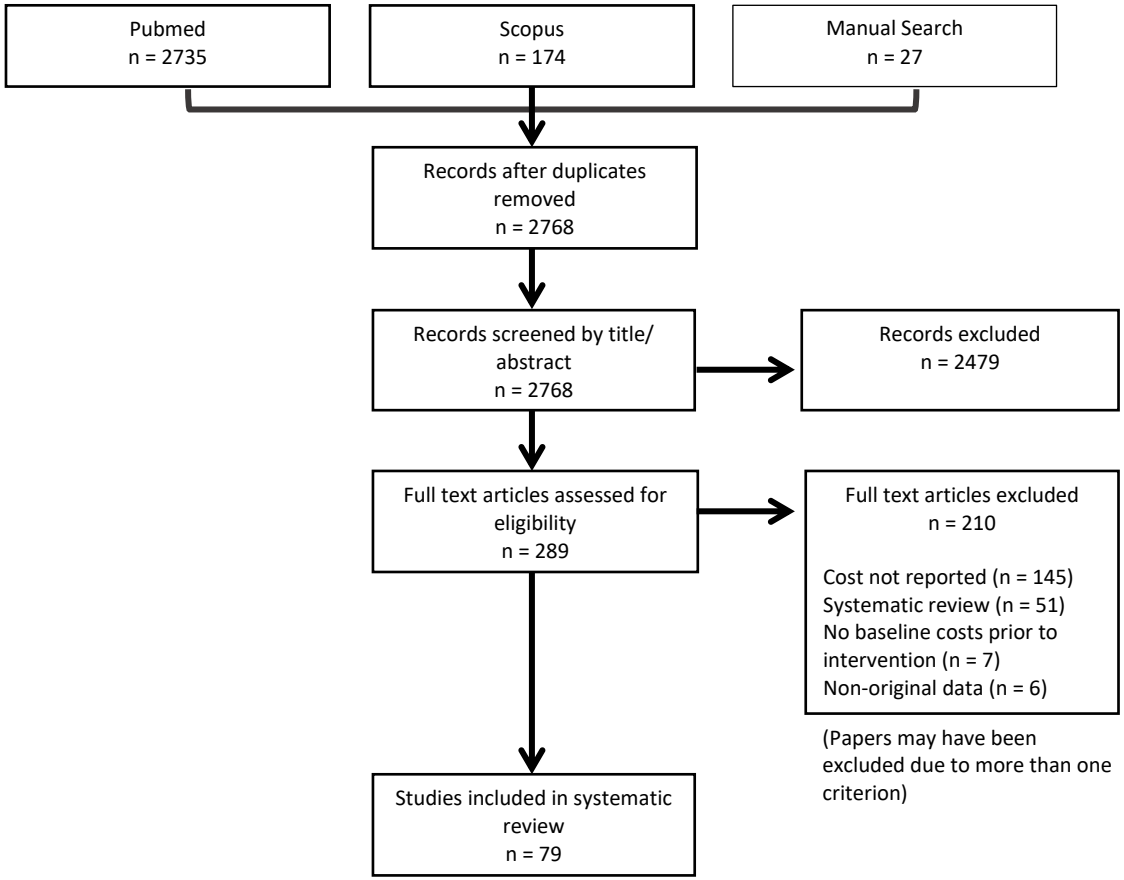

Figure 1: Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) flow diagram. The PRISMA diagram details the search and selection process applied during the overview. The search yielded a total of 2768 citations. Studies were selected based on the inclusion criteria; studies reporting the cost of medication non-adherence using original cost data. Intervention studies were required to report baseline data. Seventy nine original studies met the inclusion criteria.

Results

Study Selection

Search strategies retrieved 2768 potential articles after duplicates were removed. Two hundred and eighty nine articles were selected for full text review. Seventy nine studies were included in the review (Figure 1). Numerous other papers do discuss non-adherence costs however addressed tangential issues or did not present primary relevant data. Many studies failed to report the monetary value of medication non-adherence associated with a range of cost estimate indicators.

Characteristics of individual studies

Sixty-six studies (83%) were conducted in the Unites States[10 22-86], four in Europe[87-90], four in Asia[91-94], three in Canada[95-97], one in the United Kingdom[98] and one across multiple countries throughout Europe and the United Kingdom[99]. Publication years ranged from 1997 to 2017; in accordance with the Cochrane Handbook for Systematic Reviews no date restriction filters were used[18] with earlier studies following the same pattern of association between medication non-adherence and increasing healthcare costs. Individual studies reported a large variety of costs, calculated by varying means. Forty-four studies (56%) reported unadjusted costs[22 26 27 30 32-36 38-43 46 48-50 52-56 58 63-68 72 75 81-83 86 88-90 92-94 99], 21 (26%) adjusted costs[10 23-25 29 31 44 51 57 59-61 71 73 76-78 84 85 87 91], 11 a combination of adjusted and unadjusted[28 37 45 47 62 69 70 74 79 80 97], two unadjusted and predicted[95 96] and one predicted costs[98]. The method of determining non-adherence ranged significantly between studies with majority of papers using pharmacy and/or healthcare claims data (97%)[10 22-29 31-52 55 57 59-88 92-97]. Some studies used a combination of surveys or questionnaires, observational assessment, previous study data and disease state specific recommended guidelines. Medication possession ratio (MPR) was the most used method to calculate patient non-adherence with 51 studies (63%) reporting non-adherence based on this measure[24 25 28 29 32-36 40-44 46 47 49-51 55 57 58 60-64 67-78 81 82 86-88 92-97]; however, the cut-off points to define medication

non-adherence differed with some studies classifying non-adherence as less than 80% medication possession and others through sub-classification of percentage ranges (e.g., 0-20%, 20-40%, 40-60%, 60-80%, 80-100%). The proportion of days covered (PDC) was the next most common measure of non-adherence (11%)[31 37 45 48 52 79 80 83-85], with all other studies using an array of measures including self-report[98], urine testing[56], observational assessment[99], time to discontinuation[59], cumulative possession ratio[23], disease specific medication management guidelines[66 89], Morisky 4-Item scale[53], medication gaps[38], prescription refill rates[22 27] and medication supplies[10]. The main characteristics of the included studies are summarised in online supplementary eTable 2.

Quality assessment and classification of economic evaluations

The quality assessment of economic evaluations yielded 10 studies of high[33 37 40 50 51 57 71 75 87 93], 59 of medium[10 22-26 28-32 34-36 38 39 41-48 53-56 58 59 61-64 66 67 69 70 72 73 76-82 84-86 88 89 91 94-99] and ten of low quality[27 49 60 65 68 74 83 90 92]. Scores ranged from 26.1% to 87.5% (mean 62.63%). Only one study identified the form of economic evaluation used and justified it in relation to the questions that were being addressed [71]. The item 'the choice of discount rate is stated and justified' was applicable only to studies covering a time period of more than one year; all studies that cover more than one year failed to identify or explain why costs had not been discounted. Details of the analysis and interpretation of results were lacking in the majority of studies resulting in medium or low quality scores.

Through use of Drummond's distinguishing characteristics of healthcare evaluations criteria[20] it is apparent that no full economic evaluation was conducted in any of the included studies. All studies performed partial economic evaluations of varying extents. The classification of economic evaluations resulted in 59 cost description studies (74% of those included), 15 cost outcome descriptions and five cost analysis studies (online supplementary eTable 2).

Medication non-adherence and costs

The cost analysis of studies (figure 2 and figure 3) reported annual medication non-adherence costs incurred by the patient per year. The adjusted total cost of non-adherence across all disease groups ranged from $949 to $52,341, while the unadjusted total cost ranged from $669 to $162,699. Figure 2 and figure 3 highlight the minimum, maximum and interquartile range of annual costs incurred by patients across disease groups where three or more studies were included for review. All cause costs encompass non-adherence costs incurred in mixed disease state studies, taking into account other confounding factors such as comorbidities.

Many different indicators were used to estimate medication non-adherence costs with no clear definition of what was incorporated in each cost component. The composition of included costs to estimate total cost or total healthcare cost varied significantly between studies, thus indicators were grouped for analysis based on the original studies classification of the cost. The main ones were total cost or total healthcare cost (83%), pharmacy costs (70%), outpatient costs (50%), inpatient costs (46%), medical costs (29%), emergency department costs (27%), and hospitalisation costs (18%) (online supplementary eTable 2). Avoidable costs (e.g., unnecessary hospitalisations, physician office visits and healthcare resource use) were not well defined with majority of studies failing to quantify these costs.

Lower levels of adherence across all measures (*e.g.,* MPR, PDC) were generally associated with higher total costs. From those that reported total or total healthcare costs, 39 studies (49%) reported non-adherence costs to be greater than adherence costs[24 25 27 29 31 32 34 37-39 42 43 47 49 50 55 56 58 61-65 70-78 84 86 87 96-99] and 11 studies (15%) reported non-adherence costs to be less than adherence costs[23 26 36 44 59 63 66 81 92 94 95]. Four reported fluctuating findings based on varying non-adherence cost subcategories[33 48 67 93] and two studies reported conflicting findings between adjusted and unadjusted costs [79 80]. Higher all cause total non-adherence costs and lower disease group specific non-adherence costs were reported in four studies[41 68 85 91], whereas Hansen et al[47] reported all

cause total non-adherence costs to be lower ($18540 vs. $52302) but disease group specific non-adherence total costs to be higher ($3,879 vs. $2,954).

The association between non-adherence and cost was determined through use of a variety of scaling systems. The most used methods were MPR and PDC. These measures could then further be subcategorised based on the percentage of adherence/non-adherence. The 80-100% category was classified as the most adherent group across both scales, with the most common definition of non-adherence being <80% MPR or PDC.

Cost of medication non-adherence via disease group

Cancer exhibited more than double the cost variation of all other disease groups ($114,101). Osteoporosis ($43,240 vs. $42,734), diabetes mellitus ($7,077 vs. $6,808) and mental health ($16,110 vs. $23,408) cost variations were similar between adjusted and unadjusted costs while cardiovascular disease adjusted costs were more than double unadjusted costs ($16,124 vs. $6,943). Inpatient costs represented the greatest proportion of costs contributing to total costs and/or total healthcare costs for cardiovascular disease, diabetes mellitus, osteoporosis, mental health, epilepsy and parkinson's disease. HIV/AIDS, cancer and gastrointestinal disease groups highest proportion of costs were attributed to pharmacy costs while outpatient costs were greatest in musculoskeletal conditions. Direct costs had greater economic bearing than indirect costs across all disease groups. Cost comparisons across disease groups are summarised in online supplementary eTable 3.

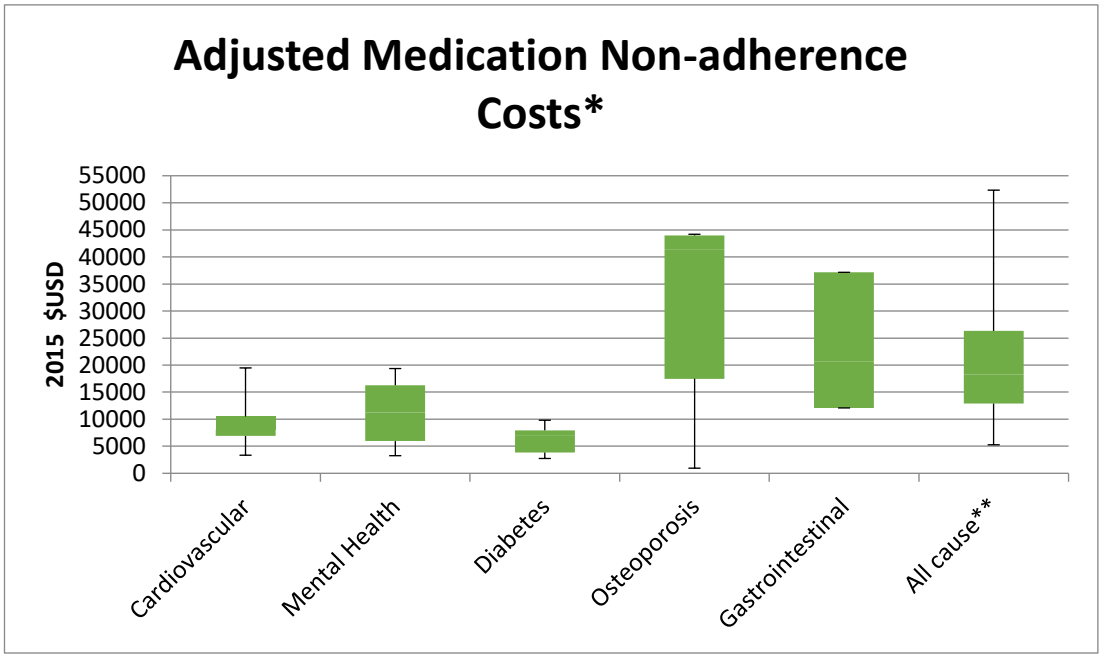

Figure 2: Annual adjusted medication non-adherence costs per patient per year. Encompasses the minimum, maximum and interquartile range of adjusted annual costs incurred by patients across disease groups where three or more studies were included for review. Gastrointestinal only included three studies limiting the range of costs. All cause costs encompass non-adherence costs incurred in mixed disease state studies, taking into account other confounding factors such as comorbidities.

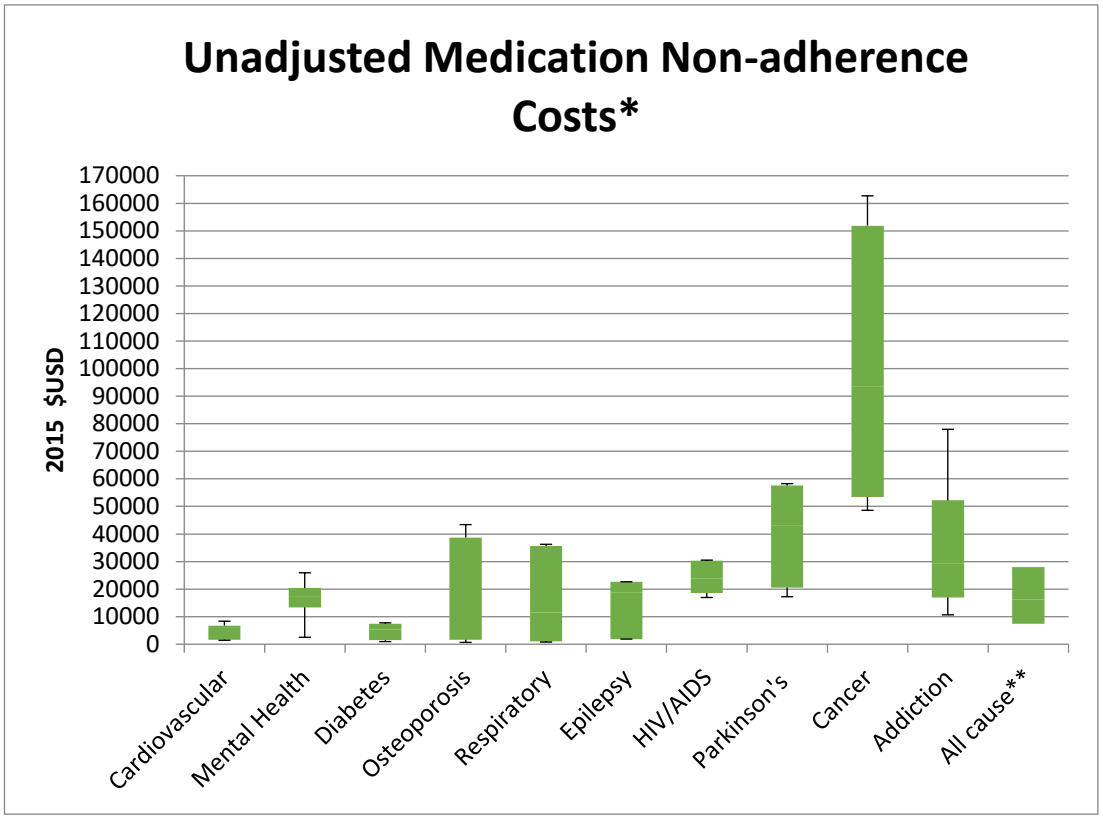

Figure 3: Annual unadjusted medication non-adherence costs per patient per year. Encompasses the minimum, maximum and interquartile range of unadjusted annual costs incurred by patients across disease groups where three or more studies were included for review. Epilepsy and addiction only included three studies limiting the range of costs. All cause costs encompass non-adherence costs incurred in mixed disease state studies, taking into account other confounding factors such as comorbidities.

1. Cardiovascular Disease

Twelve studies measured the economic impact of medication non-adherence in cardiovascular disease [10 24 31 61 62 65 67 76 81 93 95 96]. Six studies reported adjusted costs [10 24 31 61 62 76] with annual costs being extrapolated for two of these[31 61]. Total healthcare costs and/or total costs were assessed in all of the studies with the major indicators measured including pharmacy costs[10 31 61 62 76], medical costs[10 24 31 61 76] and outpatient costs[31 62]. The annual economic cost of non-adherence ranged from $3,347 to $19,472. Sokol et al[10] evaluated the economic impact of medication non-adherence across three cardiovascular conditions; hypertension, hypercholesterolemia and chronic heart failure. For all three cardiovascular conditions examined, pharmacy costs were higher for the 80-100% adherent group than for the less adherent groups. Total costs and medical costs were lower for the adherent groups of hypertension and hypercholesterolemia patients. However, for chronic heart failure patients, total costs and medical costs were lower for the 1-19% and 20-39% adherent groups than for the 80-100% adherent groups.

Unadjusted costs were measured in six studies with the annual total healthcare costs and/or total costs of non-adherence ranging from $1,433 to $8,377 [65 67 81 93 95 96]. Rizzo et al[65] reported cost findings through subgroup analysis of five conditions. For all conditions the total healthcare costs were higher for non-adherent groups compared with adherent. While Zhao et al[81], categorised participants into adherence subgroups; finding that total healthcare costs were lower for the non-adherent population. The remaining studies used five key indicators to determine the economic impact: inpatient costs[67 93], outpatient costs[67 93], pharmacy costs[67 95 96], medical costs[95 96] and hospitalisation costs[95 96].

2. Mental Health

The analyses used to report the economic impact of medication non-adherence in mental health varied widely. Also, 11 of 14 studies provided a total non-adherence cost estimate in mental health[23 25 27 52 59 66 73 82 91 98 99], with annual cost

data being extrapolated for 4 of these[27 66 82 99]. Six studies used adjusted costs, finding that the total annual cost of non-adherence per patient ranged from $3,252 to $19,363 [23 25 59 60 73 91]. Bagalman et al[25] focused primarily on the indirect costs associated with non-adherence – short-term disability, workers compensation and paid time off costs while Robertson et al[82] highlighted the association between medication non-adherence and incarceration, with findings indicating incarceration and arrest costs are higher for worsening degrees of non-adherence. All other studies addressed direct costs. The main indicators used to measure the direct economic impact of medication non-adherence were pharmacy costs[23 39 52 59 60 66 73 99], inpatient costs[39 60 66 98 99], outpatient costs[23 39 59 66 99] and hospitalisation costs[22 23 59 99].

The total unadjusted cost for medication non-adherence ranged from $2,512 to $25,920 as reported in four studies [52 66 82 99]. Becker et al[27] used a subgroup analysis to classify patients based on their adherence level. For every 25% decrement in the rate of adherence (75-100%, 50-74%, 25-49%, <25%), non-adherence total costs increased. The negligible adherence group (<25%) incurred annual costs that were $3,018 more than those of the maximal adherence group (75-100%).

Knapp et al[98] outlined the predicted cost of non-adherence with reference to relative impact and other factors associated with resource use and costs in patients with schizophrenia. Total costs ($116,434) were substantially higher than the other two indicators, which were inpatient costs ($13,577) and external services costs ($3,241).

3. Diabetes mellitus:

Eleven studies reported a cost measurement of the impact of medication non-adherence with reference to the health system and the individual[40 45 47 51 74 76 83 84 92 94 97]. One study estimated that the total US cost attributable to non-adherence in diabetes was slightly >$5 billion[51]. Five studies reported the adjusted total healthcare costs and/or total costs with annual costs per patient ranging from $2,741 to $9,819 [47 51 74 76 84 97]. One study reported total costs in relation to

subgroup analysis based on MPR level[74], and another reported total healthcare costs through subgroup analysis of commercially insured and Medicare supplemental patients[76]. Curtis et al[84] used a diabetic population to report all cause costs, with non-adherence costs being higher than adherence costs across all outcome indicators bar pharmacy costs.

A further four studies reported unadjusted cost findings[40 83 92 94] with an additional four studies reporting unadjusted costs in in combination with adjusted values[45 47 74 97]. Unadjusted total healthcare costs and/or total costs ranged from $1,142 to $7,951. Extrapolated annual costs were determined for two studies based on cost data presented [40 94].

The most prominent indicators used to determine costs were pharmacy costs[40 45 47 74 76 83 84 97], outpatient costs[40 47 76 84 94 97], inpatient costs[47 76 97] and hospitalisation costs[51 92 94]. All studies assessed the direct costs associated with medication non-adherence. One study evaluated the relationship between non-adherence and short term disability costs in addition to assessing direct costs[45].

4. Osteoporosis:

The cost of medication non-adherence in relation to osteoporosis was predominately examined through analysis of the direct costs associated with non-adherence using total healthcare costs and/or total costs, inpatient costs, outpatient costs, pharmacy costs and emergency department costs. Two studies further assessed the economic impact of non-adherence through evaluation of fracture related costs [48 88]. Also, 4 out of 11 studies reported the adjusted cost of medication non-adherence in addition to reporting unadjusted costs [28 79 80 87]. Three studies further classified non-adherence through subgroup analysis, with Briesacher et al[28] using MPR 20% interval increases and the two studies conducted by Zhao et al[79 80] using PDC, with ≥80% classified as high adherence, 50-79% medium adherence and <50% low adherence . In the studies conducted by Zhao et al[79 80], total healthcare costs were highest for the medium adherence group ($41,402 and $44,190) followed by the highest adherence group ($37,553 and $43,863), and lowest for the low adherence

group ($34,019 and $43,771). These annual costs were extrapolated from study data. In contrast, Briesacher et al[28] modelled the subgroup analyses against the lowest adherence group (<20% MPR), finding that costs decreased as adherence increased.

Overall, the unadjusted total healthcare costs and/or total costs of non-adherence ranged from $669 to $43,404. Studies that further classified patients based on subgroups had the wider cost ranges. In the three studies that reported the lowest level of non-adherence to be PDC <50%, the cost of this category ranged from $16,938 to $43,404 [48 79 80].

One study examined only the medical costs of non-adherence through MPR subgroup analysis in commercial and Medicare supplemental populations. The findings were that, for all levels of non-adherence, costs of non-adherence were higher for Medicare supplemental patients [46].

5. **Respiratory Disease:**

The majority of studies reported unadjusted cost of medication non-adherence, with significant variation in the method of adherence classification[36 38 53 64 89]. Two studies used MPR[36 64], one the Morisky 4-Item scale[53], one the Global Initiative for Chronic Obstructive Lung Disease (GOLD) 2007 Guidelines[89] and one a 37 day gap in claims data[38]. Joshi et al[53] reported on the indirect costs of medication non-adherence through consideration of losses in total productivity costs, absenteeism costs and presenteeism costs, while all remaining studies examined direct costs. Delea et al[36] reported a direct relationship between decreases in medication non-adherence level and total costs, whereas Quittner et al[64] reported an inverse relationship between decreases in medication non-adherence level and total healthcare cost. The total expenses associated with the lowest subgroup of adherence across all measures ranged from $804 to $36,259. In contrast Davis et al[85] used adjusted costs across four subclassifications of PDC adherence ranges to demonstrate that non-adherence costs were lower than adherence costs in all costing outcomes reported except hospitalisation costs.

6. **Gastrointestinal Disease:**

Three of five studies reported the adjusted annual cost of medication non-adherence per patient using the MPR method [44 57 71]. Of these, two reported the total cost ($12,085 and $37,151)[44 71] with the main contributors to the overall total cost being inpatient costs (22% and 37%), outpatient costs (57% and 17%) and pharmacy costs (20% and 45%).

The remaining two studies used infusion rates to assess non-adherence with neither reporting the total cost nor total healthcare costs[30 54]. Carter et al[30] reported hospitalisation costs to be $42,854 while Kane et al[54] reported a significantly lower cost at $5,566 in addition to other direct cost contributors.

7. Epilepsy:

Three studies reported the economic impact of medication non-adherence in epilepsy. All reported unadjusted costs using an MPR cut off of <80%[35 42 43]. The main economic indicators used to assess total costs were inpatient costs ($2,289 to $6,874), emergency department visit costs ($331 to $669) and pharmacy costs ($442 to $1,067). Davis et al[35] modelled the costs of the non-adherent group against the adherent group. The annual costs reported by Faught et al[43] were extrapolated from original cost data. The total cost of non-adherence in epilepsy ranged from $1,866 to $22,673.

8. HIV/AIDS:

The economic impact of medication non-adherence for HIV and AIDS patients reported amongst all three studies was similar [26 32 63]. Two of the three studies examined the costs only for HIV[26 32], while Pruitt et al[63] assessed the cost in AIDS as well as HIV. The total unadjusted costs for non-adherent HIV patients ranged from $16,957 to $30,068 with one study further categorising patients with HIV as having either a high viral load or low viral load[26]. The total cost of non-adherence in AIDS was $30,523[63]. All studies used comparable indicators (total cost, inpatient cost, outpatient cost, pharmacy cost) to determine the cost of non-adherence.

9. Parkinson's Disease:

The direct costs associated with Parkinson's disease were assessed in all three studies. The unadjusted total cost ranged from $10,988 to $52,023 [34 37 72]. Wei et al[72] further subgrouped patients into MPR adherence percentage categories, and found that costs increased in all economic indicators (inpatient costs and outpatient costs) as adherence decreased, except for pharmacy costs which decreased with non-adherence. One study additionally reported the adjusted cost, estimating that $10,290 could be attributed to medication non-adherence annually[37].

10. Musculoskeletal Conditions:

Differing subgroup analyses was used to measure the impact of medication non-adherence on the annual cost incurred by patients. One study assessed both the direct and indirect costs of non-adherence[50], one assessed only the medical costs[69] and one examined the direct costs in commercial and Medicare supplemental patient populations[78]. Zhao et al[78] reported the adjusted annual cost in the commercial population to be $22,609, and in the Medicare supplemental group, $28,126. Ivanova et al[50] reported only unadjusted costs and the annual total cost of $3,408. This figure was extrapolated from study data provided. The main indicators used to evaluate the economic impact of non-adherence were inpatient costs, outpatient costs, pharmacy costs and medical costs. Outpatient costs made the largest contribution to the overall total.

11. Cancer:

Two studies evaluated the effects of medication non-adherence in cancer[33 75]. One study reported total annual costs of $119,416[75], while the other gave a subgroup analysis based on classified adherence levels[33]. In general, the lowest two adherence subgroups (<50% and 50-90%) reported the highest total healthcare costs ($162,699 and $67,838). This trend followed for inpatient costs, outpatient costs and other costs, but the reverse relationship was found for pharmacy costs.

12. Addiction:

The adjusted annual total healthcare cost of medication non-adherence was reported as $53,504[56] while the unadjusted cost ranged from $16,996 to $52,213 [56 70 86]. Leider et al[56] reported the main contributors to this cost to be outpatient costs ($10,829) and pharmacy costs ($8,855), whereas Tkacz et al[70] and Ruetsch et al[86]reported them to be inpatient costs ($28,407 and $5,808) and outpatient costs ($15,460 and $5,743).

13. Metabolic conditions other than diabetes mellitus:

One study measured the influence of medication non-adherence on direct healthcare costs in metabolic conditions, reporting an unadjusted attributable total cost of $138,525[55]. The economic indicators used to derive this cost were inpatient costs ($16,192), outpatient costs ($111,100), emergency department visit costs ($801) and pharmacy costs ($3,538).

14. Blood conditions:

Candrilli et al[29] reported cost findings on the relationship between non-adherence and healthcare costs, giving an adjusted total cost estimate of $13,458 for non-adherence classified as MPR <80%.

15. All causes:

In addition to disease-specific studies of the economic impact of medication non-adherence, 28 studies reported the all-causes costs, encompassing cost drivers such as comorbidities. In seven of these studies, annual costs were extrapolated from the original data[47 50 61 64 66 85 99]. Eleven studies reported on economic indicators without giving total cost or total healthcare cost[22 45 46 54 55 57 60 81 83 90 99], and one study reported on costs per episode of non-adherence[90] .

The adjusted cost of medication non-adherence was reported in 14 studies with an estimated range of $5,271 to $52,341 [10 29 31 57 59-61 71 76 77 84 85 87 91]. Sokol et al[10] reported the all-cause cost of non-adherence through subgroup analysis of

disease states and MPR levels, while Pittman et al[61] reported only using MPR level breakdown.

Fifteen studies reported the unadjusted economic impact of medication non-adherence with an estimated range of $1,037 to $53,793 [22 41 46 50 54 55 58 64-66 68 81 83 90 99]. A further four studies reported adjusted and unadjusted costs[37 45 47 97]. The most frequent indicators used to measure the economic impact were total healthcare costs and/or total costs (71%), pharmacy costs (75%), inpatient costs (46%), outpatient costs (46%), medical costs (28%) and emergency department visit costs (25%).

Meta-Analysis

Statistical analysis was attempted to collate the large collection of results from individual studies for the purpose of integrating the findings on the cost of medication non-adherence. However, the criterion for a meta-analysis could not be met due to the heterogeneity in study design and lack of required statistical parameters in particular standard deviation[100]. Combining studies that differ substantially in design and other factors would have yielded meaningless summary results.

Discussion

This systemic review broadens the scope of knowledge associated with the economic impact of medication non-adherence across different disease groups while building upon previous reviews where greater focus was on targeting overall risk factors or conceptual issues associated with medication non-adherence. Medication non-adherence was generally associated with higher healthcare costs. A large variety of outcomes were used to measure the economic impact including total cost or total healthcare cost, pharmacy costs, inpatient costs, outpatient costs, emergency department costs, medical costs and hospitalisation costs.

The costs reported reflect the annual economic impact to the health system per patient. None of the studies estimated broader economic implications such as avoidable costs arising from higher disease prevalence with studies failing to quantify avoidable costs separately to direct and indirect costs possibly due to coding restraints in healthcare claims databases. The majority of studies took the patient or healthcare provider perspective, estimating additional costs associated with non-adherence when compared with adherence. Current literature identifies and quantifies key disease groups that contribute to the economic burden of non-adherence, but no research has attempted to synthesise costs across disease states within major healthcare systems. Comparisons across disease groups would benefit the development of health planning and policy yet prove problematic to interpret due to the varying scope of their inclusion (e.g., mental health vs. Parkinsons disease). Similarly, there is substantial variation in the differential cost of adherence amongst disease groups with certain diseases requiring greater cost inputs (e.g., cancer and supportive care costs). Further exploration of non-adherence behaviour and associated costs is required to adequately quantify the overall cost of non-adherence to healthcare systems as the available data are subject to considerable uncertainty. Given the complexity of medication non-adherence in terms of varying study designs, methods of estimation and adherence definitions there is a limitation as to the ability to truly estimate costs attributed to non-adherence until further streamlined processes are defined.

Significant differences existed in the range of costs reported within and amongst disease groups. No consistent approach to the estimation of costs or levels of adherence has been established. Many different cost indicators were used, with few studies defining exactly what that cost category incorporated, so it is not surprising that cost estimates spanned wide ranges. Prioritisation of healthcare interventions to address medication non-adherence is required to address the varying economic impact across disease groups. Determining the range of costs associated with medication non-adherence facilitates the extrapolation of annual national cost

estimates attributable to medication non-adherence thus enabling greater planning in terms of health policy to help counteract increasing avoidable costs.

The economic, clinical and humanistic consequences of medication non-adherence will continue to grow as the burden of chronic diseases grows worldwide. Evolution of health systems must occur to adequately address the determinants of adherence through use of effective health interventions. Haynes et al [101] highlights that "increasing the effectiveness of adherence interventions may have a far greater impact on the health of the population than any improvement in specific medical treatments". Improving medication adherence provides an opportunity for major cost savings to healthcare systems. Predictions of population health outcomes through use of treatment efficacy data needs to be used in conjunction with adherence rates to inform planning and project evaluation[4]. The correlation between increased non-adherence and higher disease prevalence should be used to inform policy makers to help circumvent avoidable costs to the healthcare system.

The metric of adherence estimation varied substantially within and across disease groups; likely affecting the comparisons between studies. However, Hess et al [102], who compared six key adherence measures on the same study participants, found that the measures produced similar adherence values for all participants, although PDC and continuous measure of medication gaps produced slightly lower values. While this highlights the comparability of the measures of medication non-adherence, it further justifies the need to agree on consistent methods for estimating non-adherence through use of pharmacy claims data.

MPR was the most commonly used measure to estimate medication non-adherence. MPR was used in 63% of studies, followed by PDC, which was used in 11%. These percentages were consistent with those found recently by Sattler et al [103]. Even though the measures of medication non-adherence may be comparable, the definition of MPR and the cut-off points to define non-adherence differed significantly. Dragomir et al[95] defined MPR as the total days' supply of medication dispensed in the period, divided by the follow up period, with the assumption of 100% adherence during hospitalisation; Wu et al[76] removed the number of

hospitalised days from the calculation; and Pittman et al[61] calculated the total number of days between the dates of the last filling of a prescription in the first six months in a given year and the first filling of a prescription in the 365 days before the last filling. Non-adherence could also be further classified into subcategories within MPR and PDC based on percentages. Thirty studies defined non-adherence as MPR< 80%, and 12 studies categorised non-adherence into varying percentage subgroups. While Karve et al[104] validated the empirical basis for selecting 80% as a reasonable cut-off point based on predicting subsequent hospitalisations in patients across a broad array of chronic diseases, 76 of the 79 studies included in this review examined more than just hospitalisation costs as an indicator metric. Further research is required to identify and standardise non-adherence thresholds using other outcomes such as laboratory, productivity and pharmacy measures.

Within the 79 studies covered, 35 different indicators were used to measure the cost of non-adherence and 19 reporting styles were identified. Because of the resultant heterogeneity, a meta-analysis was impossible. It is imperative that a standardised approach be established to measure and report the economic impact of medication non-adherence. The core outcome set must take into consideration the perspective of the intended audience and the proportion of non-adherence cost that is attributable to each outcome to determine an appropriate model[105]. The critical indicators based on the findings of this review include total costs, pharmacy costs, inpatient costs, outpatient costs, emergency department visit costs, medical costs and hospitalisation costs for analysis based on direct costs. For indirect analysis the core outcomes include short term disability costs, workers compensation costs, paid time off costs, absenteeism costs and productivity costs. We suggest that further analysis of the contribution of each outcome to the overall cost of non-adherence be undertaken to help develop a tool that can be used for future research.

Many studies have examined the relationship between non-adherence and economic outcomes using a cross-sectional analysis[51]. The implications of this are that potentially crucial confounders such as baseline status are ignored. In addition, a cross-sectional analysis may obscure temporality: for example, did greater

adherence result in reduced costs and improved health outcomes, or was the patient healthier initially and more capable of being adherent? A longitudinal design is needed to overcome this limitation.

Economic evaluations inform decisions on how to best make use of scarce societal health resources through offering an organised consideration of the range of possible alternative courses of action and the evidence of the likely effects of each[20]. While none of the studies taken separately could inform a choice between alternative courses of action, they did provide key evidence for decision makers about costs associated with medication non-adherence. Pharmacy claims data were used by the majority of studies to model cost estimates. Three-quarters of the studies were classified as cost descriptions, providing a cost or outcome overview of the health consequences associated with non-adherence. Ten studies garnered a high quality classification, potentially limiting the overall conclusions that are able to be drawn and emphasised the need for future study design to incorporate elements allowing full economic evaluations to be conducted. Hughes et al[106] highlighted the need for more information on the consequences of non-adherence, so that economic evaluations could reflect the potential long-term effect of this growing problem.

Of the 79 included studies, 66 of the studies were conducted in the United States. Conversion of costs to a common currency (US dollars) facilitated the comparison of studies and disease groups. Comparison of costs between healthcare systems is difficult as no two are the same and as healthcare is generally more expensive in the United States cost estimates may not reflect average values. Thus caution needs to be taken when interpreting results however findings help to represent the significance of the economic burden medication non-adherence plays. Analysis of studies not conducted in the United States support the finding that generally medication non-adherence incurs greater costs for all cost indicator outcomes other than pharmacy costs.

Due to the advances in technology available to record and assess medication non-adherence, the inclusion of studies undertaken in the late 1990s and early 2000s may have affected the comparability of results, despite the fact that these studies met the

inclusion criteria[22 23 65 73 74 98]. The quality of data presents a limitation. Information on disease groups with fewer included studies may be less reliable than information on those with more. However, our findings affirm the pattern of association between non-adherence and increasing healthcare costs.

Conclusion

Medication non-adherence places a significant cost burden on healthcare systems. However, differences in methodological strategies make the comparison amongst studies challenging and reduce the ability for the true economic magnitude of the problem to be expressed in a meaningful manner. Further research is required to develop a streamlined approach to classify patient adherence. An economic model that adequately depicts the current landscape of the non-adherence problem using key economic indicators could help to stratify costs and inform key policy and decision makers. Use of existing data could help to better define costs and provide valuable input into the development of an economic framework to standardise the economic impact of medication non-adherence.

Contributors: RLC, VGC, SB, FFL and MF conceived the paper. RLC and VGC performed all the data extraction and quality assessment. RLC drafted the initial form and all revisions of this manuscript. All other authors (RLC, VGC, SB, FFL, MF) made significant contributions to the manuscript and read and modified the drafts. All authors read and approved the final manuscript.

Funding: This research received no specific grant from any funding agency in the public, commercial or not-for-profit sectors.

Competing interests: None declared

Data sharing statement: All data from systematic review available in paper and supplementary material.

Acknowledgement: RLC research is supported by an Australian Government Research Training Program Scholarship.

References

1. Centres for Disease Control and Prevention. Chronic Disease Prevention and Health Promotion. Available from: http://www.cdc.gov/chronicdisease/overview Accessed June 24, 2016
2. World Health Organisation, National Institute of Aging, National Institute of Health and US Department of Health and Human Services. Global Health and Ageing. Published October 2011. Available from: http://www.who.int/ageing/publications/global_health.pdf Accessed June 24, 2016
3. Congressional Budget Office . Offsetting effects of prescription drug use on medicare's spending for medical services. Congressional Budget Office Report. Published November 2012. Available from: http://www.cbo.gov/sites/default/files/cbofiles/attachments/43741-MedicalOffsets-11-29-12.pdf Accessed Aug 10, 2017
4. World Health Organisation. Adherence to Long Term Therapies; Evidence for Action. Published 2003. Available from: http://www.who.int/chp/knowledge/publications/adherence_full_report.pdf?ua=1 Accessed November 6, 2015
5. Horne R WJ, Barber N, Elliot R, Morgan M. Concordance, adherence and compliance in medicine taking. Report for the National Coordinating Centre for NHS Service Delivery and Organization R & D (NCCSDO). 2005
6. New England Healthcare Institute.Thinking outside the pillbox: a system-wide approach to improving patient medication adherence for chronic disease. Published August 2009. Available from: http://www.nehi.net/publications/44/thinking_outside_the_pillbox_a_systemwide_approach_to_improving_patient_medication_adherence_for_chronic_disease. Accessed June 24, 2016
7. Pharmaceutical Group of the European Union. Targeting adherence. Improving patient outcomes in Europe through community pharmacists' intervention. Published May 2008. Available from: http://www.pgeu.eu/policy/5-adherence.html. Accessed January 28, 2016
8. IMS Institute for Healthcare Informatics. Advancing the responsible use of medicines; applying levers for change. Published October 2012. Available from: http://pharmanalyses.fr/wp-content/uploads/2012/10/Advancing-Responsible-Use-of-Meds-Report-01-10-12.pdf. Accessed March 10, 2016
9. AIHW 2016. Health expenditure Australia 2014–15. Health and welfare expenditure series no. 57. Cat. no. HWE 67. Canberra: AIHW.
10. Sokol MC, McGuigan KA, Verbrugge RR, et al. Impact of medication adherence on hospitalization risk and healthcare cost. Medical care 2005;**43**:521-30
11. Vermiere E, Avonts D, Van Royen P, et al. Context and health outcomes. Lancet (London, England) 2001;**357**(9273):2059-60
12. American Pharmacists Association/APhA AP . Medication Compliance-Adherence-Persistence (CAP) Digest. Washington DC. American Pharmacists Association and Pfizer Pharmaceuticals; 2003.
13. Egede LE, Gebregziabher M, Dismuke CE, et al. Medication nonadherence in diabetes: longitudinal effects on costs and potential cost savings from improvement. Diabetes care 2012;**35**(12):2533-9 doi: 10.2337/dc12-0572[published Online First: Epub Date]|.

14. Bach PB. New Math on Drug Cost-Effectiveness. The New England journal of medicine 2015;**373**(19):1797-9 doi: 10.1056/NEJMp1512750[published Online First: Epub Date]|.
15. Roebuck MC, Liberman JN, Gemmill-Toyama M, et al. Medication Adherence Leads To Lower Health Care Use And Costs Despite Increased Drug Spending. Health affairs 2011;**30**(1):91-99 doi: 10.1377/hlthaff.2009.1087[published Online First: Epub Date]|.
16. OECD. *Health at a Glance 2015*: OECD Publishing.
17. Moher D, Liberati A, Tetzlaff J, et al. Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. Annals of internal medicine 2009;**151**(4):264-9, w64
18. Higgins JPT, Green S (editors). Cochrane Handbook for Systematic Reviews of Interventions Version 5.1.0 [updated March 2011]. The Cochrane Collaboration, 2011.
19. Shemilt I, Thomas J, Morciano M. A web-based tool for adjusting costs to a specific target currency and price year. Evidence & Policy: A Journal of Research, Debate and Practice 2010;**6**(1):51-59
20. Drummond MF, Sculpher MJ, Claxton K, et al. *Methods for the economic evaluation of health care programmes*: Oxford university press, 2015.
21. Drummond MF, Jefferson TO. Guidelines for authors and peer reviewers of economic submissions to the BMJ. The BMJ Economic Evaluation Working Party. Bmj 1996;**313**(7052):275-83
22. Svarstad BL, Shireman TI, Sweeney JK. Using drug claims data to assess the relationship of medication adherence with hospitalization and costs. Psychiatric services (Washington, DC) 2001;**52**:805-11
23. Gilmer TP, Dolder CR, Lacro JP, et al. Adherence to treatment with antipsychotic medication and health care costs among Medicaid beneficiaries with schizophrenia. The American journal of psychiatry 2004;**161**:692-9
24. Aubert RE, Yao J, Xia F, et al. Is there a relationship between early statin compliance and a reduction in healthcare utilization? The American journal of managed care 2010;**16**:459-66
25. Bagalman E, Yu-Isenberg KS, Durden E, et al. Indirect costs associated with nonadherence to treatment for bipolar disorder. Journal of occupational and environmental medicine / American College of Occupational and Environmental Medicine 2010;**52**:478-85 doi: 10.1097/JOM.0b013e3181db811d[published Online First: Epub Date]|.
26. Barnett PG, Chow A, Joyce VR, et al. Determinants of the Cost of Health Services Used by Veterans With HIV. Medical care 2011;**49**:848-56 doi: 10.1097/MLR.0b013e31821b34c0[published Online First: Epub Date]|.
27. Becker MA, Young MS, Ochshorn E, et al. The relationship of antipsychotic medication class and adherence with treatment outcomes and costs for Florida Medicaid beneficiaries with schizophrenia. Administration and policy in mental health 2007;**34**:307-14 doi: 10.1007/s10488-006-0108-5[published Online First: Epub Date]|.
28. Briesacher BA, Andrade SE, Yood RA, et al. Consequences of poor compliance with bisphosphonates. Bone 2007;**41**:882-7 doi: 10.1016/j.bone.2007.07.009[published Online First: Epub Date]|.
29. Candrilli SD, O'Brien SH, Ware RE, et al. Hydroxyurea adherence and associated outcomes among Medicaid enrollees with sickle cell disease. American journal of

hematology 2011;**86**:273-7 doi: 10.1002/ajh.21968[published Online First: Epub Date]|.
30. Carter CT, Waters HC, Smith DB. Impact of infliximab adherence on Crohn's disease-related healthcare utilization and inpatient costs. Advances in therapy 2011;**28**:671-83 doi: 10.1007/s12325-011-0048-7[published Online First: Epub Date]|.
31. Casciano JP, Dotiwala ZJ, Martin BC, et al. The costs of warfarin underuse and nonadherence in patients with atrial fibrillation: a commercial insurer perspective. Journal of managed care pharmacy : JMCP 2013;**19**:302-16
32. Cooke CE, Lee HY, Xing S. Adherence to antiretroviral therapy in managed care members in the United States: a retrospective claims analysis. Journal of managed care pharmacy : JMCP 2014;**20**:86-92
33. Darkow T, Henk HJ, Thomas SK, et al. Treatment interruptions and non-adherence with imatinib and associated healthcare costs: a retrospective analysis among managed care patients with chronic myelogenous leukaemia. PharmacoEconomics 2007;**25**:481-96
34. Davis KL, Edin HM, Allen JK. Prevalence and cost of medication nonadherence in Parkinson's disease: evidence from administrative claims data. Movement disorders : official journal of the Movement Disorder Society 2010;**25**(4):474-80 doi: 10.1002/mds.22999[published Online First: Epub Date]|.
35. Davis KLC, S. D.; Edin, H. M. Prevalence and cost of nonadherence with antiepileptic drugs in an adult managed care population. Epilepsia 2008;**49**(3):446-54 doi: 10.1111/j.1528-1167.2007.01414.x[published Online First: Epub Date]|.
36. Delea TE, Stanford RH, Hagiwara M, et al. Association between adherence with fixed dose combination fluticasone propionate/salmeterol on asthma outcomes and costs*. Current medical research and opinion 2008;**24**:3435-42 doi: 10.1185/03007990802557344[published Online First: Epub Date]|.
37. Delea TE, Thomas SK, Hagiwara M. The association between adherence to levodopa/carbidopa/entacapone therapy and healthcare utilization and costs among patients with Parkinson's disease: a retrospective claims-based analysis. CNS drugs 2011;**25**:53-66 doi: 10.2165/11538970-000000000-00000[published Online First: Epub Date]|.
38. Diehl JL, Daw JR, Coley KC, et al. Medical utilization associated with palivizumab compliance in a commercial and managed medicaid health plan. Journal of managed care pharmacy : JMCP 2010;**16**:23-31
39. Eaddy M, Grogg A, Locklear J. Assessment of compliance with antipsychotic treatment and resource utilization in a Medicaid population. Clinical therapeutics 2005;**27**:263-72 doi: 10.1016/j.clinthera.2005.02.003[published Online First: Epub Date]|.
40. Egede LE, Gebregziabher M, Dismuke CE, et al. Medication Nonadherence in Diabetes: Longitudinal effects on costs and potential cost savings from improvement. Diabetes care 2012;**35**:2533-39 doi: 10.2337/dc12-0572[published Online First: Epub Date]|.
41. Eisenberg DF, Placzek H, Gu T, et al. Cost and consequences of noncompliance to oral bisphosphonate treatment. Journal of managed care & specialty pharmacy 2015;**21**(1):56-65 doi: 10.18553/jmcp.2015.21.1.56[published Online First: Epub Date]|.
42. Ettinger AB, Manjunath R, Candrilli SD, et al. Prevalence and cost of nonadherence to antiepileptic drugs in elderly patients with epilepsy. Epilepsy & behavior : E&B

2009;**14**:324-9 doi: 10.1016/j.yebeh.2008.10.021[published Online First: Epub Date]|.
43. Faught RE, Weiner JR, Guérin A, et al. Impact of nonadherence to antiepileptic drugs on health care utilization and costs: findings from the RANSOM study. Epilepsia 2009;**50**:501-9 doi: 10.1111/j.1528-1167.2008.01794.x[published Online First: Epub Date]|.
44. Gosselin A, Luo R, Lohoues H, et al. The impact of proton pump inhibitor compliance on health-care resource utilization and costs in patients with gastroesophageal reflux disease. Value in health : the journal of the International Society for Pharmacoeconomics and Outcomes Research 2009;**12**:34-9 doi: 10.1111/j.1524-4733.2008.00399.x[published Online First: Epub Date]|.
45. Hagen SE, Wright DW, Finch R, et al. Impact of compliance to oral hypoglycemic agents on short-term disability costs in an employer population. Population health management 2014;**17**:35-41 doi: 10.1089/pop.2013.0009[published Online First: Epub Date]|.
46. Halpern R, Becker L, Iqbal SU, et al. The association of adherence to osteoporosis therapies with fracture, all-cause medical costs, and all-cause hospitalizations: a retrospective claims analysis of female health plan enrollees with osteoporosis. Journal of managed care pharmacy : JMCP 2011;**17**:25-39
47. Hansen RA, Farley JF, Droege M, et al. A retrospective cohort study of economic outcomes and adherence to monotherapy with metformin, pioglitazone, or a sulfonylurea among patients with type 2 diabetes mellitus in the United States from 2003 to 2005. Clinical therapeutics 2010;**32**:1308-19 doi: 10.1016/j.clinthera.2010.07.011[published Online First: Epub Date]|.
48. Hazel-Fernandez L, Louder AM, Foster SA, et al. Association of teriparatide adherence and persistence with clinical and economic outcomes in Medicare Part D recipients: a retrospective cohort study. BMC musculoskeletal disorders 2013;**14**:4 doi: 10.1186/1471-2474-14-4[published Online First: Epub Date]|.
49. Huybrechts KF, Ishak KJ, Caro JJ. Assessment of compliance with osteoporosis treatment and its consequences in a managed care population. Bone 2006;**38**:922-8 doi: 10.1016/j.bone.2005.10.022[published Online First: Epub Date]|.
50. Ivanova JI, Bergman RE, Birnbaum HG, et al. Impact of medication adherence to disease-modifying drugs on severe relapse, and direct and indirect costs among employees with multiple sclerosis in the US. Journal of medical economics 2012;**15**:601-9 doi: 10.3111/13696998.2012.667027[published Online First: Epub Date]|.
51. Jha AK, Aubert RE, Yao J, et al. Greater adherence to diabetes drugs is linked to less hospital use and could save nearly $5 billion annually. Health affairs (Project Hope) 2012;**31**:1836-46 doi: 10.1377/hlthaff.2011.1198[published Online First: Epub Date]|.
52. Jiang Y, Ni W. Estimating the Impact of Adherence to and Persistence with Atypical Antipsychotic Therapy on Health Care Costs and Risk of Hospitalization. Pharmacotherapy 2015;**35**(9):813-22 doi: 10.1002/phar.1634[published Online First: Epub Date]|.
53. Joshi AV, Madhavan SS, Ambegaonkar A, et al. Association of medication adherence with workplace productivity and health-related quality of life in patients with asthma. The Journal of asthma : official journal of the Association for the Care of Asthma 2006;**43**:521-6 doi: 10.1080/02770900600857010[published Online First: Epub Date]|.

54. Kane SV, Chao J, Mulani PM. Adherence to infliximab maintenance therapy and health care utilization and costs by Crohn's disease patients. Advances in therapy 2009;**26**:936-46 doi: 10.1007/s12325-009-0069-7[published Online First: Epub Date]|.
55. Lee A, Song X, Khan I, et al. Association of cinacalcet adherence and costs in patients on dialysis. Journal of medical economics 2011;**14**:798-804 doi: 10.3111/13696998.2011.627404[published Online First: Epub Date]|.
56. Leider HL, Dhaliwal J, Davis EJ, et al. Healthcare costs and nonadherence among chronic opioid users. The American journal of managed care 2011;**17**:32-40
57. Mitra D, Hodgkins P, Yen L, et al. Association between oral 5-ASA adherence and health care utilization and costs among patients with active ulcerative colitis. BMC gastroenterology 2012;**12**:132 doi: 10.1186/1471-230X-12-132[published Online First: Epub Date]|.
58. Modi A, Siris ES, Tang J, et al. Cost and consequences of noncompliance with osteoporosis treatment among women initiating therapy. Current medical research and opinion 2015;**31**(4):757-65 doi: 10.1185/03007995.2015.1016605[published Online First: Epub Date]|.
59. Offord S, Lin J, Mirski D, et al. Impact of early nonadherence to oral antipsychotics on clinical and economic outcomes among patients with schizophrenia. Advances in therapy 2013;**30**:286-97 doi: 10.1007/s12325-013-0016-5[published Online First: Epub Date]|.
60. Offord S, Lin J, Wong B, et al. Impact of oral antipsychotic medication adherence on healthcare resource utilization among schizophrenia patients with Medicare coverage. Community mental health journal 2013;**49**:625-9 doi: 10.1007/s10597-013-9638-y[published Online First: Epub Date]|.
61. Pittman DG, Chen W, Bowlin SJ, et al. Adherence to statins, subsequent healthcare costs, and cardiovascular hospitalizations. The American journal of cardiology 2011;**107**:1662-6 doi: 10.1016/j.amjcard.2011.01.052[published Online First: Epub Date]|.
62. Pittman DG, Tao Z, Chen W, et al. Antihypertensive medication adherence and subsequent healthcare utilization and costs. The American journal of managed care 2010;**16**:568-76
63. Pruitt Z, Robst J, Langland-Orban B, et al. Healthcare costs associated with antiretroviral adherence among medicaid patients. Applied health economics and health policy 2015;**13**:69-80 doi: 10.1007/s40258-014-0138-1[published Online First: Epub Date]|.
64. Quittner AL, Zhang J, Marynchenko M, et al. Pulmonary medication adherence and health-care use in cystic fibrosis. Chest 2014;**146**:142-51 doi: 10.1378/chest.13-1926[published Online First: Epub Date]|.
65. Rizzo JAS, W. R. Variations in compliance among hypertensive patients by drug class: implications for health care costs. Clinical therapeutics 1997;**19**(6):1446-57; discussion 24-5
66. Robinson RL, Long SR, Chang S, et al. Higher costs and therapeutic factors associated with adherence to NCQA HEDIS antidepressant medication management measures: analysis of administrative claims. Journal of managed care pharmacy : JMCP 2006;**12**:43-54
67. Stroupe KT, Teal EY, Tu W, et al. Association of Refill Adherence and Health Care Use Among Adults with Hypertension in an Urban Health Care System. Pharmacotherapy 2006;**26**:779-89 doi: 10.1592/phco.26.6.779[published Online First: Epub Date]|.

68. Sunyecz JA, Mucha L, Baser O, et al. Impact of compliance and persistence with bisphosphonate therapy on health care costs and utilization. Osteoporosis international : a journal established as result of cooperation between the European Foundation for Osteoporosis and the National Osteoporosis Foundation of the USA 2008;**19**:1421-9 doi: 10.1007/s00198-008-0586-2[published Online First: Epub Date]|.
69. Tan H, Cai Q, Agarwal S, et al. Impact of adherence to disease-modifying therapies on clinical and economic outcomes among patients with multiple sclerosis. Advances in therapy 2011;**28**:51-61 doi: 10.1007/s12325-010-0093-7[published Online First: Epub Date]|.
70. Tkacz J, Volpicelli J, Un H, et al. Relationship between buprenorphine adherence and health service utilization and costs among opioid dependent patients. Journal of substance abuse treatment 2014;**46**:456-62 doi: 10.1016/j.jsat.2013.10.014[published Online First: Epub Date]|.
71. Wan GJ, Kozma CM, Slaton TL, et al. Inflammatory bowel disease: healthcare costs for patients who are adherent or non-adherent with infliximab therapy. Journal of medical economics 2014;**17**:384-93 doi: 10.3111/13696998.2014.909436[published Online First: Epub Date]|.
72. Wei Y-J, Palumbo FB, Simoni-Wastila L, et al. Antiparkinson drug adherence and its association with health care utilization and economic outcomes in a Medicare Part D population. Value in health : the journal of the International Society for Pharmacoeconomics and Outcomes Research 2014;**17**:196-204 doi: 10.1016/j.jval.2013.12.003[published Online First: Epub Date]|.
73. White TJV, Ann; Ory, Caron; Dezii, Christopher M.; Chang, Eunice. Economic Impact of Patient Adherence with Antidepressant Therapy Within a Managed Care Organization. Disease Management & Health Outcomes 2003;**11**(12):817-22 doi: 10.2165/00115677-200311120-00006[published Online First: Epub Date]|.
74. White TJV, Ann; Chang, Eunice; Dezii, Christopher M.; Abrams, Geoffrey D. The Costs of Non-Adherence to Oral Antihyperglycemic Medication in Individuals with Diabetes Mellitus and Concomitant Diabetes Mellitus and Cardiovascular Disease in a Managed Care Environment. Disease Management & Health Outcomes 2004;**12**(3):181-88 doi: 10.2165/00115677-200412030-00004[published Online First: Epub Date]|.
75. Wu EQ, Johnson S, Beaulieu N, et al. Healthcare resource utilization and costs associated with non-adherence to imatinib treatment in chronic myeloid leukemia patients. Current medical research and opinion 2010;**26**:61-69 doi: 10.1185/03007990903396469[published Online First: Epub Date]|.
76. Wu J, Seiber E, Lacombe VA, et al. Medical utilization and costs associated with statin adherence in Medicaid enrollees with type 2 diabetes. The Annals of pharmacotherapy 2011;**45**:342-9 doi: 10.1345/aph.1P539[published Online First: Epub Date]|.
77. Wu N, Chen S, Boulanger L, et al. Duloxetine compliance and its association with healthcare costs among patients with diabetic peripheral neuropathic pain. Journal of medical economics 2009;**12**:192-202 doi: 10.3111/13696990903240559[published Online First: Epub Date]|.
78. Zhao Y, Chen S-Y, Wu N, et al. Medication Adherence and Healthcare Costs among Fibromyalgia Patients Treated with Duloxetine. Pain Practice 2011;**11**:381-91 doi: 10.1111/j.1533-2500.2010.00431.x[published Online First: Epub Date]|.
79. Zhao Y, Johnston SS, Smith DM, et al. Association between teriparatide adherence and healthcare utilization and costs among hip fracture patients in the United States.

Bone 2014;**60**:221-6 doi: 10.1016/j.bone.2013.12.016[published Online First: Epub Date]|.
80. Zhao Y, Johnston SS, Smith DM, et al. Association between teriparatide adherence and healthcare utilization and costs in real-world US kyphoplasty/vertebroplasty patients. Osteoporosis International 2013;**24**:2525-33 doi: 10.1007/s00198-013-2324-7[published Online First: Epub Date]|.
81. Zhao Y, Zabriski S, Bertram C. Associations between statin adherence level, health care costs, and utilization. Journal of managed care & specialty pharmacy 2014;**20**:703-13
82. Robertson AG, Swanson JW, Van Dorn RA, et al. Treatment participation and medication adherence: effects on criminal justice costs of persons with mental illness. Psychiatric services (Washington, DC) 2014;**65**(10):1189-91 doi: 10.1176/appi.ps.201400247[published Online First: Epub Date]|.
83. Buysman EK, Anderson A, Bacchus S, et al. Retrospective Study on the Impact of Adherence in Achieving Glycemic Goals in Type 2 Diabetes Mellitus Patients Receiving Canagliflozin. Adv Ther 2017;**34**(4):937-53 doi: 10.1007/s12325-017-0500-4[published Online First: Epub Date]|.
84. Curtis SE, Boye KS, Lage MJ, et al. Medication adherence and improved outcomes among patients with type 2 diabetes. The American journal of managed care 2017;**23**(7):e208-e14
85. Davis JR, Wu B, Kern DM, et al. Impact of Nonadherence to Inhaled Corticosteroid/LABA Therapy on COPD Exacerbation Rates and Healthcare Costs in a Commercially Insured US Population. American health & drug benefits 2017;**10**(2):92-102
86. Ruetsch C, Tkacz J, Nadipelli VR, et al. Heterogeneity of nonadherent buprenorphine patients: subgroup characteristics and outcomes. The American journal of managed care 2017;**23**(6):e172-e79
87. Kjellberg J, Jorgensen AD, Vestergaard P, et al. Cost and health care resource use associated with noncompliance with oral bisphosphonate therapy: an analysis using Danish health registries. Osteoporosis International 2016;**27**(12):3535-41 doi: 10.1007/s00198-016-3683-7[published Online First: Epub Date]|.
88. Olsen KR, Hansen C, Abrahamsen B. Association between refill compliance to oral bisphosphonate treatment, incident fractures, and health care costs--an analysis using national health databases. Osteoporosis international : a journal established as result of cooperation between the European Foundation for Osteoporosis and the National Osteoporosis Foundation of the USA 2013;**24**:2639-47 doi: 10.1007/s00198-013-2365-y[published Online First: Epub Date]|.
89. Miravitlles M, Sicras A, Crespo C, et al. Costs of chronic obstructive pulmonary disease in relation to compliance with guidelines: a study in the primary care setting. Therapeutic advances in respiratory disease 2013;**7**:139-50 doi: 10.1177/1753465813484080[published Online First: Epub Date]|.
90. Alvarez Payero M, Martinez Lopez de Castro N, Ucha Samartin M, et al. Medication non-adherence as a cause of hospital admissions. Farmacia hospitalaria : organo oficial de expresion cientifica de la Sociedad Espanola de Farmacia Hospitalaria 2014;**38**(4):328-33 doi: 10.7399/fh.2014.38.4.7660[published Online First: Epub Date]|.
91. Joe S, Lee JS. Association between non-compliance with psychiatric treatment and non-psychiatric service utilization and costs in patients with schizophrenia and related disorders. BMC psychiatry 2016;**16**(1):444 doi: 10.1186/s12888-016-1156-3[published Online First: Epub Date]|.

92. Hong JS, Kang HC. Relationship between oral antihyperglycemic medication adherence and hospitalization, mortality, and healthcare costs in adult ambulatory care patients with type 2 diabetes in South Korea. Medical care 2011;**49**:378-84 doi: 10.1097/MLR.0b013e31820292d1[published Online First: Epub Date]|.
93. Dilokthornsakul P, Chaiyakunapruk N, Nimpitakpong P, et al. The Effects of Medication Supply on Hospitalizations and Health-Care Costs in Patients with Chronic Heart Failure. Value in Health 2012;**15**:S9-S14 doi: 10.1016/j.jval.2011.11.019[published Online First: Epub Date]|.
94. An S-Y, Kim HJ, Chun KH, et al. Clinical and economic outcomes in medication-adherent and -nonadherent patients with type 2 diabetes mellitus in the Republic of Korea. Clinical therapeutics 2014;**36**:245-54 doi: 10.1016/j.clinthera.2013.12.012[published Online First: Epub Date]|.
95. Dragomir A, Cote R, White M, et al. Relationship between adherence level to statins, clinical issues and health-care costs in real-life clinical setting. Value in health : the journal of the International Society for Pharmacoeconomics and Outcomes Research 2010;**13**(1):87-94 doi: 10.1111/j.1524-4733.2009.00583.x[published Online First: Epub Date]|.
96. Dragomir A, Côté R, Roy L, et al. Impact of adherence to antihypertensive agents on clinical outcomes and hospitalization costs. Medical care 2010;**48**:418-25 doi: 10.1097/MLR.0b013e3181d567bd[published Online First: Epub Date]|.
97. Gentil L, Vasiliadis HM, Preville M, et al. Adherence to Oral Antihyperglycemic Agents Among Older Adults With Mental Disorders and Its Effect on Health Care Costs, Quebec, Canada, 2005-2008. Preventing chronic disease 2015;**12**:E230 doi: 10.5888/pcd12.150412[published Online First: Epub Date]|.
98. Knapp M, King D, Pugner K, et al. Non-adherence to antipsychotic medication regimens: associations with resource use and costs. The British journal of psychiatry : the journal of mental science 2004;**184**:509-16
99. Hong J, Reed C, Novick D, et al. Clinical and economic consequences of medication non-adherence in the treatment of patients with a manic/mixed episode of bipolar disorder: results from the European Mania in Bipolar Longitudinal Evaluation of Medication (EMBLEM) study. Psychiatry research 2011;**190**:110-4 doi: 10.1016/j.psychres.2011.04.016[published Online First: Epub Date]|.
100. Deeks JJ HJ, Altman DG (editors). Cochrane Handbook for Systematic Reviews of Interventions Version 5.1.0 [updated March 2011]. . The Cochrane Collaboration, 2011
101. Haynes RB, McDonald H, Garg AX, et al. Interventions for helping patients to follow prescriptions for medications. The Cochrane database of systematic reviews 2002(2):CD000011 doi: 10.1002/14651858.CD000011[published Online First: Epub Date]|.
102. Hess LM, Raebel MA, Conner DA, et al. Measurement of adherence in pharmacy administrative databases: a proposal for standard definitions and preferred measures. The Annals of pharmacotherapy 2006;**40**(7-8):1280-88 doi: 10.1345/aph.1H018[published Online First: Epub Date]|.
103. Sattler EL, Lee JS, Perri M, 3rd. Medication (re)fill adherence measures derived from pharmacy claims data in older Americans: a review of the literature. Drugs & aging 2013;**30**(6):383-99 doi: 10.1007/s40266-013-0074-z[published Online First: Epub Date]|.
104. Karve S, Cleves MA, Helm M, et al. An empirical basis for standardizing adherence measures derived from administrative claims data among diabetic patients.

Medical care 2008;**46**(11):1125-33 doi: 10.1097/MLR.0b013e31817924d2[published Online First: Epub Date]|.
105. Gargon E, Williamson PR, Altman DG, et al. The COMET Initiative database: progress and activities from 2011 to 2013. Trials 2014;**15**:279 doi: 10.1186/1745-6215-15-279[published Online First: Epub Date]|.
106. Hughes DA, Bagust A, Haycox A, et al. Accounting for noncompliance in pharmacoeconomic evaluations. PharmacoEconomics 2001;**19**(12):1185-97

eTable 1 Search Strategy[1]

Database	Search Strategy
PubMed	((costs[TIAB] OR "Costs and Cost Analysis"[MH] OR burden[TIAB]) AND (nonadherence[TIAB] OR ("Patient Compliance"[MH] AND ("Drug Therapy"[MH] OR medication[TIAB])) OR "Medication adherence"[MH]))
Scopus	(TITLE-ABS-KEY (medication AND compliance OR patient AND compliance)) AND (TITLE-ABS-KEY (statistical AND model)) AND (TITLE-ABS-KEY (health AND care AND cost))

[1] In accordance with the Cochrane Handbook for Systematic Reviews no date restriction filters were used.

eTable 2: Studies identified with costs reported by adherence level and disease group

Author, Year, Country	Objective	Study Characteristics	Adherence (as reported in paper)	Outcomes/ Indicators	Results (USD, 2015)	Quality
Cardiovascular Disease						
*Aubert et al**[1]*** 2010 US	To investigate whether compliance during the first 2 years of statin therapy is associated with reduced hospitalisation rates and direct medical costs during year 3.	Design: Retrospective cohort study Follow Up: 3 years Sample Size: 10227 (A:3512, NA:6715)	Measure: MPR Classification: MPR < 80 = non-compliant Method of Assessment: pharmacy claims data	Total Healthcare costs Medical Costs	Type of Costs: adjusted Classification: disease state specific Currency Year: USD, 2002 Cost of Nonadherence: THC:$5289.61 ($6865.90), MC:$4908.09 ($6370.60)	Quality: medium Classification: cost description
*Casciano et al**[2]*** 2013 US	To assess the economic burden of underuse and nonadherence of warfarin therapy among patients with non-valvular atrial fibrillation in a commercially insured population.	Design: Retrospective, observational, quasi-experimental study Follow Up: 18months Sample Size: 13289 (A:2852, NA:4184, NE:6253)	Measure: PDC Classification: PDC <80 = low adherence , 0 = no warfarin exposure Method of Assessment: pharmacy claims data	Total Costs Inpatient Costs Outpatient Costs Pharmacy Costs Medical Costs	Type of Costs: adjusted Classification: all cause Currency Year: USD, 2005 Cost of Nonadherence*: TC:$16612.44($19936.70), IC:$9382.56 ($11260.10), OC:$8605.92 ($10328), PC:$2388.24 ($2866.20), MC:$15235.80($18285)	Quality: medium Classification: cost description
*Dilokthornsakul et al**[3]*** 2012 Thailand	To determine the effects of medication supplies on healthcare costs and hospitalisations in patients with chronic heart failure receiving angiotensin converting enzyme	Design: Retrospective cohort study Follow Up: 1 year Sample Size: 393 (A:168, NA:219, OA:6)	Measure: MPR Classification: MPR < 80 = undersupply, MPR >120 = oversupply	Total Healthcare Costs Inpatient Costs Outpatient Costs	Type of Costs: unadjusted Classification: disease state specific Currency Year: USD, 2004 Cost of Nonadherence: THC:$1157 ($1433.06), IC:$1019 ($1262.13),	Quality: high Classification: cost description

	inhibitors or angiotensin receptor blockers.		Method of Assessment: pharmacy claims data		OC:$138 ($170.93)	
*Dragomir et al**[4]*** 2010 Canada	To evaluate the impact of low adherence to antihypertensive agents on cardiovascular outcomes and hospitalisation costs.	Design: Retrospective cohort study Follow Up: 3 years Sample Size: 56896 (A:38217, NA:18679)	Measure: MPR Classification: MPR≥80 = adherent, MPR < 80 = nonadherent Method of Assessment: pharmacy claims data	Total Healthcare Costs Pharmacy Costs Medical Costs Hospitalisation Costs	Type of Costs: unadjusted and predicted Classification: disease state specific and hospitalized patients Currency Year: CAD, 2006 Cost of Nonadherence: Unadjusted Disease state specific: THC:$7165 ($6900.87), PC: $1800 ($1733.64), MC: $1370 ($1319.50), HC: $3995 ($3847.73) Unadjusted Hospitalized patients: THC: $17397 ($16755.67), PC:$2685 ($2586.02), MC:$2608 ($2511.86), HC: $12104 ($11657.79) Predicted disease state specific: HC:$3877 ($3734.08) Predicted hospitalized patient: HC:$11715 ($11283.13)	Quality: medium Classification: cost description
*Dragomir et al**[5]*** 2010 Canada	To evaluate the impact of low adherence to statins on clinical issues and direct healthcare costs.	Design: Retrospective cohort study Follow Up: 3 years Sample Size: 55134 (A:28549, NA:26585)	Measure: MPR Classification: MPR≥80 = adherent, MPR	Total Healthcare Costs Pharmacy Costs Medical Costs	Type of Costs: unadjusted and predicted Classification: disease state specific and hospitalized patients	Quality: medium Classification: cost description

			< 80 = nonadherent Method of Assessment: pharmacy claims data	Hospitalisation Costs	Currency Year: CAD, 2005 Cost of Nonadherence: Unadjusted Disease state specific: THC:$6243 ($6175.76), PC:$2506 ($2479.01), MC:$1241 ($1227.63), HC:$2496 ($2469.12) Unadjusted Hospitalized patients: THC:$14725 ($14566.40), PC:$3374 ($3337.66), MC:$2475 ($2448.34), HC:$8876 ($8780.40) Predicted disease state specific: HC:$2669 ($2640.25) Predicted hospitalized patient: HC$9214 ($9114.76)	
*Pittman et al**[6]*** 2011 US	To examine the relation among statin adherence, subsequent hospitalisations and healthcare costs.	Design: Retrospective cohort study Follow Up: 18 months Sample Size: 381422 (A:258013, MA:65795, LA:57614)	Measure: MPR Classification: MPR ≥ 80 = adherent, MPR >60<79% = moderate adherence, MPR <59 =low adherence Method of Assessment: pharmacy claims data	Total Healthcare Costs Pharmacy Costs Medical Costs	Type of Costs: adjusted Classification: all cause and disease state specific Currency Year: USD, 2009 Cost of Nonadherence*: all cause: THC(>80):$6798.67 ($7505.66), THC(60-79):$7072.67 ($7808.16), THC(<59):$7401.33 ($8170.99), PC(>80):$1767.33 ($1951.11),	Quality: medium Classification: cost description

					PC(60-79):$1789.33 ($1975.40), PC(<59):$1937.33 ($2138.79), MC(>80):$4472.67 ($4937.78), MC(60-79):$4840.67 ($5344.05, MC(<59):$5138.67 ($5673.04) Disease state specific: PC(>80):$558.67 ($616.77), PC(60-79):$442.67 ($488.70), PC(<59):$325.33 ($359.16), MC(>80):$1596.67 ($1762.71), MC(60-79):$1722 ($1901.07), MC(<59):$1792.67 ($1979.09)	
*Pittman et al**[7]*** 2010 US	To evaluate the relationship between adherence to antihypertensive medications and subsequent hospitalisations, emergency department visits and costs of care.	Design: Retrospective cohort study Follow Up: 2 years Sample Size: 625620(A:467006, MA:96226, LA:62388)	Measure: MPR Classification: MPR ≥ 80 = adherent, MPR >60<79% = moderate adherence, MPR <59 =low adherence Method of Assessment: pharmacy claims data	Total Healthcare Costs Outpatient Costs ED Costs Pharmacy Costs Hospitalisation Costs	Type of Costs: adjusted and unadjusted Classification: disease state specific Currency Year: USD, 2008 Cost of Nonadherence: Adjusted: THC(>80):$7261 ($8077.79), THC(60-79):$7530 ($8377.05), THC(<59):$7370 ($8199.05), OC(>80):$3390 ($3771.34), OC(60-79):$3705 ($4121.77), OC(<59):$3776 ($4200.76), EDC(>80):$101 ($112.36), EDC(60-79):$134 ($149.07), EDC(<59):$172 ($191.35), PC(>80):$2383 ($2651.06),	Quality: medium Classification: cost description

					PC(60-79):$1932 ($2149.33), PC(<59):$1509 ($1678.75), HC(>80):$1386 ($1541.91), HC(60-79):$1759 ($1956.87), HC(<59):$1913 ($2128.19) Unadjusted: THC(>80):$7182 ($7989.90), THC(60-79):$7560 ($8410.42), THC(<59):$7995 ($8894.35), OC(>80):$3396 ($3778.01), OC(60-79):$3635 ($4043.90), OC(<59):$3887 ($4324.25), EDC(>80):$102 ($113.47), EDC(60-79):$131 ($145.74), EDC(<59):$172 ($191.35), PC(>80):$2317 ($2577.64), PC(60-79):$2034 ($2262.80), PC(<59):$1880 ($2091.48), HC(>80):$1366 ($1519.66), HC(60-79):$1759 ($1956.87), HC(<59):$2057 ($2288.39)	
*Rizzo et al**[8]*** 1997 US	To investigate variations in compliance with four classes of antihypertensive agents-diuretics, ACEIs, CCBs and ß-blockers and the health care costs associated with various degrees of compliance.	Design: Retrospective cohort study Follow Up: 12 months Sample Size: 7211(P:2668, NC:3101, NP:649, T:793)	Measure: ordinary least square regression analysis Classification: >80% = persistent, ≥30<80% = non-compliance,	Total Healthcare Costs	Type of Costs: unadjusted Classification: all cause and disease state specific Currency Year: USD, 1994 Cost of Nonadherence: All cause: THC(>80):$341 ($509.66), THC(30-80):$694 ($1037.26), THC(<30):$735 ($1098.53) Disease state specific: Renal:	Quality: low Classification: cost description

			<30% = non-persistence Method of Assessment: pharmacy claims data		THC(>80):$2135 ($3190.98), THC(30-80):$2488 ($3718.58), THC(<30):$2529 ($3779.86), Acute MI: THC(>80):$1358 ($2029.67), THC(30-80):$1711 ($2557.27), THC(<30):$1752 ($2618.55), Diabetes: THC(>80):$770 ($1150.85), THC(30-80):$1123 ($1678.44), THC(<30):$1164 ($1739.72), CHF: THC(>80):$698 ($1043.23), THC(30-80):$1051 ($1570.83), THC(<30):$1092 ($1632.11), Angina: THC(>80):$702 ($1049.21), THC(30-80):$1055 ($1576.81), THC(<30):$1096 ($1638.09)	
*Sokol et al**[9]*** 2005 US	To evaluate the impact of medication adherence on healthcare utilisation and cost for 4 chronic conditions that are major drivers of drug spending: diabetes, hypertension, hypercholesterolemia, and congestive heart failure.	Design: Retrospective cohort observational study Follow Up: 12 months Sample Size: 137277 Diabetes:(≥80: 1801, 60-79: 599, 40-59: 419, 20-39: 259, <19: 182) Hypertension:(≥80: 5804, 60-79: 921, 40-59: 562, 20-39: 344, <19: 350)	Measure: medication supply Classification: 1-19%, 20-39%, 40-59%, 60-79%, 80-100% Method of Assessment: pharmacy claims data	Total Costs Pharmacy Costs Medical Costs	Type of Costs: adjusted Classification: all cause and disease state specific Currency Year: USD, 1998 Cost of Nonadherence: All cause: Diabetes: TC(1-19):$16498 ($23071.58), TC(20-39):$13077 ($18287.49), TC(40-59):$12978 ($18149.05), TC(60-79):$11484 ($16059.77),	Quality: medium Classification: cost description

	Hypercholesterolemia: (≥80: 1754, 60-79: 520, 40-59: 324, 20-39: 216, <19: 167) CHF: (≥80: 518, 60-79: 107, 40-59: 82, 20-39: 70, <19: 86)	TC(80-100):$8886 ($12426.60), PC(1-19):$1312 ($1834.76), PC(20-39):$1877 ($2624.89), PC(40-59):$1970 ($2754.94), PC(60-79):$2121 ($2966.11), PC(80-100):$2510 ($3510.10), MC(1-19):$15186 ($21236.82), MC(20-39):$11200 ($15662.61), MC(40-59):$11008 ($15394.10), MC(60-79):$9363 ($13093.66), MC(80-100):$6377 ($8917.90), Hypertension: TC(1-19):$9747 ($13630.66), TC(20-39):$11238 ($15715.75), TC(40-59):$9491 ($13272.66), TC(60-79):$8929 ($12486.73), TC(80-100):$8386 ($11272.38), PC(1-19):$916 ($1280.98), PC(20-39):$952 ($1331.32), PC(40-59):$1123 ($1570.46), PC(60-79):$1271 ($1777.43), PC(80-100):$1817 ($2540.98), MC(1-19):$8831 ($12349.69), MC(20-39):$10286 ($14384.43), MC(40-59):$8368 ($11702.20), MC(60-79):$7658 ($10709.31),

MC(80-100):$6570 ($9187.80),
Hypercholesterolemia:
TC(1-19):$10916 ($15265.45),
TC(20-39):$7982 ($11162.40),
TC(40-59):$6756 ($9447.91),
TC(60-79):$8412 ($11763.74),
TC(80-100):$6752 ($9442.31),
PC(1-19):$1067 ($1492.14),
PC(20-39):$1152 ($1611.01),
PC(40-59):$1247 ($1743.86),
PC(60-79):$1736 ($2427.70),
PC(80-100):$1972 ($2757.74),
MC(1-19):$9849($13773.30),
MC(20-39):$6830 ($9551.39),
MC(40-59):$5509 ($7704.04),
MC(60-79):$6676 ($9336.03),
MC(80-100):$4780 ($6684.58),
CHF:
TC(1-19):$23964 ($33512.38),
TC(20-39):$19188
($26833.40),
TC(40-59):$26311
($36794.54),
TC(60-79):$29785
($41652.74),
TC(80-100):$22164
($30995.18),
PC(1-19):$1961 ($2742.35),
PC(20-39):$2055 ($2873.81),
PC(40-59):$2208 ($3087.77),
PC(60-79):$3412 ($4771.50),
PC(80-100):$3107 ($4344.97),

MC(1-19):$22003 ($30770.03),
MC(20-39):$17133
($23959.59),
MC(40-59):$24103
($33706.77),
MC(60-79):$26373
($36881.24),
MC(80-100):$19056
($26648.81)
Disease state specific:
Diabetes:
TC(1-19):$8867 ($12400.03),
TC(20-39):$7124 ($9916.90),
TC(40-59):$6522 ($9120.67),
TC(60-79):$6291 ($8797.63),
TC(80-100):$4570 ($6390.90),
PC(1-19):$55 ($76.91),
PC(20-39):$165 ($230.74),
PC(40-59):$285 ($398.56),
PC(60-79):$404 ($564.97),
PC(80-100):$763 ($1067.02),
MC(1-19):$8812 ($12323.11),
MC(20-39):$6959 ($9731.79),
MC(40-59):$6237 ($8722.11),
MC(60-79):$5887 ($8232.66),
MC(80-100):$3808 ($5325.29),
Hypertension:
TC(1-19):$4878 ($6821.62),
TC(20-39):$6062 ($8477.39),
TC(40-59):$5297 ($7407.57),
TC(60-79):$5262 ($7358.63),
TC(80-100):$4871 ($6811.84),

PC(1-19):$31 ($43.35),
PC(20-39):$89($124.46),
PC(40-59):$184 ($257.31),
PC(60-79):$285 ($398.56),
PC(80-100):$489 ($683.84),
MC(1-19):$4847 ($6778.27),
MC(20-39):$5973 ($8352.92),
MC(40-59):$5113 ($7150.26),
MC(60-79):$4977 ($6960.07),
MC(80-100):$4383 ($6129.39),
Hypercholesterolemia:
TC(1-19):$6888 ($9632.50),
TC(20-39):$4999 ($6990.84),
TC(40-59):$3825 ($5349.06),
TC(60-79):$5541 ($7748.79),
TC(80-100):$3924($5487.51),
PC(1-19):$78 ($109.08),
PC(20-39):$213 ($297.87),
PC(40-59):$373 ($521.62),
PC(60-79):$603 ($843.26),
PC(80-100):$801 ($1120.16),
MC(1-19):$6810 ($9523.42),
MC(20-39):$4786 ($6692.97),
MC(40-59):$3452 ($4827.44),
MC(60-79):$4938 ($6905.53),
MC(80-100):$3124 ($4368.75),
CHF:
TC(1-19):$9841 ($13762.12),
TC(20-39):$7733 ($10814.19),
TC(40-59):$11378
($15911.53),

					TC(60-79):$13924 ($19471.98), TC(80-100):$12698 ($17787.48), PC(1-19):$15 ($20.98), PC(20-39):$90 ($125.86), PC(40-59):$134 ($187.39), PC(60-79):$158 ($220.95), PC(80-100):$437 ($611.12), MC(1-19):$9826 ($13741.14), MC(20-39):$7643 ($10688.33), MC(40-59):$11244 ($15724.14), MC(60-79):$13766 ($19251.02), MC(80-100):$12261 ($17146.36)	
*Stroupe et al**[10]*** 2006 US	To determine the rates of undersupply, appropriate supply, and oversupply of antihypertensive drugs as measured by refill adherence, among patient with complicated and uncomplicated hypertension and to examine the association of refill adherence with hospitalisation and healthcare costs among these patients.	Design: Retrospective cohort study Follow Up: 3.3 years Sample Size: 15206 (not specified)	Measure: MPR Classification: MPR<80 = undersupply, MPR >120 = oversupply Method of Assessment: pharmacy claims data	Total Healthcare Costs Inpatient Costs Outpatient Costs Pharmacy Costs	Type of Costs: unadjusted Classification: disease state specific Currency Year: USD, 2002 Cost of Nonadherence**: THC:$6032.5 ($7830.11), IC:$2067 ($2682.94), OC:$3965 ($5146.52), PC:$130 ($168.74)	Quality: medium Classification: cost description
*Wu et al**[11]*** 2011 US	To study statin adherence and assess associated medical utilisation and healthcare costs	Design: Retrospective cohort study Follow Up: 1 year	Measure: MPR Classification: MPR≥80 =	Total Healthcare Costs	Type of Costs: adjusted Classification: all cause and disease state specific	Quality: medium Classification:

	in patients with type 2 diabetes, based on national Medicaid database.	Sample Size: 1705 (A:624, NA:1081)	adherent, MPR <80 = nonadherent Method of Assessment: pharmacy claims data	Pharmacy Costs Medical Costs	Currency Year: USD, 2005 Cost of Nonadherence: all cause: THC:$17807 ($21370.30), PC:$4915 ($5898.52) MC:$12892 ($15471.77) Disease state specific: THC:$2789 ($3347.10), PC:$489($586.85) MC:$2300 ($2760.25)	cost description
*Zhao et al**[12]*** 2014 US	To evaluate the associations between statin adherence level, healthcare costs, hospital admissions and emergency room visits after statin therapy is taken for 1 year.	Design: Retrospective cohort study Follow Up: 1 year Sample Size: 10312 (96-100: 2453, 90-95: 1496, 85-89: 584, 80-84: 768, 70-79: 960, 60-69: 777, 40-59: 1687, <40:1587)	Measure: MPR Classification: <40%, 40-59%, 60-69%, 70-79%, 80-84%, 85-89%, 90-95%, 96-100% Method of Assessment: pharmacy claims data, census data	Total Healthcare Costs Pharmacy Costs Medical Costs	Type of Costs: unadjusted Classification: all cause and disease state specific Currency Year: USD, 2010 Cost of Nonadherence: all cause: PC(96-100):$2976.80 ($3247.04), PC(90-95):$2826.99 ($3083.63), PC(85-89):$2795.39 ($3049.16), PC(80-84):$2690.89 ($2935.17), PC(70-79):$2192.83 ($2391.90), PC(60-69):$2323.27 ($2534.18), PC(40-59):$2153.93 ($2349.47), PC(<40):$1749.18 ($1907.97) Disease state specific: THC(96-100):$6536.05 ($7129.40), THC(90-95):$6493.80 ($7083.31),	Quality: medium Classification: cost description

					THC(85-89):$6459.40 ($7045.79), THC(80-84):$6227.47 ($6792.80), THC(70-79):$5713.47 ($6232.14), THC(60-69):$5875.26 ($6408.62), THC(40-59):$5817.58 ($6345.70), THC(<40):$5249.12 ($5725.64), PC(96-100):$449.86 ($490.70), PC(90-95):$439.74 ($479.66), PC(85-89):$458.83 ($500.48), PC(80-84):$423.15 ($461.56), PC(70-79):$356.74 ($389.13), PC(60-69):$371.30 ($405.01), PC(40-59):$279.21 ($304.56), PC(<40):$133.92 ($146.08), MC(96-100):$3559.25 ($3882.36), MC(90-95):$3666.81 ($3999.69), MC(85-89):$3664 ($3996.62), MC(80-84):$3586.58 ($3912.17), MC(70-79):$3520.64 ($3840.25), MC(60-69):$3551.99 ($3874.44), MC(40-59):$3663.65 ($3996.24), MC(<40):$3499.95 ($3817.68)	
Mental Health						
*Bagalman et al**[13]***	To examine the association between treatment adherence	Design: Retrospective cohort study	Measure: MPR	Total Costs	Type of Costs: adjusted	Quality: medium

2010 US	and indirect productivity costs within a cohort of commercially insured employees with bipolar disorder.	Follow Up: 1 year Sample Size: 1258 (A:444, NA:814)	Classification: MPR≥80 = adherent, MPR <80 = nonadherent Method of Assessment: pharmacy claims data	Short term disability cost Workers compensation cost Paid time off cost	Classification: disease state specific Currency Year: USD, 2005 Cost of Nonadherence: TC:$6894 ($8273.53), STDC:$2134 ($2561.03), WCC:$762 ($914.48), PTOC:$3998 ($4798.03)	Classification: cost description
*Becker et al**[14]*** 2007 US	Examine treatment outcomes and costs associated with adherence rates by antipsychotic medication class for Medicaid beneficiaries.	Design: Retrospective cohort study Follow Up: 2 years Sample Size: 10330 (>75%:6609, 50-74%:1276, 25-49%:1940, <25%:505)	Measure: prescription refill rate Classification: 75-100% = maximal adherence, 50-74.9% = moderate adherence, 25-49.9% = minimal adherence, <25% = negligible adherence Method of Assessment: pharmacy claims data	Total Costs	Type of Costs: unadjusted Classification: disease state specific Currency Year: USD, 2006 Cost of Nonadherence*: TC(75-100):$13564 ($15792.91), TC(50-74):$13772 ($16035.09), TC(25-49):$15792 ($18387.03), TC(<25):$16156 ($18810.84)	Quality: low Classification: cost description
*Eaddy et al**[15]*** 2005 US	To evaluate the effect of partial compliance of patients with prescribed oral atypical and	Design: Retrospective database analysis Follow Up: 1 year	Measure: continuous multiple	Inpatient costs Outpatient costs	Type of Costs: unadjusted Classification: disease state specific	Quality: medium Classification:

	conventional antipsychotic agents and the corresponding impact on resource utilisation.	Sample Size: 7864 (<80%:2655, 80-125%:5065, >125%:144)	interval medications available Classification: <80% = partially compliant, 80-125% = compliant, >125% = overly compliant Method of Assessment: pharmacy claims data	Pharmacy costs Medical costs Physician office visit costs Other costs	Currency Year: USD, 2002 Cost of Nonadherence*: IC:$3780 ($4906.39), OC:$504 ($654.19), PC:$1872 ($2429.83), MC:$6228 ($8083.86), POC:$1944 ($2523.29) OtC:$12 ($15.58)	cost description
*Gilmer et al**[16]*** 2004 US	To evaluate the relationship between adherence to treatment with antipsychotic medication and health expenditures. Secondary objective was to identify risk factors predictive of non-adherence.	Design: Retrospective database analysis Follow Up: 1 year Sample Size: 1619 (<49%:388, 50-79%:259, 80-100%:664, >110%:308)	Measure: cumulative possession ratio Classification: <49% = nonadherent, 50-79% = partially adherent, 80-100% = adherent, >110% = excess medication fillers Method of Assessment:	Total costs Outpatient costs Pharmacy costs Hospitalisation costs	Type of Costs: adjusted Classification: disease state specific Currency Year: USD, 1999 Cost of Nonadherence: TC:$8168 ($11261.74), OC:$3464 ($4776.04), PC:$1542 ($2126.05), HC:$3413 ($4705.72)	Quality: medium Classification: cost description

			pharmacy claims data			
*Hong et al**[17]*** 2011 UK	To investigate clinical and economic consequences of medication non-adherence in the treatment of bipolar disorder following a manic or mixed episode.	Design: Prospective observational study Follow Up: 21 months Sample Size: 1341(A:1024, NA:317)	Measure: assessed by treating psychiatrist Classification: adherent vs. nonadherent Method of Assessment: observational assessment	Total costs Inpatient costs Outpatient costs Pharmacy costs Hospitalisation costs	Type of Costs: unadjusted Classification: all cause and disease state specific Currency Year: GBP, 2008 Cost of Nonadherence*: all cause: PC:£55.43 ($94.47) Disease state specific: TC:£5846.29 ($9964.10) IC:£2740.57 ($4670.88), OC:£1082.86 ($1845.57), PC:£1630.29 ($2778.58), HC:£337.14 ($574.60)	Quality: medium Classification: cost description
*Jiang et al**[18]*** 2015 US	To estimate the impact of adherence to and persistence with atypical antipsychotics on healthcare costs and risk of hospitalisation by controlling potential sources of endogeneity	Design: Retrospective cohort study Follow Up: 2 years Sample Size: 32374 (A:11642, NA:20732)	Measure: PDC Classification: (PDC≥80% = adherent, PDC<80% = nonadherent) Method of Assessment: medical and pharmacy claims data	Total costs Pharmacy costs Medical services costs	Type of Costs: unadjusted Classification: disease state specific Currency Year: USD, 2011 Cost of Nonadherence: Disease state specific: TC:$14141 ($14517.37) PC:$3971 ($4076.69), MSC:$10170 ($10440.68)	Quality: low Classification: cost description
*Joe et al**[19]*** 2016 South Korea	To investigate the association between psychiatric medication non-compliance and psychiatric and non-psychiatric service utilisation and costs.	Design: Retrospective cohort study Follow Up: 1 year Sample Size: 7848 (A:2774, NA:2774, P:1956, NP:1956)	Measure: percentage of days of psychiatric prescription (PDP)	Total costs	Type of Costs: adjusted Classification: all cause and disease state specific Currency Year: USD, 2011 Cost of Nonadherence: all cause:	Quality: medium Classification: cost outcome description

			Classification: PDP≥80% = adherent, PDP<80% = nonadherent; persistent = continued medication without interruption ≥ 56 day, non-persistent = at least one medication interruption > 56 days Method of Assessment: health insurance data		TC:$4961 ($5271.40) Disease state specific: TC:$3061 ($3252.50)	
*Knapp et al**[20]*** 2004 UK	To assess the relative impact of non-adherence and other factors associated with resource use and costs incurred by people with schizophrenia.	Design: Retrospective cohort study Follow Up: 1 year Sample Size: 658 (A:549, NA:109)	Measure: self-report Classification: adherent vs. nonadherent Method of Assessment: survey	Total costs Inpatient costs External services costs	Type of Costs: predicted Classification: disease state specific Currency Year: GBP, 2001 Cost of Nonadherence: TC:£57580 ($116434.12) IC:£6714 ($13576.57), ESC:£1603 ($3241.47)	Quality: medium Classification: cost analysis
*Offord et al**[21]*** 2013 US	To quantify early nonadherence to antipsychotic medications in patients with schizophrenia and its impact on short-term	Design: Retrospective cohort study Follow Up: 1 year	Measure: time to discontinuation	Total costs Outpatient costs Pharmacy costs	Type of Costs: adjusted Classification: all cause and disease state specific Currency Year: USD, 2008	Quality: medium Classification:

	antipsychotic adherence, healthcare utilisation and costs.	Sample Size: 1462 (A:589, NA:873)	Classification: adherent vs. nonadherent Method of Assessment: pharmacy claims data	Hospitalisation costs	Cost of Nonadherence: all cause: TC:$15400 ($17132.34) OC:$5773 ($6422.40), PC:$3777 ($4201.87), HC:$5850 ($6508.06) Disease state specific: TC:$5358 ($5960.72) OC:$858 ($954.52), PC:$1549 ($1723.25), HC:$2952 ($3284.07)	cost description
*Offord et al**[22]*** 2013 US	To examine the impact of medication adherence on healthcare utilisation among Medicare insured schizophrenia patients.	Design: Retrospective cohort study Follow Up: 1 year Sample Size: 354 (A:126, NA:228)	Measure: MPR Classification: MPR ≥ 70= high adherence, MPR < 70 = low adherence Method of Assessment: pharmacy claims data	Inpatient costs Pharmacy costs	Type of Costs: adjusted Classification: all cause and disease state specific Currency Year: USD, 2008 Cost of Nonadherence: all cause: IC:$9053 ($10071.37), PC:$4267 ($4746.99), Disease state specific: IC:$2468 ($2745.62), PC:$1085 ($1207.05)	Quality: low Classification: cost description
*Robertson et al[**23**]* *2014* *US*	To examine the impact of the combination of treatment utilisation and medication possession on arrest and incarceration outcomes and on costs.	Design: Retrospective cohort study Follow Up:90 days Sample Size:1376 (90/90:637, 60/90:240, 30/90:174, 0/90:316)	Measure: MPR Classification: MPR ≥80% = adherent Method of Assessment: Medicaid claims data	Total costs Inpatient costs Outpatient costs ED costs Pharmacy costs Target case management costs	Type of Costs: unadjusted Classification: disease state specific Currency Year: USD,2005 Cost of Nonadherence*: TC(90/90):$28068 ($33495.65), TC(60/90):$21720 ($25920.11),	Quality: medium Classification: cost description

Psychiatric assessment costs	TC(30/90):$21084 ($25161.12), TC(0/90):$12516 ($14936.28),
Arrest costs	IC(90/90):$12168 ($14520.99),
Incarceration costs	IC(60/90):$10068 ($12014.90), IC(30/90):$11376 ($13575.84), IC(0/90):$5592 ($6673.35), OC(90/90):$6468 ($7718.75), OC(60/90):$4152 ($4954.89), OC(30/90):$2916 ($3479.88), OC(0/90):$2136 ($2549.05), EDC(90/90):$96 ($114.56), EDC(60/90):$108 ($128.88), EDC(30/90):$144 ($171.85), EDC(0/90):$84 ($100.24), PC(90/90):$5316 ($6343.98), PC(60/90):$3468 ($4138.63), PC(30/90):$2232 ($2663.61), PC(0/90):$984 ($1174.28), TCMC(90/90):$2100 ($2506.09), TCMC(60/90):$1404 ($1675.50), TCMC(30/90):$1596 ($1904.63), TCMC(0/90):$516 ($615.78), PAC(90/90):$240 ($286.41), PAC(60/90):$228 ($272.09), PAC(30/90):$204 ($243.45), PAC(0/90):$156 ($186.17), ArC(90/90):$780 ($930.83), ArC(60/90):$1032 ($1231.56),

					ArC(30/90):$1140 ($1360.45), ArC(0/90):$1200 ($1432.05), InC(90/90):$888 ($1059.72), InC(60/90):$1272 ($1517.97), InC(30/90):$1476 ($1761.42), InC(0/90):$1860 ($2219.68)	
*Robinson et al**[24]*** 2006 US	To determine if the type of antidepressant drug is related to adherence and assess the 6 month health care costs among newly diagnosed patients.	Design: Retrospective claims analysis Follow Up: 6 months Sample Size: 60386 (A:11526, NA:8860)	Measure: Antidepressant medication management measures Classification: meeting less than <3 medication management measures = nonadherent Method of Assessment: pharmacy claims data, Medicaid data, observational assessment	Total costs Inpatient costs Outpatient costs ED visit costs Pharmacy costs Physician office visit costs	Type of Costs: unadjusted Classification: all cause and disease state specific Currency Year: USD, 2004 Cost of Nonadherence*: all cause: TC:$12658 ($15678.21) IC:$3006 ($3723.24), OC:$6118 ($7577.76), EDC:$334 ($413.69) PC:$3200 ($3963.52), POC:$178 ($220.47) Disease state specific: TC:$2028 ($2511.88) IC:$102 ($126.34), OC:$734 ($909.13), EDC:$18 ($22.29) PC:$1174 ($1454.12), POC:$120 ($148.63)	Quality: medium Classification: cost description
*Svarstad et al**[25]*** 2001 US	To examine the relationship of medication non-adherence to hospital use and costs among severely mentally ill clients.	Design: Retrospective database analysis Follow Up: 1 year Sample Size: 619 (A:413, NA:206)	Measure: quarter pharmacy claims Classification: one or more quarters	Hospitalisation costs	Type of Costs: unadjusted Classification: all cause and disease state specific Currency Year: USD, 1990 Cost of Nonadherence: all cause: HC:$3992 ($6593.06)	Quality: medium Classification: cost description

			without a claim = nonadherent Method of Assessment: pharmacy claims data, previous study data		Disease state specific: Schizophrenia/schizoaffective disorder: HC:$3421 ($5650.01) Bipolar disorder: HC:$9701 ($16021.85), Other severe mental illness: HCD:$3024 ($4994.34)	
*White et al**[26]*** 2003 US	To evaluate the economic impact of antidepressant treatment adherence among patients treated for depression	Design: Retrospective database analysis Follow Up: 6 months Sample Size: 14190 (A:5638, NA:8552)	Measure: MPR Classification: MPR≥70% = adherent, MPR<70% = nonadherent Method of Assessment: pharmacy claims data	Total costs Pharmacy costs Medical costs	Type of Costs: adjusted Classification: disease state specific Currency Year: USD, 1999 Cost of Nonadherence: TC:$11815 ($16290.09) PC:$1123 ($1548.35), MC:$10692 ($14741.74)	Quality: medium Classification: cost description
Diabetes						
*An et al**[27]*** 2014 Korea	This study evaluated the association between medication adherence and clinical/economic outcomes in patients with type II diabetes mellitus in the republic of Korea over 3 year period.	Design: Prospective cohort study Follow Up: 3 years Sample Size: 608 (A:472, NA:136)	Measure: MPR Classification: MPR≥90% = adherent, MPR<90% = nonadherent Method of Assessment: pharmacy claims data	Total costs Outpatient costs Hospitalisation costs	Type of Costs: unadjusted Classification: disease state specific Currency Year: USD, 2007 Cost of Nonadherence*: TC:$1657.11 ($1884.14) OC: $1413.99 ($1608.20), HC: $243.11 ($276.12)	Quality: medium Classification: cost description
Buysman et al[28]	To examine the impact of real world adherence on glycaemic	Design: Retrospective database analysis	Measure: PDC	Pharmacy costs	Type of Costs: unadjusted	Quality: low Classification:

2017 *US*	control in type 2 diabetes patients treated with canagliflozin.	Follow Up: 12 months Sample Size: 2261 (A:1215, NA:1046)	Classification: PDC≥80% = highly adherent, PDC<80% = less than highly adherent Method of Assessment: healthcare claims data		Classification: all cause and disease state specific Currency Year: USD, 2014 Cost of Nonadherence: all cause: PC: $7225 ($7297.39) Disease state specific: PC: $4660 ($4706.69)	cost description
Curtis et al[29] *2017* *US*	Examine the association between adherence to glucose lowering agents and patient outcomes in an adult type 2 diabetes population	Design: Retrospective analysis Follow Up: 3 years Sample Size: 228074 (A:117864, NA:110210)	Measure: PDC Classification: PDC≥80% = adherent, PDC<80% = nonadherent Method of Assessment: healthcare claims data	Total costs Outpatient costs Pharmacy costs Acute care costs	Type of Costs: adjusted Classification: all cause Currency Year: USD, 2014 Cost of Nonadherence: TC:$38633 ($39020.09) OC: $16964 ($17134), PC: $9390 ($9484.08), ACC:$12153 ($12274.77)	Quality: medium Classification: cost description
*Egede et al**[30]*** 2012 US	To examine the longitudinal effects of medication nonadherence on key costs and estimate potential savings from increased adherence using novel methodology that accounts for shared correlation among cost categories.	Design: Retrospective cohort study Follow Up: 5 years Sample Size: 740195 (A:427390, NA:312805)	Measure: MPR Classification: MPR≥80% = adherent, MPR<80% = nonadherent Method of Assessment: pharmacy claims data	Inpatient costs Outpatient costs Pharmacy costs	Type of Costs: unadjusted Classification: disease state specific Currency Year: USD, 2006 Cost of Nonadherence*: IC:$14515.24 ($17886.40) OC: $3599.27 ($4434.16), PC: $1073.12 ($1322.42)	Quality: high Classification: cost outcome description

Gentil et al**[31]** 2015 Canada	To examine healthcare costs associated with adherence to oral antihyperglycemic agents and the effects of depression and anxiety disorders on these in older adults with type 2 diabetes	Design: Retrospective, observational cohort analysis Follow Up: 1 year Sample Size: 301 (A:224, NA:77)	Measure: MPR Classification: MPR≥80% = adherent, MPR<80% = nonadherent Method of Assessment: pharmacy claims data	Total costs Inpatient costs Outpatient costs Pharmacy costs Physician office visit costs	Type of Costs: adjusted and unadjusted Classification: all cause and disease state specific Currency Year: CAD, 2010 Cost of Nonadherence: Adjusted all cause: TC:$11124 ($9818.67), IC:$7419 ($6548.43) OC: $2687 ($2371.70), PC: $504 ($444.86), POC:$513 ($452.80) Adjusted disease state specific: TC:$4477 ($3951.65), IC:$2836 ($2503.21) OC: $1518 ($1339.87), PC###: $-444 ($-391.90), POC:$568 ($517.24) Unadjusted all cause: TC:$14979 ($13221.30), IC:$6351 ($5605.75) OC: $4058 ($3581.82), PC: $3503 ($3091.94), POC:$1066 ($940.91) Unadjusted disease state specific: TC:$9008 ($7950.97), IC:$2854 ($2519.10) OC: $2654 ($2342.57), PC: $2498 ($2204.87), POC:$1002 ($884.42)	Quality: medium Classification: cost description

*Hagen et al**[32]*** 2014 US	To evaluate the relationships between compliance with oral hypoglycemic agents and healthcare/ short term disability costs	Design: Retrospective, observational cohort analysis Follow Up: 1 year Sample Size: 4978 (A:2820, NA:2158)	Measure: PDC Classification: PDC≥80% = compliant, PDC<80% = noncompliant Method of Assessment: pharmacy claims data	Healthcare costs Pharmacy costs Medical costs Short term disability costs	Type of Costs: adjusted and unadjusted Classification: all cause and disease state specific Currency Year: USD, 2003 Cost of Nonadherence: Adjusted all cause: PC: $1668 ($2065.99), Adjusted disease state specific: HC:$7642 ($9465.39), PC:$614 ($760.50), MC:$5974 ($7399.40), STDC:$1840 ($2279.03) Unadjusted all cause: PC:$1727 ($2139.06) Unadjusted disease state specific: HC:$6919 ($8569.88), PC:$785 ($972.30), MC:$5192 ($6430.82), STDC:$1717 ($2126.68)	Quality: medium Classification: cost description
*Hansen et al**[33]*** 2010 US	To compare all cause total health care costs and diabetes mellitus specific health care costs between patients who were adherent or non-adherent to monotherapy with metformin, pioglitazone or a sulfonylurea and to examine whether cost differences varied among patients using these oral antidiabetic drugs.	Design: Retrospective, cohort study Follow Up: 2 years Sample Size: 108592 (A:63830, NA:44762)	Measure: MPR Classification: MPR≥80% = adherent, MPR<80% = nonadherent Method of Assessment: pharmacy claims data	Total Healthcare costs Inpatient costs Outpatient costs Pharmacy costs	Type of Costs: adjusted and unadjusted Classification: all cause and disease state specific Currency Year: USD, 2005 Cost of Nonadherence[#]: Adjusted all cause: THC:$13258 ($15911.01) Adjusted disease state specific: THC:$2284 ($2741.04) Unadjusted all cause:	Quality: medium Classification: cost description

					THC:$15448.50 ($18539.90), IC:$4242.33 ($5091.25), OC:$ 7377.83, PC:$3828 ($4594.01) Unadjusted disease state specific: THC:$3232.33 ($3879.15), IC:$873.50 ($1048.29), OC:$1545.67($1854.96), PC:$812.67 ($975.29)	
*Hong et al**[34]*** 2011 South Korea	To assess the relationship between initial adherence to oral antihyperglycemic medications and subsequent health outcomes.	Design: Retrospective, cohort study Follow Up: 3 years Sample Size: 40082 (A:11800, NA:28282)	Measure: MPR Classification: MPR≥80% = adherent, MPR<80% = nonadherent Method of Assessment: pharmacy claims data	Total costs Hospitalisation costs	Type of Costs: unadjusted Classification: disease state specific Currency Year: KRW, 2007 Cost of Nonadherence: TC:₩765453 ($1142.31), HC:₩397549 ($593.28)	Quality: medium Classification: cost description
*Jha et al**[35]*** 2012 US	How often do previously non-adherent patients become adherent and vice versa? Are changes in adherence associated with increased or decreased hospitalisations or emergency department visits? Are there certain subgroups of populations that seem to benefit more than others when they adhere to their medication?	Design: Retrospective, observational claims analysis Follow Up: unclear Sample Size: 135639 (A:99976, NA:36553)	Measure: MPR Classification: MPR≥80% = adherent, MPR<80% = nonadherent Method of Assessment: pharmacy claims data	Total costs ED costs Hospitalisation costs	Type of Costs: adjusted Classification: disease state specific Currency Year: USD, 2011 Cost of Nonadherence***: TC:$4680000000 ($5006563305.49), EDC:$735000000 ($786287185.80), HC:$3950000000 ($4225625012.11)	Quality: high Classification: cost outcome description

	What are the financial implications of changes in adherence for the nation at large and for Medicare?					
*White et al**[36]*** 2004 US	To assess the relationship between diabetic medication adherence, total healthcare costs and utilisation with patients with type 2 diabetes mellitus and concomitant diabetes and cardiovascular disease.	Design: Retrospective, database analysis Follow Up: 1 year Sample Size: 67029 (>95:20170, 75-95: 14074, <75:16713)	Measure: MPR Classification: MPR≥95%, MPR>75%<95%, MPR<75% Method of Assessment: pharmacy claims data	Total costs Pharmacy costs Non-pharmacy costs	Type of Costs: adjusted and unadjusted Classification: disease state specific Currency Year: USD, 2000 Cost of Nonadherence: adjusted: TC(≥95):$4835 ($6518.17), TC(75-95):$5314 ($7163.92), TC(<75):$5706 ($7692.38), PC(≥95):$1429 ($1926.47), PC(75-95):$1157 ($1559.78), PC(<75):$762 ($1027.27), NPC(≥95):$3406 ($4591.70), NPC(75-95):$4157 ($5604.14), NPC(<75):$4944 ($6665.11) Unadjusted: TC(≥95):$4809 ($6483.12), TC(75-95):$5333 ($7189.53), TC(<75):$5605 ($7556.22), PC(≥95):$1402 ($1890.07), PC(75-95):$1153 ($1554.38), PC(<75):$766 ($1032.66), NPC(≥95):$3407 ($4593.05), NPC(75-95):$4180 ($5635.15), NPC(<75):$4839 ($6523.56)	Quality: low Classification: cost analysis

*Wu et al**[37]*** 2009 US	To examine the predictors of duloxetine compliance and its association with healthcare costs among diabetic peripheral neuropathic pain (DPNP) patients.	Design: Retrospective, cohort study Follow Up: 1 year Sample Size: 2354 (A:830, NA:1524)	Measure: MPR Classification: MPR≥80%= high compliance, MPR<80% = low compliance Subgroup Analysis: commercial and Medicare supplemental Method of Assessment: pharmacy claims data	Total healthcare costs Inpatient costs Outpatient costs Pharmacy costs	Type of Costs: adjusted Classification: all cause and disease state specific Currency Year: USD, 2006 Cost of Nonadherence: adjusted all cause: THC(com):$32407 ($37732.29), THC(med):$24622 ($28668.02), IC(com):$ 12851($14692.74), IC(med):$ 6754 ($7863.85), OC(com):$11888 ($13841.50), OC(med):$10598 ($12339.52), PC(com):$7667 ($8926.88), PC(med):$7270 ($8464.65) Adjusted disease state specific: Diabetes: THC(com):$10024 ($11671.20), THC(med):$5015 ($5839.09), IC(com):$2232 ($2598.77), IC(med):$2606 ($3034.23), OC(com):$1989 ($2315.84), OC(med):$1231 ($1433.28), PC(com):$1451 ($1689.44), PC(med):$1179 ($1372.74) DPNP: THC(com):$3565 ($4150.82), THC(med):$2384 ($2775.75), IC(com):$1739 ($2024.76),	Quality: medium Classification: cost description

					IC(med):$1048 ($1220.21), OC(com):$362 ($421.49), OC(med):$181 ($210.74), PC(com):$1464 ($1704.57) PC(med):$1155 ($1344.80)	
Osteoporosis						
*Briesacher et al**[38]*** 2007 US	To assess rates of osteoporotic fractures and health care utilisation as a function of bisphosphonate compliance in usual clinical practice.	Design: Retrospective, cohort study Follow Up: 3 years Sample Size: 17988 (not specified)	Measure: MPR Classification: 80-100% = adherent, 60-79% = moderate adherence, 40-59% = moderate adherence, 20-39% = nonadherent, 0-19% = nonadherent Method of Assessment: pharmacy claims data	Total costs Inpatient costs Outpatient costs Pharmacy costs	Type of Costs: adjusted and unadjusted Classification: disease state specific Currency Year: USD, 2004 Cost of Nonadherence****: adjusted: TC(80-100):-$859 (-$1063.96), TC(60-79):-$474 (-$587.10), TC(40-59):-$366 (-$453.33), TC(20-39):$151 ($187.03), IC(80-100):-$3233 (-$4004.40), IC(60-79):-$856(-$1060.24), IC(40-59):-$6221 (-$7705.34), IC(20-39):-$585 (-$724.58), OC(80-100):-$445 (-$551.18), OC(60-79):-$538 (-$666.37), OC(40-59):-$236 (-$292.31), OC(20-39):$60 ($74.32), PC(80-100):$997 ($1234.89), PC(60-79):$923 ($1143.23), PC(40-59):$402 ($497.92), PC(20-39):$160($198.18) Unadjusted: TC(80-100):-$1273 (-$1576.74),	Quality: medium Classification: cost description

					TC(60-79):-$294 (-$364.15), TC(40-59):-$573 (-$709.72), TC(20-39):$101 ($125.10), IC(80-100):-$883 (-$1093.68), IC(60-79):-$384 (-$475.62), IC(40-59):-$597 (-$739.44), IC(20-39):-$93 (-$115.19), OC(80-100):-$774 (-$958.68), OC(60-79):-$193 (-$239.05), OC(40-59):-$145 (-$179.60), OC(20-39):$148 ($183.31), PC(80-100):$384 ($475.62), PC(60-79):$284 ($351.76), PC(40-59):$170 ($210.56), PC(20-39):$48 ($59.45)	
*Eisenberg et a**[39]*** 2015 US	To determine healthcare outcomes associated with compliance and noncompliance to bisphosphonate therapy in women diagnosed with osteoporosis	Design: Retrospective claims study Follow Up: 2 years Sample Size: 27905 (A:11368, NA:16537)	Measure: MPR Classification: (≥70% = compliant, <70% = noncompliant Method of Assessment: pharmacy claims data	Total costs Inpatient costs Outpatient costs ED costs Pharmacy costs Physician office visit costs	Type of Costs: unadjusted Classification: all cause and disease state specific Currency Year: USD, 2012 Cost of Nonadherence: all cause: TC:$7237 ($7550.72), IC:$1986 ($2072.09), OC:$2057 ($2146.17), EDC:$258 ($269.18), PC:$2197 ($2292.24), POC:$738 ($769.99) Disease state specific: TC:$674 ($703.22), IC:$334 ($348.48), OC:$77 ($80.34), EDC:$5 ($5.22),	Quality: medium Classification: cost description

					PC:$213 ($222.23), POC:$44 ($45.91)	
*Halpern et al**[40]*** 2011 US	To examine the associations of adherence to osteoporosis therapies with occurrence of closed fracture, all cause medical costs and all cause hospitalisations.	Design: Retrospective analysis Follow Up: 540 days Sample Size: 21655 (≥80%:8759, ≥50<80%:5237, <50%:7659)	Measure: MPR Classification: (≥80% = high adherence, ≥50<80% = moderate adherence, <50% = low adherence Method of Assessment: pharmacy claims data	Medical costs	Type of Costs: unadjusted Classification: all cause Currency Year: USD, 2006 Cost of Nonadherence: commercial: MC(≥80):$4295 ($5000.78), MC(50-80):$4697 ($5468.84), MC(<50):$5596 ($6515.56) Medicare: MC(≥80):$4590 ($5344.25), MC(50-80):$5536 ($6445.71), MC(<50):$5801 ($6754.25)	Quality: medium Classification: cost outcome description
*Hazel-Fernandez et al**[41]*** 2013 US	To evaluate the healthcare utilisation patterns of medicare part D beneficiaries newly initiating teriparatide and to assess the association of medication adherence and persistence with bone fracture.	Design: Retrospective cohort study Follow Up: 12 months Sample Size: 761 (≥80%:163, ≥50<80%:57, <50%:541)	Measure: PDC Classification: (≥80% = high adherence, ≥50<80% = moderate adherence, <50% = low adherence Method of Assessment: pharmacy claims data	Total healthcare costs Inpatient costs Outpatient costs ED costs Pharmacy costs	Type of Costs: unadjusted Classification: disease state specific and fracture related Currency Year: USD, 2010 Cost of Nonadherence*: Disease state specific: THC(≥80):$21033 ($22942.39), THC(50-80):$25574 ($27895.62), THC(<50):$15528 ($16937.64), IC(≥80):$2198 ($2397.54), IC(50-80):$8448 ($9214.91), IC(<50):$4897 ($5341.55), OC(≥80):$5151 ($5618.61), OC(50-80):$6439 ($7023.54), OC(<50):$5806 ($6333.07), EDC(≥80):$211 ($230.15),	Quality: medium Classification: cost outcome description

					EDC(50-80):$330 ($359.96), EDC(<50):$465 ($507.21), PC(≥80):$13472 ($14695), PC(50-80):$10358 ($11298.31), PC(<50):$4361 ($4756.89) Fracture related: THC(≥80):$12670 ($13820.19), THC(50-80):$9292 ($10135.53), THC(<50):$4419 ($4820.16), IC(≥80):$366 ($399.23), IC(50-80):$830 ($905.35), IC(<50):$1325 ($1445.28), OC(≥80):$1048 ($1143.14), OC(50-80):$955 ($1041.70), OC(<50):$767 ($836.63), EDC(≥80):$6 ($6.54), EDC(50-80):$9 ($9.82), EDC(<50):$44 ($47.99), PC(≥80):$10810 ($11791.34), PC(50-80):$7420 ($8093.59), PC(<50):$2068 ($2255.73)	
*Huybrechts et al**[42]*** 2006 US	To evaluate non-compliance with osteoporosis medications as well as its implications for health and economic outcomes in actual practice.	Design: Retrospective cohort study Follow Up: 5 years Sample Size: 38120 (A:9530, NA:28590)	Measure: MPR Classification: (≥80% = compliant, <50% = noncompliant) Method of Assessment:	Total costs Medical costs Institutional costs	Type of Costs: unadjusted Classification: disease state specific Currency Year: USD, 2000 Cost of Nonadherence: TC:$7200 ($9706.44), MC:$1476 ($1989.84), InstC:$5736 ($7732.80)	Quality: low Classification: cost description

			pharmacy claims data			
*Kjellberge al**[43]*** 2016 Denmark	To estimate the rate of oral bisphosphonate compliance among Danish women and to examine the association of noncompliance with health care resource use and cost.	Design: Retrospective cohort study Follow Up: 1 year Sample Size: 38234 (A:26806, NA:11428)	Measure: MPR Classification: (≥70% = compliant, <70% = noncompliant) Method of Assessment: pharmacy claims data	Total costs Medical costs	Type of Costs: adjusted Classification: all cause and disease state specific Currency Year: Euro, 2011 Cost of Nonadherence: all cause: TC:€4933 ($6209.58), MC:€3471 ($4369.20), Disease state specific: TC:€754 ($949.12), MC:€426 ($536.24),	Quality: high Classification: cost outcome description
*Modi et al**[44]*** 2015 US	To evaluate compliance with osteoporosis treatments and determine fracture and healthcare burden associated with noncompliance	Design: Retrospective cohort study Follow Up: 1 year Sample Size: 27913 (A:23430, NA:34483)	Measure: MPR Classification: (≥80% = compliant, <80% = noncompliant) Method of Assessment: healthcare claims data	Total costs Inpatient costs Outpatient costs ED costs Pharmacy costs Medical costs Other costs	Type of Costs: unadjusted Classification: all cause and disease state specific Currency Year: USD, 2011 Cost of Nonadherence: all cause: TC:$11749 ($12484.12), IC:$8768 ($9316.60), OC:$3945 ($4191.83), EDC:$104 ($110.51), PC:$2981 ($3167.52), MC:$8768 ($9316.60), OtC:$997 ($1059.38) Disease state specific: TC:$630 ($669.42), IC:$443 ($470.72), OC:$158 ($167.89), EDC:$3 ($3.19), PC:$325 ($345.33),	Quality: medium Classification: cost outcome description

					OtC:$26 ($27.63)	
*Olsen et al**[45]*** 2013 Denmark	To assess the association between refill compliance and all cause health care costs.	Design: Retrospective observational study Follow Up: 2 years Sample Size: 47176 (not specified)	Measure: MPR Classification: (≥80% = optimal compliance, >50<80% = suboptimal compliance, <50% = low compliance Method of Assessment: pharmacy claims data	Fracture costs	Type of Costs: unadjusted Classification: fracture site specific Currency Year: DKK, 2010 Cost of Nonadherence: Hip fracture: FC(50-80):kr817575.50 ($74531.41), FC(<50):kr4454954 ($549987.04) Spine fracture: FC(50-80):kr174700 ($21568.12), FC(<50):kr226472 ($27959.14) Humerus fracture: FC(50-80):kr117776.50 ($14540.12), FC(<50):kr795217.50 ($98173.70) Forearm fracture: FC(50-80):-kr463024 (-$57162.70), FC(<50):kr45072.50 ($8665.81) Other fracture: FC(50-80):-kr19261.50 (-$2377.93), FC(<50):kr684067.50 ($84451.66)	Quality: medium Classification: cost analysis
*Sunyecz et al**[46]*** 2008	To examine the relationship between persistence and compliance with	Design: Retrospective observational study Follow Up: 3 years	Measure: MPR Classification: (≥80% =	Total healthcare costs	Type of Costs: unadjusted Classification: all cause and disease state specific	Quality: low Classification:

US	bisphosphonate therapy and total and osteoporosis related costs and healthcare resource utilisation in a cohort of female bisphosphonate naïve users.	Sample Size: 32944 (A:12186, NA:20758)	compliant, <80% = noncompliant) Method of Assessment: pharmacy claims data	Inpatient costs Outpatient costs ED costs Pharmacy costs Radiology costs	Currency Year: USD, 2005 Cost of Nonadherence: All cause: THC:$23660 ($28394.52), IC:$18839 ($22608.81), OC:$10061 ($12074.27), EDC:$832 ($988.49), PC:$6941 ($8329.94), RC:$1079 ($1294.91) Disease state specific: THC:$1602 ($1922.57), IC:$14074 ($16890.30), OC:$501 ($601.25), EDC:$452 ($542.45), PC:$918 ($1101.70), RC:$184 ($220.82)	cost description
*Zhao et al**[47]*** 2014 US	To examine the association between teriparatide adherence and healthcare utilisation and costs among hip fracture patients.	Design: Retrospective cohort study Follow Up: 36 months Sample Size: 824 (≥80:362, 50-80%:219, <50%:243)	Measure: PDC Classification: (≥80% = high, 50-80% = medium, <50% = low) Method of Assessment: pharmacy claims data	Total healthcare costs Inpatient costs Outpatient costs Pharmacy costs	Type of Costs: adjusted and unadjusted Classification: disease state specific Currency Year: USD, 2010 Cost of Nonadherence*: Adjusted: THC(≥80):$34428 ($37553.4), THC(50-80):$37956 ($41401.68), THC(<50):$31188 ($34019.28), IC(≥80):$7548 ($8233.20), IC(50-80):$11520 ($1256.80), IC(<50):$11556 ($12605.04), OC(≥80):$9312 ($10157.40),	Quality: medium Classification: cost description

					OC(50-80):$12816 ($13979.40), OC(<50):$13044 ($14228.16), PC(≥80):$18864 ($20576.52), PC(50-80):$13116 ($14306.64), PC(<50):$7452 ($8128.44) Unadjusted: THC(≥80):$37464 ($40865.04), THC(50-80):$35076 ($38260.20), THC(<50):$29484 ($32160.60), IC(≥80):$7092 ($7735.80), IC(50-80):$11100 ($12107.64), IC(<50):$10632 ($11597.16), OC(≥80):$9900 ($10798.68), OC(50-80):$11352 ($12382.56), OC(<50):$11988 ($13076.28), PC(≥80):$20484 ($22343.52), PC(50-80):$12624 ($13770), PC(<50):$6864 ($7487.16)	
*Zhao et al**[48]*** 2013 US	To examine the association between teriparatide (TPTD) adherence and healthcare utilisation and costs in real world US kyphoplasty/vertebroplasty (KV) patients.	Design: Retrospective observational cohort study Follow Up: 36 months Sample Size: 1568 (≥80: 783, 50-80%: 382, <50%: 403)	Measure: PDC Classification: (≥80% = high, 50-80% = medium, <50% = low) Method of Assessment: pharmacy claims data	Total healthcare costs Inpatient costs Outpatient costs Pharmacy costs	Type of Costs: adjusted and unadjusted Classification: disease state specific Currency Year: USD, 2010 Cost of Nonadherence*: Adjusted: THC(≥80):$40212 ($43862.52), THC(50-80):$40512 ($44189.76),	Quality: medium Classification: cost description

					THC(<50):$40128 ($43770.84), IC(≥80):$8136 ($8874.60), IC(50-80):$12060 ($13154.76), IC(<50):$15444 ($43404.36), OC(≥80):$12924 ($14097.24), OC(50-80):$14928 ($16283.16), OC(<50):$17568 ($19162.80), PC(≥80):$19392 ($21152.40), PC(50-80):$13908 ($15170.52), PC(<50):$8700 ($9843.24) Unadjusted: THC(≥80):$42768 ($46650.48), THC(50-80):$36780 ($40118.88), THC(<50):$39792 ($43404.36), IC(≥80):$7620 ($8311.80), IC(50-80):$12228 ($13338.12), IC(<50):$15768 ($17199.48), OC(≥80):$14580 ($15903.60), OC(50-80):$12108 ($13207.20), OC(<50):$15324 ($16715.16), PC(≥80):$20568 ($22435.20), PC(50-80):$12444 ($13573.68), PC(<50):$8700 ($9489.84)	
Respiratory Disease						
Davis et al[49] 2017	To assess the association between adherence levels to	Design: Observational cohort study	Measure: PDC	Total costs	Type of Costs: adjusted	Quality: medium

US	different inhaled corticosteroid/long acting β_2-adrenergic agonist and COPD exacerbation rates and costs in commercially insured population	Follow Up: 12 months Sample Size: 13657 (≥80%: 1898, ≥50<80%: 1971, ≥30 <50%: 2443, <30% :7345)	Classification: (≥80 = adherent, ≥50<80% = mildly nonadherent, ≥30 <50% = moderately nonadherent, <30% highly nonadherent) Method of Assessment: commercially insured healthcare claims data	Outpatient costs Pharmacy costs Hospitalisation costs	Classification: all cause and disease state specific Currency Year: USD, 2014 Cost of Nonadherence*: All cause: TC(≥80):$22546 ($22772.24), TC(50-80):$25545 ($25800.95), TC(30-50):$24303 ($24546.51), TC(<30):$25148 ($25399.98), OC(≥80):$7816 ($7894.31), OC(50-80):$8225 ($8307.41), OC(30-50):$8365 ($8448.81), OC(<30):$8857 ($8945.74), PC(≥80):$7954 ($8033.70), PC(50-80):$6862 ($6930.76), PC(30-50):$5485 ($5539.96), PC(<30):$4395 ($4439.04), HC(≥80):$6106 ($6167.51), HC(50-80):$9391 ($9485.09), HC(30-50):$9171 ($9262.89), HC(<30):$10849 ($10957.70) Disease state specific: TC(≥80):$8075.33 ($8156.24), TC(50-80):$7053 ($7123.67), TC(30-50):$6623 ($6689.36), TC(<30):$5644 ($5700.55), OC(≥80):$2194.33 ($2216.32), OC(50-80):$1947 ($1966.51), OC(30-50):$1997 ($2017.01), OC(<30):$2152 ($2173.56),	Classification: cost description

					PC(≥80):$4464 ($4508.73), PC(50-80):$3345 ($3378.52), PC(30-50):$2307 ($2330.12), PC(<30):$1569 ($1584.72), HC(≥80):$1074.67 ($1085.44), HC(50-80):$1155 ($1166.57), HC(30-50):$1619 ($1635.22), HC(<30):$1405 ($1419.08)	
*Delea et al**[50]*** 2008 US	To assess the association between adherence with fluticasone propionate/salmeterol combination product in a single inhaler and asthma care utilisation and costs in asthma patients in typical US clinical practice	Design: Retrospective longitudinal cohort study Follow Up: 24 months Sample Size: 12907 (≥75: 2612, 50-75%: 3608, 25-50%: 5035, <25%: 1652)	Measure: MPR Classification: (≥75, 50-75%, 25-50%, <25%) Method of Assessment: pharmacy claims data	Total costs Outpatient costs ED costs Other costs	Type of Costs: unadjusted Classification: disease state specific Currency Year: USD, 2003 Cost of Nonadherence*: TC(≥75):$1564 ($1990.27), TC(50-75):$1128 ($1435.44), TC(25-50):$900 ($1145.30), TC(<25):$632 ($804.25), OC(≥75):$1272 ($1618.69), OC(50-75):$852 ($1084.21), OC(25-50):$600 ($763.53), OC(<25):$388 ($493.75), EDC(≥75):$32 ($40.72), EDC(50-75):$36 ($45.81), EDC(25-50):$60 ($76.35), EDC(<25):$48 ($61.08), OtC(≥75):$292 ($371.59), OtC(50-75):$276 ($351.22), OtC(25-50):$300 ($381.77), OtC(<25):$240 ($305.41)	Quality: medium Classification: cost description
*Diehl et al**[51]*** 2010 US	To evaluate respiratory-related medical outcomes and cost for infants who were prescribed and	Design: Retrospective claims analysis Follow Up: 7 months	Measure: 37 day gap in claims	Total costs Pharmacy costs Services costs	Type of Costs: unadjusted Classification: disease state specific	Quality: medium Classification:

	received palivizumab in accordance with the dosing schedule recommended by the American Academy of Paediatrics in 2006 versus those who did not.	Sample Size: 245 (A:73, NA:172)	Classification: (>37 day gap in claims = noncompliant) Method of Assessment: pharmacy claims data		Currency Year: USD, 2007 Cost of Nonadherence: TC:$19093.46 ($21656.12), PC:$7647.40 ($8673.81), SC**:$11604.03 ($13161.45)	cost description
*Joshi et al**[52]*** 2006 US	Examine the association of medication adherence with workplace productivity and health related quality of life in asthma patients.	Design: quantitative analysis Follow Up: Sample Size: 385 (high:150, medium:73, low: 162)	Measure: Morisky scale Classification: (0= high adherence, 1-2 = medium adherence, >2 = low adherence) Method of Assessment: questionnaire	Total productivity cost Absenteeism costs Presenteeism costs	Type of Costs: unadjusted Classification: disease state specific Currency Year: USD, 2002 Cost of Nonadherence##: TPC(0):$1210.90 ($1571.73), TPC(1-2):$1428.50 ($1854.17), TPC(>2):$1073.10 ($1392.87), AbC(0):$633.70 ($822.53), AbC(1-2):$608.90 ($790.34), AbC(>2):$474.80 ($616.28), PrC(0):$577.20 ($749.20), PrC(1-2):$819.60 ($1063.83), PrC(>2):$598.30 ($776.59)	Quality: medium Classification: cost outcome description
*Miravitlles et al**[53]*** 2013 Spain	To analyse the economic impact of non-adherence to the global initiative for obstructive lung disease (GOLD) guidelines in patients with chronic obstructive pulmonary disease (COPD).	Design: multicentre, retrospective, observational study Follow Up: 18 months Sample Size: 1365 (A:246, NA:1119)	Measure: GOLD 2007 Guidelines Classification: (adherent, nonadherent) Method of Assessment: GOLD guidelines	ED costs Pharmacy costs Physician office visit costs Hospitalisation costs Primary care costs Interdisciplinary visit costs	Type of Costs: unadjusted Classification: disease state specific Currency Year: EUR, 2009 Cost of Nonadherence: EDC:€40.83 ($57.91), PC:€771.50 ($1094.27), POC:€106.29 ($150.76), HC:€101.61 ($144.12) PCC:€123.84 ($175.65),	Quality: medium Classification: cost description

				Medical test costs Radiology costs Laboratory costs	IntC:€321.44 ($455.92), MTC:€36.66 ($51.99), RC:€24.24 ($34.38), LC:€17.35 ($24.61)	
*Quittner et al**[54]*** 2014 US	To evaluate associations of adherence to pulmonary medications, age, healthcare use and cost among cystic fibrosis patients.	Design: retrospective, cohort study Follow Up: 2 years Sample Size: 3287 (≥80%: 663, 50-80%: 949, <50%: 1675)	Measure: MPR Classification: (≥80% = high adherence, 50-80% = moderate adherence, <50% = low adherence) Method of Assessment: pharmacy claims data	Total healthcare costs	Type of Costs: unadjusted Classification: all cause and disease state specific Currency Year: USD, 2011 Cost of Nonadherence*: All cause: THC(≥80):$35749.50 ($38244.05), THC(50-80):$45031.50 ($48173.73), THC(<50):$50284.50 ($53793.28) Disease state specific: THC(≥80):$23764 ($25422.22), THC(50-80):$33132.50 ($35444.44), THC(<50):$33894 ($36259.07)	Quality: medium Classification: cost description
Gastrointestinal Disease						
*Carter et al**[55]*** 2011 US	To further evaluate the impact of adherence to infliximab on CD related utilisation and inpatient costs in the first year of treatment using a different definition of adherence and a larger more diverse claims database.	Design: retrospective, observational cohort claims analysis Follow Up: 12 months Sample Size: 638 (A:466, NA:172)	Measure: number of infusions in 12 month period Classification: (7-9 infusions = adherent, <7	Hospitalisation costs	Type of Costs: unadjusted Classification: disease state specific Currency Year: USD, 2007 Cost of Nonadherence: HC:$37783 ($42854.12)	Quality: medium Classification: cost outcome description

			infusions = nonadherent) Method of Assessment: health claims data			
*Gosselin et al**[56]*** 2009 US	To examine the effects of gastroesophageal reflux disease (GERD) patients compliance with PPI therapy on health care resource utilisation and costs.	Design: retrospective cohort study Follow Up: Sample Size: 41837 (A:28321, NA:13516)	Measure: MPR Classification: (≥80% = adherent, <80% = nonadherent) Method of Assessment: pharmacy claims data	Total costs Inpatient costs Outpatient costs Pharmacy costs Medical costs	Type of Costs: adjusted Classification: disease state specific Currency Year: USD, 2003 Cost of Nonadherence: TC:$9497 ($12085.43), IC:$2116 ($2692.72), OC:$5458 ($6945.59), PC:$1922 ($2445.85), MC:$7575 ($9639.58)	Quality: medium Classification: cost description
*Kane et al**[57]*** 2009 US	To evaluate adherence to infliximab maintenance therapy and the impact of medication adherence on healthcare utilisation and costs by patients.	Design: retrospective cohort analysis Follow Up: 12 months Sample Size: 571 (A:375, NA:196)	Measure: number of infusions in 12 month period Classification: (≥8 infusions = adherent, <7 infusions = nonadherent) Method of Assessment: health claims data	Outpatient costs ED costs Pharmacy costs Medical costs Hospitalisation costs	Type of Costs: unadjusted Classification: all cause and disease state specific Currency Year: USD, 2004 Cost of Nonadherence: All cause: OC:$6679 ($8272.62), EDC:$314 ($388.92), MC:$16129 ($19977.40), HC:$6893 ($8537.68) Disease state specific: OC:$3931 ($4868.94), EDC:$91 ($112.71), PC:$18751 ($23225.01), MC:$10243 ($12686.99), HC:$4494 ($5566.27)	Quality: medium Classification: cost outcome description

*Mitra et al**[58]*** 2012 US	To assess the association between adherence to oral 5-aminosalicylates (5-ASAs) and all cause costs and health care utilisation among patients with active ulcerative colitis.	Design: retrospective, observational cohort study Follow Up: 12 months Sample Size: 1693 (A:476, NA:1216)	Measure: MPR Classification: (≥80% = adherent, <80% = nonadherent) Method of Assessment: pharmacy claims data	Inpatient costs Outpatient costs ED costs Pharmacy costs Ancillary costs Non-pharmacy costs	Type of Costs: adjusted Classification: all cause and disease state specific Currency Year: USD, 2010 Cost of Nonadherence: All cause: PC:$1541.60 ($1681.55) Disease state specific: IC:$28726.65 ($31334.47), OC:$1145.67 ($1249.67), EDC:$635.95 ($693.68), AC:$4923.29 ($5370.23), NPC:$14226.32 ($15517.79)	Quality: high Classification: cost description
*Wan et al**[59]*** 2014 US	To examine the effect of adherence versus non-adherence on healthcare costs in patients with inflammatory bowel disease.	Design: retrospective cohort analysis Follow Up: 360 days Sample Size: 1646 (A:674, NA:972)	Measure: MPR Classification: (≥80% = adherent, <80% = nonadherent) Method of Assessment: pharmacy claims data	Total costs Total healthcare costs Inpatient costs Outpatient costs ED costs Pharmacy costs	Type of Costs: adjusted Classification: all cause and disease state specific Currency Year: USD, 2009 Cost of Nonadherence: All cause: TC:$47411 ($52341.27), THC:$32522 ($35903.96), IC:$17634 ($19467.76), OC:$10909 ($12043.43), EDC:$458 ($505.63), PC:$18410 ($20324.46) Disease state specific: TC:$33652 ($37151.47), THC:$18764 ($20715.27), IC:$12564 ($13870.53), OC:$5890 ($6502.50), EDC:$48 ($52.99), PC:$15150 ($16725.45)	Quality: high Classification: cost description

Epilepsy						
*Davis et al**[60]*** 2008 US	To assess the extent of refill non-adherence with antiepileptic drugs (AEDs) and the potential association between AED non-adherence and healthcare costs in an adult managed care population.	Design: retrospective claims analysis Follow Up: 12 months Sample Size: 10892 (A:6644, NA:4248)	Measure: MPR Classification: (≥80% = adherent, <80% = nonadherent) Method of Assessment: pharmacy claims data	Total costs Inpatient costs ED costs Pharmacy costs Other pharmacy costs	Type of Costs: unadjusted Classification: disease state specific Currency Year: USD, 2003 Cost of Nonadherence[###]: TC:$1466 ($1865.56), IC:$1799 ($2289.32), EDC:$260 ($330.86), PC:-$71 (-$90.35), OtPC:-$358 (-$455.57)	Quality: medium Classification: cost description
*Ettinger et al**[61]*** 2009 US	To assess the extent to which elderly patients diagnosed with epilepsy are non-adherent to antiepileptic drugs (AEDs) and the potential association between AED non-adherence and seizure recurrence, resource utilisation and annual direct medical costs.	Design: retrospective claims analysis Follow Up: 12 months Sample Size: 1278 (A:758, NA:520)	Measure: MPR Classification: (≥80% = adherent, <80% = nonadherent) Method of Assessment: pharmacy claims data	Total costs Inpatient costs ED costs Pharmacy costs Physician Office visit costs Ancillary costs Other pharmacy costs	Type of Costs: unadjusted Classification: disease state specific Currency Year: USD, 2003 Cost of Nonadherence: TC:$17817 ($22673.06), IC:$2714 ($3453.71), EDC:$526 ($669.36), PC:$347 ($441.58), POC:$3063 ($3897.83), AC:$8344 ($10618.18), OtPC:$2822 ($3591.14)	Quality: medium Classification: cost outcome description
*Faught et al**[62]*** 2009 US	To study the impact of non-adherence to antiepileptic drugs (AEDs) on healthcare utilisation and direct medical costs in a Medicaid population.	Design: retrospective observational open cohort design Follow Up: 4.65 years Sample Size: 33658 (A:24907, NA:8751)	Measure: MPR Classification: (≥80% = adherent, <80% = nonadherent) Method of Assessment: pharmacy claims data	Total costs Inpatient costs Outpatient costs ED costs Pharmacy costs Other pharmacy costs	Type of Costs: unadjusted Classification: disease state specific Currency Year: USD, 2002 Cost of Nonadherence[*]: TC:$14417.64 ($18713.91), IC:$6682.28 ($6873.51), OC:$2172.40 ($2819.75), EDC:$405.96 ($526.93),	Quality: medium Classification: cost description

					PC:$822.40 ($1067.46), OtPC:$4334.60 ($5626.26)	
HIV/AIDS						
*Barnett et al**[63]*** 2011 US	To characterise the cost of HIV care including combination antiretroviral treatment.	Design: retrospective observational cohort study Follow Up: 1 year Sample Size: 1896 (not specified)	Measure: antiretroviral taking behaviour Classification: (85% adherence with 3 antiretroviral therapy regimen = adherent, all other use = nonadherent) Method of Assessment: pharmacy claims data	Total costs	Type of Costs: unadjusted Classification: disease state specific; viral load count Currency Year: USD, 2006 Cost of Nonadherence**: High viral load: TC:$25824 ($30067.54) Low viral load: TC:$20509.67 ($23879.92)	Quality: medium Classification: cost description
*Cooke et al**[64]*** 2014 US	To measure adherence to antiretroviral therapy regimens in commercially insured patients with HIV infection and analyse the clinical and demographic factors associated with ≥90% adherence.	Design: retrospective claims analysis Follow Up: 1 year Sample Size: 3528 (A:1737, NA:640)	Measure: MPR Classification: (≥90% = adherent, <90% = nonadherent) Method of Assessment: pharmacy claims data	Total healthcare costs Inpatient costs Outpatient costs Pharmacy costs	Type of Costs: unadjusted Classification: disease state specific Currency Year: USD, 2011 Cost of Nonadherence: THC:$18868 ($20184.58), IC:$2700 ($2888.40), OC:$915 ($978.85), PC:$15253 ($16317.33)	Quality: medium Classification: cost description
*Pruitt et al**[65]*** 2015 US	To examine Medicaid insured HIV positive and AIDS diagnosed patient groups separately to	Design: retrospective cohort study Follow Up: 2 years	Measure: MPR Classification: (≥90% =	Total costs Inpatient costs	Type of Costs: unadjusted Classification: disease state specific	Quality: medium Classification:

	determine association of ART adherence to mean monthly total healthcare expenditures in the 24 month measurement period.	Sample Size: 502 (A:56, NA:176)	adherent, <90% = nonadherent) Method of Assessment: pharmacy claims data	Outpatient costs Pharmacy costs Other pharmacy costs Behavioural health inpatient costs	Currency Year: USD, 2009 Cost of Nonadherence*: HIV: TC:$15360 ($16957.32), IC:$3864 ($4265.76), OC:$3948 ($4358.52), PC:$4956 ($5471.40), OtPC:$1764 ($1947.48), BHIC:$840 ($927.36) AIDS: TC:$27648 ($30523.08), IC:$13008 ($14360.76), OC:$5880 ($6491.52), PC:$5640 ($6226.56), OtPC:$2580 ($2848.32), BHIC:$528 ($582.96)	cost description
Parkinson's Disease						
*Davis et al**[66]*** 2010 US	To assess the extent to which patients diagnosed with Parkinson's disease are non-adherent with antiparkinson therapy and the potential association between non-adherence and all cause medical costs.	Design: retrospective administrative claims study Follow Up: 12 months Sample Size: 3119 (A:1211, NA:1908)	Measure: MPR Classification: (≥80% = adherent, <80% = nonadherent) Method of Assessment: pharmacy claims data	Total costs Pharmacy costs Medical costs	Type of Costs: unadjusted Classification: disease state specific Currency Year: USD, 2001 Cost of Nonadherence: TC:$18511 ($24262.36), PC:$2684 ($3537.36), MC:$15827 ($20859.12)	Quality: medium Classification: cost outcome description
*Delea et al**[67]*** 2011 US	To assess the associations between adherence to levodopa/carbidopa/entacapone therapy and healthcare utilisation and costs.	Design: retrospective historical cohort study Follow Up: 12 months Sample Size: 1215 (A:617, NA:598)	Measure: PDC Classification: (≥80% = satisfactory,	Total costs Inpatient costs Pharmacy costs Other costs	Type of Costs: adjusted and unadjusted Classification: all cause and disease state specific Currency Year: USD, 2005	Quality: high Classification: cost description

			<80% = unsatisfactory) Method of Assessment: pharmacy claims data		Cost of Nonadherence: Adjusted all cause: TC:$19686 ($23625.30), IC:$5954 ($7145.43), PC:$6391 ($7669.88), OtC:$8795 ($10554.94) Adjusted disease state specific: TC:$8574 ($10289.71), IC:$3705 ($4446.39), PC:$3850 ($4620.41), OtC:$1884 ($2261) Unadjusted all cause: TC:$19362 ($23236.46), IC:$5463 ($6556.18), PC:$6158 ($7390.26), OtC:$7740 ($9288.82) Unadjusted disease state specific: TC:$9156 ($10988.18), IC:$3238 ($3885.94), PC:$3789 ($4547.20), OtC:$2129 ($2555.03)	
*Wei et al**[68]*** 2014 US	To examine the associations of adherence to antiparkinson drugs with healthcare utilisation and economic outcomes.	Design: retrospective cross-sectional study Follow Up: 19 months Sample Size: 7583 (90-100%:3948, 80-89%:1456, ≤79%:2179)	Measure: MPR Classification: (>90<100% = high, >80<89% = moderate, ≤79% = low) Method of Assessment: pharmacy claims data	Total costs Inpatient costs Outpatient costs Pharmacy costs	Type of Costs: unadjusted Classification: disease state specific Currency Year: USD, 2007 Cost of Nonadherence: TC(90-100):$36407 ($41293.43), TC(80-89):$43417 ($49244.29), TC(≤79):$45867 ($52023.13),	Quality: medium Classification: cost description

					IC(90-100):$15294 ($17346.71), IC(80-89):$21603 ($24502.49), IC(≤79):$24727 ($28045.78), OC(90-100):$10155 ($11517.97), OC(80-89):$11838 ($13426.86), OC(≤79):$12889 ($14618.92), PC(90-100):$10957 ($12427.61), PC(80-89):$9976 ($11314.95), PC(≤79):$8251 ($9358.42)	
Musculoskeletal						
*Ivanova et al**[69]*** 2012 US	To compare the rates of severe relapse and total direct and indirect costs over a 2 year period between US based employees with MS who were adherent and non-adherent to disease modifying drugs.	Design: retrospective cohort study Follow Up: 2 years Sample Size: 648 (A:448, NA:200)	Measure: MPR Classification: (≥80% = adherent, <80% = nonadherent) Method of Assessment: pharmacy claims data	Total costs Total healthcare costs Inpatient costs Outpatient costs ED costs Pharmacy costs Medical costs Short term disability costs Absenteeism cost	Type of Costs: unadjusted Classification: all cause, disease state specific and indirect Currency Year: USD, 2007 Cost of Nonadherence*: All cause: TC:$8079 ($9276.76), THC:$6022 ($6830.25), IC:$1030.50 ($1168.81), OC:$3231 ($3664.65), EDC:$143.50 ($162.76), PC:$1617 ($1834.03), MC:$4405.50 ($4996.79) Disease state specific: TC:$3005 ($3408.32), IC:$505 ($572.78), OC:$1710 ($1939.51),	Quality: high Classification: cost outcome description

					EDC:$37 ($41.97), PC:$753 ($854.07), MC:$2252 ($2554.26) Indirect: STDC:$1231 ($1396.22), AbC:$826 ($936.86)	
*Tan et al**[70]*** 2011 US	To assess the impact of treatment adherence on MS related hospitalisations (inpatient), ER visits, MS relapses and medical costs.	Design: retrospective cohort study Follow Up: 12 months Sample Size: 2446 (A:1459, NA:987)	Measure: MPR Classification: (≥80% = adherent, <80% = nonadherent) Method of Assessment: pharmacy claims data	Medical costs	Type of Costs: adjusted and unadjusted Classification: disease state specific Currency Year: USD, 2007 Cost of Nonadherence: Adjusted: MC:$4348 ($5062.49) Unadjusted: MC:$5179 ($6030.04)	Quality: medium Classification: cost description
*Zhao et al**[71]*** 2011 US	To examine predictors associated with duloxetine adherence and its association with healthcare costs among fibromyalgia patients.	Design: retrospective cohort analysis Follow Up: 12 months Sample Size: 5435 (A:1744, NA:3691)	Measure: MPR Classification: (≥80% = adherent, <80% = nonadherent) Method of Assessment: pharmacy claims data	Total costs Inpatient costs Outpatient costs Pharmacy costs	Type of Costs: adjusted Classification: disease state specific Currency Year: USD, 2008 Cost of Nonadherence: commercial: TC:$20323 ($22609.12), IC:$4808 ($5348.85), OC:$9822 ($10926.87), PC:$5693 ($6333.40) Medicare: TC:$25282 ($28125.96), IC:$8604 ($9571.86), OC:$10068 ($11200.54), PC:$6611 ($7354.67)	Quality: medium Classification: cost analysis
Cancer						

*Darkow et al**[72]*** 2007 US	Estimate the association between treatment interruptions and non-adherence with imatinib and healthcare costs for US managed care patients.	Design: retrospective observational cohort analysis Follow Up: 12 months Sample Size: 267 (≥95%:120, 90-95%:25, 50-90%:69, <50%:53)	Measure: MPR Classification: (≥95% = very high, >90<95% = high, >50<90% = intermediate, <50% = low) Method of Assessment: pharmacy claims data	Total healthcare costs Inpatient costs Outpatient costs ED costs Pharmacy costs Medical costs Other pharmacy costs Other costs	Type of Costs: unadjusted Classification: disease state specific Currency Year: USD, 2004 Cost of Nonadherence: THC(≥95):$42250 ($52330.90), THC(90-95):$39236 ($48597.76), THC(50-90):$54770 ($67838.19), THC(<50):$131357 ($162698.93), IC(≥95):$1156 ($1431.82), IC(90-95):$1362 ($1686.97), IC(50-90):$19096 ($23652.33), IC(<50):$81572 ($101035.18), OC(≥95):$9299 ($11517.75), OC(90-95):$11148 ($13807.93), OC(50-90):$14631 ($18121.97), OC(<50):$33956 ($42057.94), EDC(≥95):$36 ($44.59), EDC(90-95):$568 ($703.53), EDC(50-90):$104 ($128.81), EDC(<50):$183 ($226.66), PC(≥95):$29056 ($35988.80), PC(90-95):$23693 ($29346.18), PC(50-90):$18330 ($22703.56), PC(<50):$8733 ($10816.70),	Quality: high Classification: cost description

					MC(≥95):$10731 ($13291.43), MC(90-95):$13452 ($16661.66), MC(50-90):$34202 ($42362.64), MC(<50):$116892 ($144782.57),OtPC(≥95):$2462 ($3049.44), OtPC(90-95):$2091 ($2589.92), OtPC(50-90):$2238 ($2771.99), OtPC(<50):$5732 ($7099.66), OtC(≥95):$241 ($298.50), OtC(90-95):$374 ($463.24), OtC(50-90):$371 ($459.52), OtC(<50):$1181 ($1462.79)	
*Wu et al**[73]*** 2010 US	To examine the association between adherence with imatinib and direct healthcare costs and resource utilisation	Design: retrospective observational cohort analysis Follow Up: 12 months Sample Size: 592 (A:350, NA:242)	Measure: MPR Classification: (≥85% = high adherence, <85% = low adherence) Method of Assessment: pharmacy claims data	Total costs Inpatient costs Outpatient costs ED costs Pharmacy costs Other pharmacy costs	Type of Costs: unadjusted Classification: disease state specific Currency Year: USD, 2008 Cost of Nonadherence: TC:$107341 ($119415.73), IC:$44498 ($49503.55), OC:$34097 ($37932.55), EDC:$248 ($275.90), PC:$22846 ($25415.93), OtPC:$5652 ($6287.79)	Quality: medium Classification: cost description
Addiction						
*Leider et al**[74]*** 2011 US	To assess the economic burden of chronic opioid users and to determine whether opioid	Design: retrospective claims based analysis Follow Up: 12 months	Measure: urine testing	Total healthcare costs	Type of Costs: unadjusted Classification: disease state specific	Quality: medium

	regimen non-adherence contributes to increased healthcare costs.	Sample Size: 2100 (A:442, NA:1658)	Classification: (positive test = nonadherent, negative test = adherent) Method of Assessment: health claims data	Inpatient costs Outpatient costs ED costs Pharmacy costs Medical costs	Currency Year: USD, 2008 Cost of Nonadherence: THC:$26433 ($29406.43), IC:$6361 ($7076.55), OC:$9734 ($10828.97), EDC:$421 ($468.36), PC:$7960 ($8855.42), MC:$1957 ($2177.14)	Classification: cost analysis
Ruetsch et al[75] 2017 US	To examine patient characteristics and outcomes associated with nonadherence to buprenorphine and to identify specific patterns of nonadherent behaviour.	Design: cross sectional, retrospective analysis health claims data Follow Up: 12 months Sample Size: 477 (A:172, NA:305)	Measure: MPR Classification: (≥80% = adherent, <80% = nonadherent) Method of Assessment: health claims data	Total healthcare costs Inpatient costs Outpatient costs ED costs Pharmacy costs Physician office visit costs Medical costs	Type of Costs: unadjusted Classification: disease state specific Currency Year: USD, 2013 Cost of Nonadherence: THC:$16555 ($16995.62), IC:$5657 ($5807.57), OC:$5594 ($5742.89), EDC:$1147 ($1177.53), PC:$2365 ($2427.95), POC:$1765 ($1811.98), MC:$14190 ($14567.68)	Quality: medium Classification: cost description
*Tkacz et al**[76]*** 2014 US	To estimate the healthcare service utilisation and costs associated with buprenorphine medication assisted therapy adherence among a sample of opioid dependent members.	Design: retrospective cohort analysis Follow Up: 12 months Sample Size: 455 (A:146, NA:309)	Measure: MPR Classification: (≥80% = adherent, <80% = nonadherent) Method of Assessment: pharmacy claims data	Total healthcare costs Inpatient costs Outpatient costs ED costs Pharmacy costs	Type of Costs: adjusted and unadjusted Classification: disease state specific Currency Year: USD, 2010 Cost of Nonadherence: Adjusted: THC:$49051 ($53503.88), IC:$26470 ($28872.96), OC:$14570 ($15892.67), EDC:$4439 ($4841.98),	Quality: medium Classification: cost description

					PC:$3581 ($3906.09) Unadjusted: THC:$47868 ($52213.49), IC:$26043 ($28407.20), OC:$14173 ($15459.63), EDC:$4058 ($4426.39), PC:$3557 ($3879.91)	
Metabolic conditions other than diabetes mellitus						
*Lee et al**[77]*** 2011 US	To assess the relationship between medication adherence and healthcare costs among US patients on dialysis given cinacalcet to manage secondary hypoparathyroidism.	Design: retrospective cohort study Follow Up: 12 months Sample Size: 4923 (A:1372, NA:1304)	Measure: MPR Classification: (≥80% = high adherent, <80% = low adherent) Method of Assessment: pharmacy claims data	Total costs Inpatient costs Outpatient costs ED costs Pharmacy costs Other pharmacy costs	Type of Costs: unadjusted Classification: all cause and disease state specific Currency Year: USD, 2010 Cost of Nonadherence: All cause: PC:$5556 ($6060.38) Disease state specific: TC:$126996 ($138524.78), IC:$14844 ($16191.55), OC:$101854 ($111100.37), EDC:$734 ($800.63), PC:$3244 ($3538.49), OtPC:$9564 ($10432.23)	Quality: medium Classification: cost description
Blood						
*Candrilli et al**[78]*** 2011 US	To investigate the relationships among hydroxyurea adherence, healthcare utilisation and healthcare costs.	Design: retrospective longitudinal study Follow Up: 12 months Sample Size: 312 (A:110, NA:202)	Measure: MPR Classification: (≥80% = adherent,	Total costs Inpatient costs ED costs Pharmacy costs	Type of Costs: adjusted Classification: all cause and disease state specific Currency Year: USD, 2008 Cost of Nonadherence:	Quality: medium Classification: cost description

			<80% = nonadherent) Method of Assessment: pharmacy claims data	Physician office visit costs Ancillary costs	All cause: TC:$ 20436 ($22734.83), IC:$9780 ($10880.15), EDC:$837 ($931.15), PC:$2579 ($2869.11), POC:$3483 ($3874.80), AC:$3911 ($4350.95) Disease state specific: TC:$12097 ($13457.78), IC:$7315 ($8137.86), EDC:$552 ($614.09), PC:$158 ($175.77), POC:$1865 ($2074.79), AC:$2466 ($2743.40)	
All						
*Alvarez Payero et al**[79]*** 2014 Spain	To determine the profile of patients who are admitted to hospital as a result of non-adherence and to obtain an estimate of the economic impact for the hospital.	Design: retrospective observational study Follow Up: 1527 days Sample Size: 87 (A:21, NA:66)	Measure: pharmacy records Classification: (>75% = adherent, ≤75% = nonadherent) Method of Assessment: pharmacy and hospital claims data	Hospitalisation costs	Type of Costs: unadjusted Classification: all cause Currency Year: EUR, 2012 Cost of Nonadherence####: All cause: HC:€6275.80 ($8893.94)	Quality: low Classification: cost outcome description

A: adherent, NA: non-adherent, MA: moderate adherence, LA: low adherence, NC: non-compliance, NP: non-persistent, P: persistent, T: turbulent, NE: no exposure, CHF: chronic heart failure, THC: total healthcare costs, TC: total costs, IC: inpatient costs, OC: outpatient costs, EDC: emergency department visit costs, PC: pharmacy costs, MC: medical costs, HC: hospitalisation costs, POC: physician office visit costs, NPC: non-pharmacy costs, AC: ancillary costs, OtPC: other pharmacy costs, PAC: psychiatric assessment costs, TCMC: targeted case management costs, ArC: arrest costs, InC: incarceration costs, RC: radiology costs, SC: services costs, InstC:

institutional costs, ESC: external services costs, MSC: medical services costs, PCC: primary care costs, MTC: medical test costs, FC: fracture costs, LC: laboratory costs, IntC: interdisciplinary costs, BHIC: behavioural health inpatient costs, STDC: short term disability costs, WCC: workers compensation costs, PTOC: paid time off costs, TPC: total productivity costs, AbC: absenteeism costs, PrC: presenteeism costs, ACC: acute care costs, OtC: other costs, com: commercial patients, med: Medicare supplemental patients, USD: United States dollar, GBP: Great British Pound, EUR: Euro, DKK: Danish krone, CAD: Canadian dollar, KRW: South Korean won

*: extrapolated annual cost; **: subgroups averaged; ***: national estimate of cost; ****: negative value as costs modelled against lowest adherence group; #: extrapolated annual cost and subgroups averaged; ##: cost represents losses in workplace productivity; ###: negative value as costs modelled against adherent group; ####: cost per episode of nonadherence

1. Aubert RE, Yao J, Xia F, et al. Is there a relationship between early statin compliance and a reduction in healthcare utilization? The American journal of managed care 2010;**16**:459-66
2. Casciano JP, Dotiwala ZJ, Martin BC, et al. The costs of warfarin underuse and nonadherence in patients with atrial fibrillation: a commercial insurer perspective. Journal of managed care pharmacy : JMCP 2013;**19**:302-16
3. Dilokthornsakul P, Chaiyakunapruk N, Nimpitakpong P, et al. The Effects of Medication Supply on Hospitalizations and Health-Care Costs in Patients with Chronic Heart Failure. Value in Health 2012;**15**:S9-S14 doi: 10.1016/j.jval.2011.11.019[published Online First: Epub Date]|.
4. Dragomir A, Côté R, Roy L, et al. Impact of adherence to antihypertensive agents on clinical outcomes and hospitalization costs. Medical care 2010;**48**:418-25 doi: 10.1097/MLR.0b013e3181d567bd[published Online First: Epub Date]|.
5. Dragomir A, Cote R, White M, et al. Relationship between adherence level to statins, clinical issues and health-care costs in real-life clinical setting. Value in health : the journal of the International Society for Pharmacoeconomics and Outcomes Research 2010;**13**(1):87-94 doi: 10.1111/j.1524-4733.2009.00583.x[published Online First: Epub Date]|.
6. Pittman DG, Chen W, Bowlin SJ, et al. Adherence to statins, subsequent healthcare costs, and cardiovascular hospitalizations. The American journal of cardiology 2011;**107**:1662-6 doi: 10.1016/j.amjcard.2011.01.052[published Online First: Epub Date]|.
7. Pittman DG, Tao Z, Chen W, et al. Antihypertensive medication adherence and subsequent healthcare utilization and costs. The American journal of managed care 2010;**16**:568-76
8. Rizzo JAS, W. R. Variations in compliance among hypertensive patients by drug class: implications for health care costs. Clinical therapeutics 1997;**19**(6):1446-57; discussion 24-5
9. Sokol MC, McGuigan KA, Verbrugge RR, et al. Impact of medication adherence on hospitalization risk and healthcare cost. Medical care 2005;**43**:521-30
10. Stroupe KT, Teal EY, Tu W, et al. Association of Refill Adherence and Health Care Use Among Adults with Hypertension in an Urban Health Care System. Pharmacotherapy 2006;**26**:779-89 doi: 10.1592/phco.26.6.779[published Online First: Epub Date]|.
11. Wu J, Seiber E, Lacombe VA, et al. Medical utilization and costs associated with statin adherence in Medicaid enrollees with type 2 diabetes. The Annals of pharmacotherapy 2011;**45**:342-9 doi: 10.1345/aph.1P539[published Online First: Epub Date]|.
12. Zhao Y, Zabriski S, Bertram C. Associations between statin adherence level, health care costs, and utilization. Journal of managed care & specialty pharmacy 2014;**20**:703-13
13. Bagalman E, Yu-Isenberg KS, Durden E, et al. Indirect costs associated with nonadherence to treatment for bipolar disorder. Journal of occupational and environmental medicine / American College of Occupational and Environmental Medicine 2010;**52**:478-85 doi: 10.1097/JOM.0b013e3181db811d[published Online First: Epub Date]|.

14. Becker MA, Young MS, Ochshorn E, et al. The relationship of antipsychotic medication class and adherence with treatment outcomes and costs for Florida Medicaid beneficiaries with schizophrenia. Administration and policy in mental health 2007;**34**:307-14 doi: 10.1007/s10488-006-0108-5[published Online First: Epub Date]|.
15. Eaddy M, Grogg A, Locklear J. Assessment of compliance with antipsychotic treatment and resource utilization in a Medicaid population. Clinical therapeutics 2005;**27**:263-72 doi: 10.1016/j.clinthera.2005.02.003[published Online First: Epub Date]|.
16. Gilmer TP, Dolder CR, Lacro JP, et al. Adherence to treatment with antipsychotic medication and health care costs among Medicaid beneficiaries with schizophrenia. The American journal of psychiatry 2004;**161**:692-9
17. Hong J, Reed C, Novick D, et al. Clinical and economic consequences of medication non-adherence in the treatment of patients with a manic/mixed episode of bipolar disorder: results from the European Mania in Bipolar Longitudinal Evaluation of Medication (EMBLEM) study. Psychiatry research 2011;**190**:110-4 doi: 10.1016/j.psychres.2011.04.016[published Online First: Epub Date]|.
18. Jiang Y, Ni W. Estimating the Impact of Adherence to and Persistence with Atypical Antipsychotic Therapy on Health Care Costs and Risk of Hospitalization. Pharmacotherapy 2015;**35**(9):813-22 doi: 10.1002/phar.1634[published Online First: Epub Date]|.
19. Joe S, Lee JS. Association between non-compliance with psychiatric treatment and non-psychiatric service utilization and costs in patients with schizophrenia and related disorders. BMC psychiatry 2016;**16**(1):444 doi: 10.1186/s12888-016-1156-3[published Online First: Epub Date]|.
20. Knapp M, King D, Pugner K, et al. Non-adherence to antipsychotic medication regimens: associations with resource use and costs. The British journal of psychiatry : the journal of mental science 2004;**184**:509-16
21. Offord S, Lin J, Mirski D, et al. Impact of early nonadherence to oral antipsychotics on clinical and economic outcomes among patients with schizophrenia. Advances in therapy 2013;**30**:286-97 doi: 10.1007/s12325-013-0016-5[published Online First: Epub Date]|.
22. Offord S, Lin J, Wong B, et al. Impact of oral antipsychotic medication adherence on healthcare resource utilization among schizophrenia patients with Medicare coverage. Community mental health journal 2013;**49**:625-9 doi: 10.1007/s10597-013-9638-y[published Online First: Epub Date]|.
23. Robertson AG, Swanson JW, Van Dorn RA, et al. Treatment participation and medication adherence: effects on criminal justice costs of persons with mental illness. Psychiatric services (Washington, DC) 2014;**65**(10):1189-91 doi: 10.1176/appi.ps.201400247[published Online First: Epub Date]|.
24. Robinson RL, Long SR, Chang S, et al. Higher costs and therapeutic factors associated with adherence to NCQA HEDIS antidepressant medication management measures: analysis of administrative claims. Journal of managed care pharmacy : JMCP 2006;**12**:43-54
25. Svarstad BL, Shireman TI, Sweeney JK. Using drug claims data to assess the relationship of medication adherence with hospitalization and costs. Psychiatric services (Washington, DC) 2001;**52**:805-11
26. White TJV, Ann; Ory, Caron; Dezii, Christopher M.; Chang, Eunice. Economic Impact of Patient Adherence with Antidepressant Therapy Within a Managed Care Organization. Disease Management & Health Outcomes 2003;**11**(12):817-22 doi: 10.2165/00115677-200311120-00006[published Online First: Epub Date]|.

27. An S-Y, Kim HJ, Chun KH, et al. Clinical and economic outcomes in medication-adherent and -nonadherent patients with type 2 diabetes mellitus in the Republic of Korea. Clinical therapeutics 2014;**36**:245-54 doi: 10.1016/j.clinthera.2013.12.012[published Online First: Epub Date]|.
28. Buysman EK, Anderson A, Bacchus S, et al. Retrospective Study on the Impact of Adherence in Achieving Glycemic Goals in Type 2 Diabetes Mellitus Patients Receiving Canagliflozin. Adv Ther 2017;**34**(4):937-53 doi: 10.1007/s12325-017-0500-4[published Online First: Epub Date]|.
29. Curtis SE, Boye KS, Lage MJ, et al. Medication adherence and improved outcomes among patients with type 2 diabetes. The American journal of managed care 2017;**23**(7):e208-e14
30. Egede LE, Gebregziabher M, Dismuke CE, et al. Medication Nonadherence in Diabetes: Longitudinal effects on costs and potential cost savings from improvement. Diabetes care 2012;**35**:2533-39 doi: 10.2337/dc12-0572[published Online First: Epub Date]|.
31. Gentil L, Vasiliadis HM, Preville M, et al. Adherence to Oral Antihyperglycemic Agents Among Older Adults With Mental Disorders and Its Effect on Health Care Costs, Quebec, Canada, 2005-2008. Preventing chronic disease 2015;**12**:E230 doi: 10.5888/pcd12.150412[published Online First: Epub Date]|.
32. Hagen SE, Wright DW, Finch R, et al. Impact of compliance to oral hypoglycemic agents on short-term disability costs in an employer population. Population health management 2014;**17**:35-41 doi: 10.1089/pop.2013.0009[published Online First: Epub Date]|.
33. Hansen RA, Farley JF, Droege M, et al. A retrospective cohort study of economic outcomes and adherence to monotherapy with metformin, pioglitazone, or a sulfonylurea among patients with type 2 diabetes mellitus in the United States from 2003 to 2005. Clinical therapeutics 2010;**32**:1308-19 doi: 10.1016/j.clinthera.2010.07.011[published Online First: Epub Date]|.
34. Hong JS, Kang HC. Relationship between oral antihyperglycemic medication adherence and hospitalization, mortality, and healthcare costs in adult ambulatory care patients with type 2 diabetes in South Korea. Medical care 2011;**49**:378-84 doi: 10.1097/MLR.0b013e31820292d1[published Online First: Epub Date]|.
35. Jha AK, Aubert RE, Yao J, et al. Greater adherence to diabetes drugs is linked to less hospital use and could save nearly $5 billion annually. Health affairs (Project Hope) 2012;**31**:1836-46 doi: 10.1377/hlthaff.2011.1198[published Online First: Epub Date]|.
36. White TJV, Ann; Chang, Eunice; Dezii, Christopher M.; Abrams, Geoffrey D. The Costs of Non-Adherence to Oral Antihyperglycemic Medication in Individuals with Diabetes Mellitus and Concomitant Diabetes Mellitus and Cardiovascular Disease in a Managed Care Environment. Disease Management & Health Outcomes 2004;**12**(3):181-88 doi: 10.2165/00115677-200412030-00004[published Online First: Epub Date]|.
37. Wu N, Chen S, Boulanger L, et al. Duloxetine compliance and its association with healthcare costs among patients with diabetic peripheral neuropathic pain. Journal of medical economics 2009;**12**:192-202 doi: 10.3111/13696990903240559[published Online First: Epub Date]|.
38. Briesacher BA, Andrade SE, Yood RA, et al. Consequences of poor compliance with bisphosphonates. Bone 2007;**41**:882-7 doi: 10.1016/j.bone.2007.07.009[published Online First: Epub Date]|.

39. Eisenberg DF, Placzek H, Gu T, et al. Cost and consequences of noncompliance to oral bisphosphonate treatment. Journal of managed care & specialty pharmacy 2015;**21**(1):56-65 doi: 10.18553/jmcp.2015.21.1.56[published Online First: Epub Date]|.
40. Halpern R, Becker L, Iqbal SU, et al. The association of adherence to osteoporosis therapies with fracture, all-cause medical costs, and all-cause hospitalizations: a retrospective claims analysis of female health plan enrollees with osteoporosis. Journal of managed care pharmacy : JMCP 2011;**17**:25-39
41. Hazel-Fernandez L, Louder AM, Foster SA, et al. Association of teriparatide adherence and persistence with clinical and economic outcomes in Medicare Part D recipients: a retrospective cohort study. BMC musculoskeletal disorders 2013;**14**:4 doi: 10.1186/1471-2474-14-4[published Online First: Epub Date]|.
42. Huybrechts KF, Ishak KJ, Caro JJ. Assessment of compliance with osteoporosis treatment and its consequences in a managed care population. Bone 2006;**38**:922-8 doi: 10.1016/j.bone.2005.10.022[published Online First: Epub Date]|.
43. Kjellberg J, Jorgensen AD, Vestergaard P, et al. Cost and health care resource use associated with noncompliance with oral bisphosphonate therapy: an analysis using Danish health registries. Osteoporosis International 2016;**27**(12):3535-41 doi: 10.1007/s00198-016-3683-7[published Online First: Epub Date]|.
44. Modi A, Siris ES, Tang J, et al. Cost and consequences of noncompliance with osteoporosis treatment among women initiating therapy. Current medical research and opinion 2015;**31**(4):757-65 doi: 10.1185/03007995.2015.1016605[published Online First: Epub Date]|.
45. Olsen KR, Hansen C, Abrahamsen B. Association between refill compliance to oral bisphosphonate treatment, incident fractures, and health care costs--an analysis using national health databases. Osteoporosis international : a journal established as result of cooperation between the European Foundation for Osteoporosis and the National Osteoporosis Foundation of the USA 2013;**24**:2639-47 doi: 10.1007/s00198-013-2365-y[published Online First: Epub Date]|.
46. Sunyecz JA, Mucha L, Baser O, et al. Impact of compliance and persistence with bisphosphonate therapy on health care costs and utilization. Osteoporosis international : a journal established as result of cooperation between the European Foundation for Osteoporosis and the National Osteoporosis Foundation of the USA 2008;**19**:1421-9 doi: 10.1007/s00198-008-0586-2[published Online First: Epub Date]|.
47. Zhao Y, Johnston SS, Smith DM, et al. Association between teriparatide adherence and healthcare utilization and costs among hip fracture patients in the United States. Bone 2014;**60**:221-6 doi: 10.1016/j.bone.2013.12.016[published Online First: Epub Date]|.
48. Zhao Y, Johnston SS, Smith DM, et al. Association between teriparatide adherence and healthcare utilization and costs in real-world US kyphoplasty/vertebroplasty patients. Osteoporosis International 2013;**24**:2525-33 doi: 10.1007/s00198-013-2324-7[published Online First: Epub Date]|.
49. Davis JR, Wu B, Kern DM, et al. Impact of Nonadherence to Inhaled Corticosteroid/LABA Therapy on COPD Exacerbation Rates and Healthcare Costs in a Commercially Insured US Population. American health & drug benefits 2017;**10**(2):92-102

50. Delea TE, Stanford RH, Hagiwara M, et al. Association between adherence with fixed dose combination fluticasone propionate/salmeterol on asthma outcomes and costs*. Current medical research and opinion 2008;**24**:3435-42 doi: 10.1185/03007990802557344[published Online First: Epub Date]|.
51. Diehl JL, Daw JR, Coley KC, et al. Medical utilization associated with palivizumab compliance in a commercial and managed medicaid health plan. Journal of managed care pharmacy : JMCP 2010;**16**:23-31
52. Joshi AV, Madhavan SS, Ambegaonkar A, et al. Association of medication adherence with workplace productivity and health-related quality of life in patients with asthma. The Journal of asthma : official journal of the Association for the Care of Asthma 2006;**43**:521-6 doi: 10.1080/02770900600857010[published Online First: Epub Date]|.
53. Miravitlles M, Sicras A, Crespo C, et al. Costs of chronic obstructive pulmonary disease in relation to compliance with guidelines: a study in the primary care setting. Therapeutic advances in respiratory disease 2013;**7**:139-50 doi: 10.1177/1753465813484080[published Online First: Epub Date]|.
54. Quittner AL, Zhang J, Marynchenko M, et al. Pulmonary medication adherence and health-care use in cystic fibrosis. Chest 2014;**146**:142-51 doi: 10.1378/chest.13-1926[published Online First: Epub Date]|.
55. Carter CT, Waters HC, Smith DB. Impact of infliximab adherence on Crohn's disease-related healthcare utilization and inpatient costs. Advances in therapy 2011;**28**:671-83 doi: 10.1007/s12325-011-0048-7[published Online First: Epub Date]|.
56. Gosselin A, Luo R, Lohoues H, et al. The impact of proton pump inhibitor compliance on health-care resource utilization and costs in patients with gastroesophageal reflux disease. Value in health : the journal of the International Society for Pharmacoeconomics and Outcomes Research 2009;**12**:34-9 doi: 10.1111/j.1524-4733.2008.00399.x[published Online First: Epub Date]|.
57. Kane SV, Chao J, Mulani PM. Adherence to infliximab maintenance therapy and health care utilization and costs by Crohn's disease patients. Advances in therapy 2009;**26**:936-46 doi: 10.1007/s12325-009-0069-7[published Online First: Epub Date]|.
58. Mitra D, Hodgkins P, Yen L, et al. Association between oral 5-ASA adherence and health care utilization and costs among patients with active ulcerative colitis. BMC gastroenterology 2012;**12**:132 doi: 10.1186/1471-230X-12-132[published Online First: Epub Date]|.
59. Wan GJ, Kozma CM, Slaton TL, et al. Inflammatory bowel disease: healthcare costs for patients who are adherent or non-adherent with infliximab therapy. Journal of medical economics 2014;**17**:384-93 doi: 10.3111/13696998.2014.909436[published Online First: Epub Date]|.
60. Davis KLC, S. D.; Edin, H. M. Prevalence and cost of nonadherence with antiepileptic drugs in an adult managed care population. Epilepsia 2008;**49**(3):446-54 doi: 10.1111/j.1528-1167.2007.01414.x[published Online First: Epub Date]|.
61. Ettinger AB, Manjunath R, Candrilli SD, et al. Prevalence and cost of nonadherence to antiepileptic drugs in elderly patients with epilepsy. Epilepsy & behavior : E&B 2009;**14**:324-9 doi: 10.1016/j.yebeh.2008.10.021[published Online First: Epub Date]|.

62. Faught RE, Weiner JR, Guérin A, et al. Impact of nonadherence to antiepileptic drugs on health care utilization and costs: findings from the RANSOM study. Epilepsia 2009;**50**:501-9 doi: 10.1111/j.1528-1167.2008.01794.x[published Online First: Epub Date]|.
63. Barnett PG, Chow A, Joyce VR, et al. Determinants of the Cost of Health Services Used by Veterans With HIV. Medical care 2011;**49**:848-56 doi: 10.1097/MLR.0b013e31821b34c0[published Online First: Epub Date]|.
64. Cooke CE, Lee HY, Xing S. Adherence to antiretroviral therapy in managed care members in the United States: a retrospective claims analysis. Journal of managed care pharmacy : JMCP 2014;**20**:86-92
65. Pruitt Z, Robst J, Langland-Orban B, et al. Healthcare costs associated with antiretroviral adherence among medicaid patients. Applied health economics and health policy 2015;**13**:69-80 doi: 10.1007/s40258-014-0138-1[published Online First: Epub Date]|.
66. Davis KL, Edin HM, Allen JK. Prevalence and cost of medication nonadherence in Parkinson's disease: evidence from administrative claims data. Movement disorders : official journal of the Movement Disorder Society 2010;**25**(4):474-80 doi: 10.1002/mds.22999[published Online First: Epub Date]|.
67. Delea TE, Thomas SK, Hagiwara M. The association between adherence to levodopa/carbidopa/entacapone therapy and healthcare utilization and costs among patients with Parkinson's disease: a retrospective claims-based analysis. CNS drugs 2011;**25**:53-66 doi: 10.2165/11538970-000000000-00000[published Online First: Epub Date]|.
68. Wei Y-J, Palumbo FB, Simoni-Wastila L, et al. Antiparkinson drug adherence and its association with health care utilization and economic outcomes in a Medicare Part D population. Value in health : the journal of the International Society for Pharmacoeconomics and Outcomes Research 2014;**17**:196-204 doi: 10.1016/j.jval.2013.12.003[published Online First: Epub Date]|.
69. Ivanova JI, Bergman RE, Birnbaum HG, et al. Impact of medication adherence to disease-modifying drugs on severe relapse, and direct and indirect costs among employees with multiple sclerosis in the US. Journal of medical economics 2012;**15**:601-9 doi: 10.3111/13696998.2012.667027[published Online First: Epub Date]|.
70. Tan H, Cai Q, Agarwal S, et al. Impact of adherence to disease-modifying therapies on clinical and economic outcomes among patients with multiple sclerosis. Advances in therapy 2011;**28**:51-61 doi: 10.1007/s12325-010-0093-7[published Online First: Epub Date]|.
71. Zhao Y, Chen S-Y, Wu N, et al. Medication Adherence and Healthcare Costs among Fibromyalgia Patients Treated with Duloxetine. Pain Practice 2011;**11**:381-91 doi: 10.1111/j.1533-2500.2010.00431.x[published Online First: Epub Date]|.
72. Darkow T, Henk HJ, Thomas SK, et al. Treatment interruptions and non-adherence with imatinib and associated healthcare costs: a retrospective analysis among managed care patients with chronic myelogenous leukaemia. PharmacoEconomics 2007;**25**:481-96
73. Wu EQ, Johnson S, Beaulieu N, et al. Healthcare resource utilization and costs associated with non-adherence to imatinib treatment in chronic myeloid leukemia patients. Current medical research and opinion 2010;**26**:61-69 doi: 10.1185/03007990903396469[published Online First: Epub Date]|.

74. Leider HL, Dhaliwal J, Davis EJ, et al. Healthcare costs and nonadherence among chronic opioid users. The American journal of managed care 2011;**17**:32-40
75. Ruetsch C, Tkacz J, Nadipelli VR, et al. Heterogeneity of nonadherent buprenorphine patients: subgroup characteristics and outcomes. The American journal of managed care 2017;**23**(6):e172-e79
76. Tkacz J, Volpicelli J, Un H, et al. Relationship between buprenorphine adherence and health service utilization and costs among opioid dependent patients. Journal of substance abuse treatment 2014;**46**:456-62 doi: 10.1016/j.jsat.2013.10.014[published Online First: Epub Date]|.
77. Lee A, Song X, Khan I, et al. Association of cinacalcet adherence and costs in patients on dialysis. Journal of medical economics 2011;**14**:798-804 doi: 10.3111/13696998.2011.627404[published Online First: Epub Date]|.
78. Candrilli SD, O'Brien SH, Ware RE, et al. Hydroxyurea adherence and associated outcomes among Medicaid enrollees with sickle cell disease. American journal of hematology 2011;**86**:273-7 doi: 10.1002/ajh.21968[published Online First: Epub Date]|.
79. Alvarez Payero M, Martinez Lopez de Castro N, Ucha Samartin M, et al. Medication non-adherence as a cause of hospital admissions. Farmacia hospitalaria : organo oficial de expresion cientifica de la Sociedad Espanola de Farmacia Hospitalaria 2014;**38**(4):328-33 doi: 10.7399/fh.2014.38.4.7660[published Online First: Epub Date]|.

eTable 3: Total cost or total healthcare cost comparison across disease groups

Disease State	Min adj cost per annum per person	Max adj cost per annum per person	Median adj cost per annum per person	Mean adj cost per annum per person (SD)	No. adj studies	Min unadj cost per annum per person	Max unadj cost per annum per person	Median unadj cost per annum per person	Mean unadj cost per annum per person (SD)	No. unadj studies	Total studies[1]
Cardiovascular Disease	3347	19472	8080	9204 (4076)	6	1433	8377.05	5951	4701 (2702)	7	12
Mental Health	3253	19363	11262	11052 (5696)	6	2512	25920	17211.06	16486 (6848)	7	14
Diabetes Mellitus	2741	9819	6907	6310 (2322)	7	1142	7950	5534.34	4934 (3028)	8	11
Osteoporosis	949	44190	41402	32866 (18303)	4	669	43404	9920.985	18190 (17974)	10	11
Respiratory Disease	5701	7124	6689	6505 (729)	1	804	36259	11545.78	16124 (17229)	5	6
Gastrointestinal Disease	12085	37151	20715	23317 (12734)	3					2	5
Epilepsy					0	1866	22673	18713.91	14418 (11049)	3	3
HIV/AIDS					0	16957	30523	23879.92	24322 (5979)	3	3
Parkinson's Disease				10290*	1	10988	52023	36753.32	34129 (19845)	3	3
Musculoskeletal conditions				25368*	2				3408.32*	2	3
Cancer					0	48598	162699	93626.96	99638 (51589)	2	2
Addiction				53504*	1	16996	52213	29406.40	32872 (17863)	3	3
Metabolic conditions other than diabetes mellitus					0				138525*	1	1

Blood conditions				13458*	1					0	1
All causes	5271	52341	17132	21257 (11265)	14	1037	53793	16307.93	19352 (15981)	10	30**

Costs reported in $US2015 dollars

[1]Some studies included both adjusted and unadjusted costs

*Single total cost/total healthcare cost reported

** In addition to disease-specific studies of the economic impact of medication non-adherence, studies reported the all-causes costs, encompassing cost drivers such as comorbidities. Alvarez Payero et al reported all cause costs only.

This page is intentionally left blank

Chapter 4

An evidence-based model to consolidate medication adherence cost estimation: the MACE framework

Cutler, R.L., Van der Linden, N., Benrimoj, S.I., Fernandez-Llimos, F. & Garcia-Cardenas, V. 2019, 'An evidence based model to consolidate medication adherence cost estimation: the medication adherence cost estimation framework', *Journal of Comparative Effectiveness Research*, vol, 8, no. 8, pp. 555-567.

This page is intentionally left blank

Abstract

Aim: To develop a standardized framework to determine the economic impact of medication non-adherence.

Material and methods: Secondary analysis of existing literature reported cost data, aggregating cost outcome indicators. Weighted-average cost analysis performed, determining the proportional contribution to total cost.

Results: Direct costs were reported in 92% of studies and indirect costs in 4% of studies. The three most utilized cost categories were hospital (68%), primary care (18%) and pharmacy costs (72%). Average unadjusted direct costs ranged $625-154,203 contributing to 88% of the total cost; adjusted medical costs ranged $565-56,313 representing 96% of the total cost.

Conclusion: The medication adherence cost estimation framework enables the comparison of costing studies, facilitating informed health policy decision-making based on consistent evidence and terminology.

Keywords: health economics, health policy, pharmacoeconomics, non-adherence

Introduction

Medication non-adherence is a growing epidemic with the literature and policy makers identifying it as a major clinical and economic concern[1-4] costing governments and healthcare providers $US100-290 billion annually[5]. The major findings from the WHO report 'Adherence to Long-term Therapies –evidence for action' indicates that the consequences of medication non-adherence compromise effective treatment, decrease quality of life and increase healthcare costs; increasing the effectiveness of adherence interventions will have a greater impact on patient health than improving medical treatment and health systems need to evolve to meet the changing needs of patients[6]. These findings have set the stage for significant growth in medication adherence research, including economic evaluations.

Economic evaluations are defined as 'the comparative analysis of alternative courses of action in terms of both their costs and their consequences'[7], and are conducted to inform healthcare resource allocation[8]. While all economic evaluations assess costs, the combination of cost outcome indicators (i.e. the types of costs that are included) and the methods used to calculate these costs exhibit substantial heterogeneity[9,10]. Evaluation of the costs associated with medication non-adherence within single disease studies (e.g. Osteoporosis, HIV) as well as comparisons across diseases and studies highlights the existing heterogeneity in methodological processes, leading to wide spanning results[11]. In Osteoporosis the annual adjusted cost of medication non-adherence across studies ranges from $949 to $44 190[11] per person while across multiple disease studies the range spanned $949 to $52 341[11] per person. Additionally, there is no gold standard in the method used to estimate adherence rates, with selection of the calculation of adherence usually being based on study attributes, clinical setting or resource availability, ultimately resulting in a range of differing methods, cutoff points and recommendations[12].

Given the cost burden associated with medication non-adherence, it is valuable to develop interventions which aim to reduce costs[13-21]. The global medication adherence technology and intervention market continues to expand, valued at $1.6

billion in 2016 and forecasted to reach $3.6 billion by 2023[22], with numerous interventions designed to improve medication non-adherence across clinical conditions. Despite such growth, inconsistency in the reporting of medication non-adherence has resulted in only some interventions relating to better adherence and health outcomes[23]. A lack of consistency in costing methodological approaches serve as a major limitation moving forward in adherence research[12]. Standard approaches in terminology and reporting guidelines have been established through development of the ABC taxonomy representing the gold standard for defining medication adherence behavior across three stages and the EMERGE guidelines which outline the minimum reporting criteria that should be considered in every publication about medication adherence[24-29]. However, limited guidelines have been developed to standardize the way medication non-adherence costs are measured and reported in economic evaluations[30]. Often complete adherence is assumed or it is assumed that adherence in clinical trials is the same as real-world adherence when establishing clinical effectiveness[31]. This often leads to overestimation of adherence rates and cost effectiveness[32]. Hilligsmann et al, outlines this concept in Osteoporosis where poor (real-world) adherence to oral bisphosphonates resulted in a doubling of the incremental cost effectiveness ratio (ICER) compared with perfect (assumed) adherence levels (€3,909 vs. €10,279 respectively)[32,33].

A review of the literature carried out by Hughes et al in 2001[34] and updated in 2007[30] exploring the methodologies that may be appropriate for incorporating non-adherence and non-persistence in economic evaluations demonstrates that substantial inconsistency remains in the definitions adopted, and methods and inputs used in pharmacoeconomic evaluations. Moving forward this paper aims to streamline and provide structure to the types of costs that should be included when determining the economic impact of medication non-adherence. The key cost outcome indicators that contribute the greatest proportion to total costs have been incorporated into the newly proposed medication adherence cost estimation (MACE) framework. This facilitates the inclusion of key cost outcome indicators associated

with medication non-adherence into economic evaluations, enabling greater clarity in the economic comparison of adherence intervention studies to allow the establishment of meaningful conclusions across studies.

The aim of the research is twofold: determine what cost outcome indicators are reported in the literature and the weighting they contribute to overall costs, and develop a new framework to rationalize the estimation of the cost of medication non-adherence utilizing the identified cost outcome indicators.

Methods

Secondary analysis of data reported in a recent systematic review "Economic impact of medication non-adherence by disease groups- a systematic review" was undertaken to identify cost outcome indicators utilized to report the economic impact of medication non-adherence. The review quantified the cost of medication non-adherence across different disease groups. Studies reporting the cost of medication non-adherence were included, with costs defined as any cost outcome indicator associated with medication non-adherence that was quantified with a monetary value in the original study. Studies only reporting the measure of effect of healthcare utilization in relation to adherence were excluded, as they provided no cost value. The protocol for the systematic review is available through the PROSPERO international prospective register of systematic reviews database (CRD42015027338) and the full methodology was outlined in Cutler et al[11].

Phase 1: Extraction and Classification of Costs

Phase 1 consisted of extraction of the classification of cost outcome indicators demonstrating the economic impact of medication non-adherence[11] through assignment of a monetary value to an input associated with medication non-adherence. A cost outcome indicator was defined as a category of costs that was associated with medication non-adherence, e.g. hospital costs encompass all costs associated with a hospital admission attributable to medication non-adherence. Cost

outcomes were classified according to the terminology utilized in the reported study. The following data was extracted: cost outcome indicator, monetary value assigned to each indicator, definition of the cost outcome, cost classification (e.g. direct or indirect) and disease state[11]. Three quantifiable stages of medication adherence were assessed utilizing the ABC taxonomy classification system, categorizing study measures in relation to initiation, implementation and discontinuation[24]. Initiation was defined as the first dose of a prescribed medication; participants were required to be medication naïve or reinitiating the medication regimen. Implementation describes the extent to which the prescription was taken as prescribed among the initiated cohort, examined through measures such as medication possession ratio and proportion of days covered. Discontinuation signifies the end of therapy, when a dose is omitted and no subsequent doses are taken thereafter, measured through medication gaps and time to discontinuation[24].

Phase 2: Comparison and Aggregation of Cost Outcome Indicators

Phase 2 consisted of the development of a matrix to facilitate the comparison of cost outcome indicators. The content of each related outcome, as assessed by analysis of original definitions of indicators were aggregated into subcategories. Cost outcome indicators that were classified differently but had the same definition were grouped. Costs were classified as adjusted or unadjusted based on original study reporting. All costs were converted to $USD2018 monetary values and reported per patient per annum.

Phase 3: Weighted-Average Analysis

Phase 3 consisted of the statistical analysis of the cost outcome indicators to determine what core set of costing outcomes contributed the greatest proportion to total healthcare expenditure. Only studies that reported cost outcome indicators in addition to total costs or total healthcare costs were included for weighted-average analysis. Monetary values reported for each cost outcome per study were extracted. The minimum, maximum and average value for each indicator were determined. A weighted-average for each cost outcome indicator was calculated by multiplying the

percentage of studies that included that cost component by the average cost of each indicator as a proportion of the studies total cost. A ranking of the cost indicators was then created to determine the relative importance of certain cost outcome indicators based on previously conducted studies.

Results

A descriptive synthesis of the extracted data was performed, and cost outcome indicators were identified. Given the heterogeneity in approaches used to classify cost outcome indicators of medication non-adherence, a framework outlining the key cost outcome indicators that contribute the greatest proportion to total healthcare expenditure was derived. This highlighted the core set of cost outcome indicators that have contributed substantially to the total cost of medication non-adherence.

Extraction, classification and aggregation of cost outcome indicators

Across 79 studies, 35 different cost outcome indicators were used to report the economic impact of medication non-adherence. Table 1 demonstrates the terminology used to describe the cost outcome indicators and the frequency with which these terms were identified in the literature. It further highlights the classification of cost outcome indicators into broader categories to facilitate comparison. Analysis of original study definitions facilitated the distinction between direct and indirect costs. Direct costs were reported in 92% of studies (n=73) and refer to transactions and expenditures for medical or non-medical products and services. The types of costs may include hospitalizations, prescription medications, physician fees, laboratory tests, radiological procedures as well as expenditures such as transportation, lodging, family care and home aides[35]. This core category is further subcategorized into medical costs consisting of hospital costs, primary care costs, medical test costs, and pharmacy costs in addition to direct non-medical costs. The three most utilized cost categories were hospital, primary care and pharmacy costs, 68% of studies reported hospital costs (n=54), 18% of studies reported primary

care costs (n=15) and 72% of studies reported pharmacy costs (n=57). Eleven studies (13%) reported conjointly hospital, primary care and pharmacy costs, 56% (n=45) hospital and pharmacy costs, while only one study reported hospital, primary care, medical test and pharmacy costs. Indirect costs were defined as those that occur because of loss of life or livelihood and may result from morbidity or mortality[35]. Indirect morbidity costs may occur because of being absent from work, due to decreased earning ability when working or long term disability necessitating a change in work type as well as the costs associated with premature death[35]. These costs were reported in 4% of studies (n=3) and included societal costs (1%, n=1) and productivity costs (5%, n=4). Two percent of studies (n=2) examined both direct and indirect costs to evaluate the economic impact of medication non-adherence (see supplementary table 1).

Analysis of cost outcome indicators

Weighted-average analysis of cost outcome indicators highlighted the categories that contributed the greatest proportion to the overall cost of medication non-adherence. Of the 79 included studies, 56 reported cost outcome indicator monetary values in addition to total cost (see supplementary table 2). Both unadjusted (86% of total cost) and adjusted (96% of total cost) cost analysis determined that medical costs associated with hospital costs, primary care costs and pharmacy costs contributed the greatest proportion of total cost. Analysis of the unadjusted cost outcome indicator examples determined that over 88% of costs reported in the literature were direct costs associated with medication non-adherence and arised predominately from hospital costs (53%); mainly outpatient and inpatient costs (25% and 23% respectively), primary care costs (21%) and pharmacy costs (21%) (figure 1). Similarly, for the adjusted cost outcome indicators (figure 2) over 90% of the reported costs were attributed to direct costs however, primary care costs contributed the greatest proportion 53% followed by hospital costs (30%) and pharmacy costs (17%). Average unadjusted medical costs exhibited the greatest cost range variability ($585 to $152,660) and contributed on average 86% of the total costs. Within this core category, the hospital costs subgroup accounted for 53% of total costs and ranged

from $457 to $151,118 while pharmacy costs subgroup represented 21% of total cost and ranged from $154 to $30,943 (figure 3). Average adjusted medical costs ranged from $565 to $56,313 representing 96% of the total cost while hospital costs (30%) and pharmacy costs (17%) ranged from $2,044 to $48,180 and $22 to $21,430 respectively (figure 4). Hospital costs accounted for the greatest proportion of medical costs within the unadjusted cost analysis (53%). In the adjusted cost analysis primary care costs contributed the greatest proportion to total cost (53%).

ABC Taxonomy Classification

Medication adherence, the process by which patient's take their medications as prescribed is classified into three components: initiation, implementation and discontinuation[24] (see supplementary table 1). Initiation marks when the patient takes the first dose of a prescribed regimen; 59% of studies reported initiation (n=47). All 79 studies examined and reported aspects of implementation (correspondence of the patient's actual dosing regimen to the prescribed regimen), while 33% of studies (n=26) reported discontinuation. Persistence, a measure of adherence signifying the length of time between initiation and discontinuation was reported in 22 studies.

Table 1: Literature reported cost outcome indicators[1]

Direct Costs				Indirect Costs		
			Percentage of studies (%)			Percentage of studies (%)
Medical	**Hospital (68%)**	Acute care	**1**	**Societal (1%)**	Arrest	**1**
		Inpatient	**47**		Incarceration	**1**
		Outpatient	**52**	**Productivity (5%)**	Short term disability	**4**
		Behavioural health inpatient	**1**		Workers compensation	**1**
		Emergency department visit	**29**		Paid time off	**1**
		Hospitalization	**19**		Absenteeism	**3**
	Primary care (18%)	Physician office visit	**10**		Presenteeism	**1**
		Ancillary	**4**			
		Services	**1**			
		Medical services	**1**			
		External services	**1**			
		Psychiatric assessment	**1**			
		Institutional	**1**			
		Targeted case management	**1**			
		Interdisciplinary	**1**			
	Medical tests (3%)	Fracture	**1**			
		Laboratory	**1**			
		Radiology	**3**			
	Pharmacy (72%)	Prescription medication	**72**			
		Other pharmacy	**9**			
Non-Medical	**Direct non-medical (6%)**					

[1] "Economic impact of medication non-adherence by disease groups: a systematic review," by Cutler et al, 2018 *BMJ Open;*8:e016982. doi: 10.1136/bmjopen-2017-016982

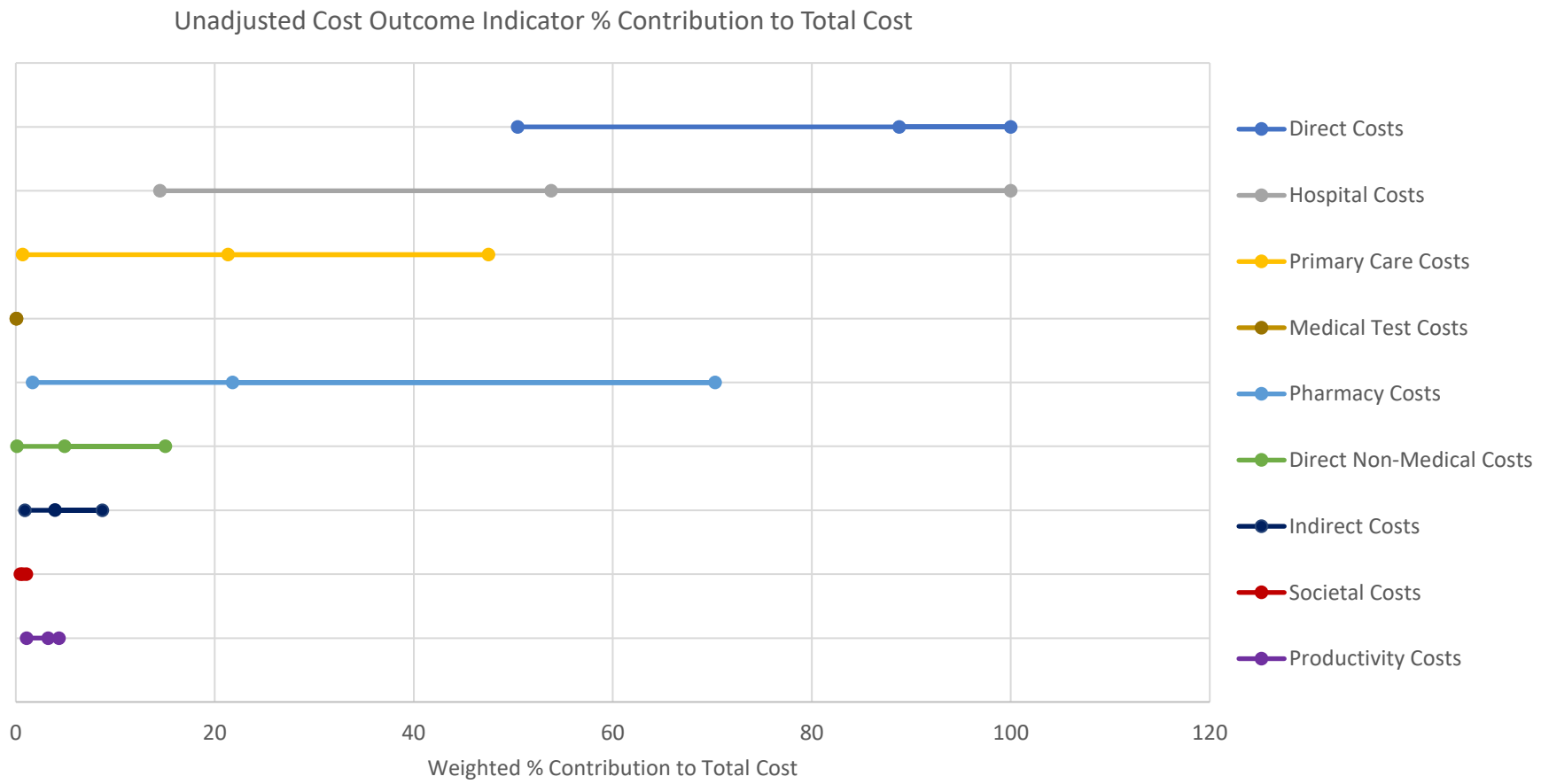

Figure 1: Unadjusted cost outcome indicator contribution to total cost. Line represents the minimum, maximum and average percentage contribution for each core category, subcategory and cost outcome indicator example towards total cost. Single points indicate only one cost value, reported for that category.

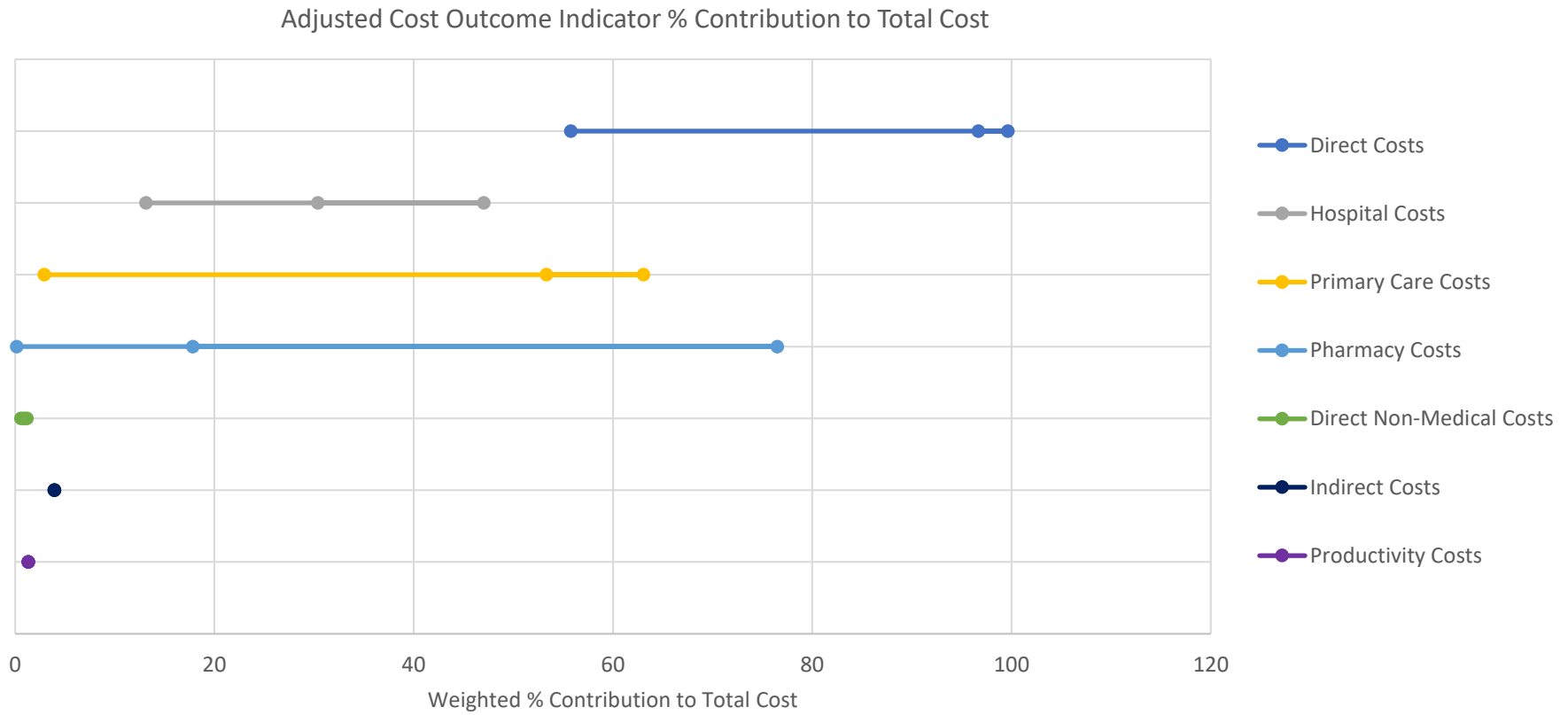

Figure 2: Adjusted cost outcome indicator contribution to total cost. Line represents the minimum, maximum and average percentage contribution for each core category, subcategory and cost outcome indicator example towards total cost. Single points indicate only one cost value, reported for that category.

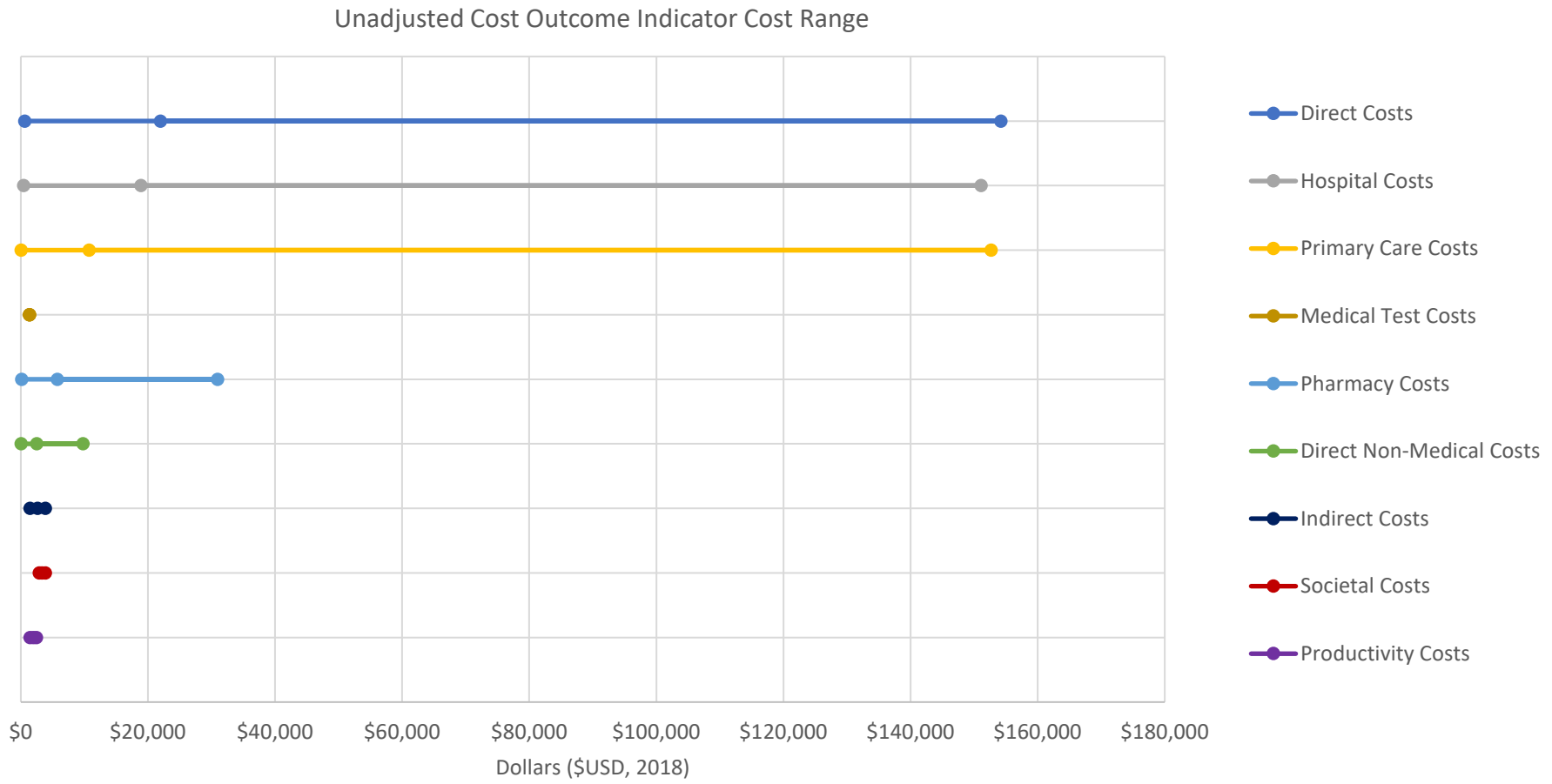

Figure 3: Unadjusted cost range $USD2018. Line represents the minimum, maximum and average cost reported for core categories, subcategories and cost outcome indicator examples. Single points indicate only one cost value, reported for that category.

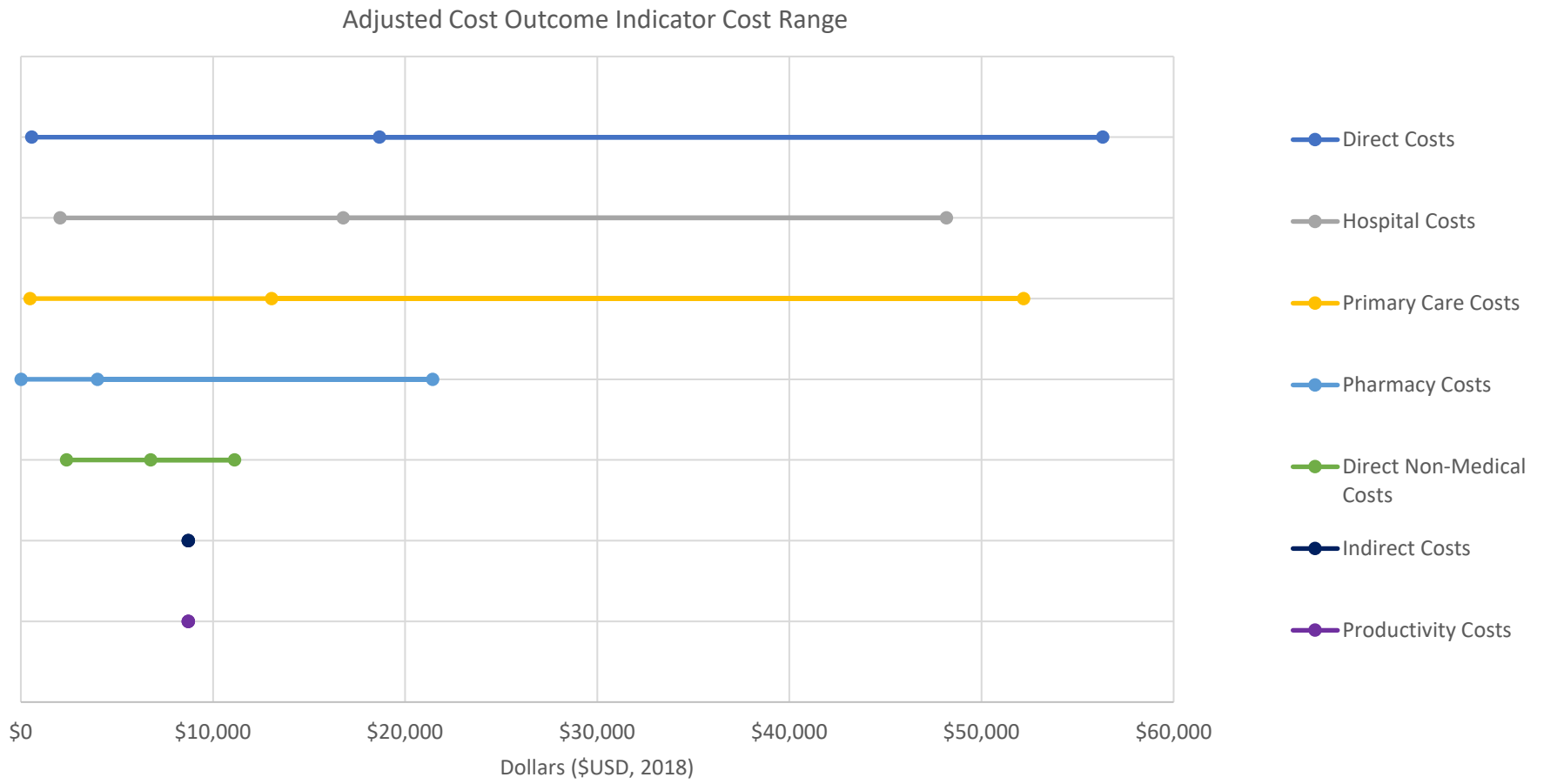

Figure 4: Adjusted cost range $USD2018. Line represents the minimum, maximum and average cost reported for core categories, subcategories and cost outcome indicator examples. Single points indicate only one cost value, reported for that category.

MACE framework

The MACE framework (table 2) relies on two core elements, making a clear distinction between direct and indirect costs. Two core cost outcome indicators emerged from the data (direct and indirect costs), with a further 7 subcategories (hospital, primary care, medical test, pharmacy, direct non-medical, societal and productivity costs) and 35 cost outcome indicator examples. The categories were derived from the 35 cost outcome indicators identified across 79 studies, with the indicators not being exhaustive to those outlined in the framework but serving as a guide for potential expenses that fall within each category.

MACE Framework Definitions

1. **Direct costs**

The first core element is *direct costs* and refers to any cost incurred due to resource use that are completely attributable to the use of a healthcare intervention of illness. These costs can be split into direct medical costs and direct non-medical costs. Direct medical costs include the cost of a defined intervention and all follow up costs for other medication and healthcare interventions in ambulatory, inpatient and nursing care. All physician and specialist care, including rehabilitation, emergency care as well as treatment or prevention of an injury, illness or disease, including the costs of testing, procedures, therapies and medications[35]. It is further categorized into hospital, primary care, medical test and pharmacy costs.

Hospital costs refer to the costs associated with the act or incidence of receiving medical care or aid at a hospital. This includes but is not limited to inpatient admissions, outpatient services, acute care and emergency department visits. Additionally, it incorporates all medical services (e.g. medication, imaging, pathology, specialist care) that are provided within the hospital setting.

Primary care costs refer to healthcare and utilization of healthcare facilities provided in the community, outside the hospital setting for diagnosis, prevention, advice or treatment of an injury, illness or disease. This includes GP visits, ancillary care,

psychiatric assessment, interdisciplinary team management, targeted case management, social worker visits, home helps and volunteer workers.

Medical test costs entail the costs of all medical procedures performed to detect, diagnose or monitor diseases, injury, susceptibility and determine a course of treatment e.g. laboratory tests, radiology costs, pathology results.

The *pharmacy cost* element incorporates utilization rates and corresponding costs associated with obtaining prescription and non-prescription medication in the community setting in addition to the provision of pharmacist services. It takes into account both disease specific and medication costs associated with comorbidities, where reported. Costs associated with prescribed medications, health aides, non-prescription medication, over the counter medications and any out-of-pocket expenses are measured.

Direct non-medical costs are expenditures as the result of an illness but are not involved in the direct purchasing of medical services. These include expenditures such as food, transportation, lodging, family care, home aides and clothing as a result of illness.

2. Indirect costs

Indirect costs are those that occur due to loss of life or livelihood, and may result from morbidity or mortality[36]. Mortality costs are the costs associated with premature death, while morbidity costs are associated with lost earning and productivity by the patient or caregivers[35].

Societal costs refer to the costs other than those associated with direct healthcare. These costs may not have been borne by the payer or provider of the healthcare services and include arrest, incarceration, opportunity costs of resources used and time spent seeking and receiving care[37]. In addition, this subcategory also considers costs incurred by society as a result of the additional use of time and

resources. It incorporates the costs imposed on society as a consequence of levies, taxes and charges[38,39].

The second subcategory, *productivity* costs, represents the additional cost burden placed on workplaces and employers due to a loss of productivity. It considers the impact medication non-adherence has on an individual's capacity to work; they may work less than they otherwise could, retire early, be absent from work more often, have lower productivity while at work, or die prematurely[40]. Additionally, informal carers may also work less or not work at all in order to care for non-adherent patients. *Productivity costs* capture the lost earnings and production due to non-adherence in terms of absenteeism (prolonged absence from work), disability pensions (financial help due to medical conditions that prevent one from working), premature death, early retirement, unemployment, reduced working hours and presenteeism (reduced capability in completing tasks in an efficient manner).

Table 2: Medication adherence cost estimation (MACE) framework

Core Category	Subcategory	Cost Examples
1. Direct costs	1.1 Hospital costs	1. Acute care costs 2. Inpatient costs 3. Behavioural health inpatient costs 4. Outpatient costs 5. Emergency department costs
	1.2 Primary care costs[†]	1. Physician office visit costs 2. Ancillary costs 3. Services costs 4. Medical services costs 5. External services costs 6. Psychiatric assessment costs 7. Institutional costs 8. Targeted case management costs 9. Interdisciplinary costs
	1.3 Medical test costs	1. Laboratory costs 2. Radiology costs 3. Fracture costs
	1.4 Pharmacy costs[‡]	1. Prescription medication costs 2. Other pharmacy costs
	1.5 Non-medical costs	1. Transport
2. Indirect costs	2.1 Societal costs	1. Arrest costs 2. Incarceration costs
	2.2 Productivity costs	1. Short term disability costs 2. Workers compensation costs 3. Paid time off costs 4. Absenteeism costs 5. Presenteeism costs

[†]Some costs examples in primary care setting may also occur in hospital costs however these cost examples refer to the costs captured in this particular setting/ subcategory independently.
[‡]Prescription medication costs may also occur in the hospital setting. When this is the case they are captured in the setting they are dispensed. Pharmacy cost subcategory refers exclusively to costs in the community setting.

Discussion

Increasing scarcity of healthcare resources, diminishing health budgets and increasing healthcare costs are compelling decision-makers to choose between alternative healthcare interventions. Increasingly the cost-effectiveness of interventions and overall healthcare gain to the population are important to determine the allocation of competing resources[41]. As the main goal of health economic analysis is to aid decisions, it is imperative that these evaluations are comparable in terms of the cost outcome indicators that they include to estimate the cost burden of medication non-adherence. Despite the growing evidence of models and methods examining the integration of medication adherence into pharmacoeconomic evaluations, limited consistency and uniformity exists in the methods and terminology used to estimate the cost outcome indicators. This dissimilarity has resulted in the generation of an array of concepts and terms being utilized in a variety of combinations to determine the economic impact of medication non-adherence. The definitions of the cost outcome indicators used vary and partially overlap, resulting in conceptual confusion, and contributing to methodological weaknesses in the field. Further methodological problems arise from the disparity in identification, measurement and valuation of non-adherence costs[42].

A framework identifying reported cost outcome indicators from 79 reviewed studies was constructed facilitating the analysis of original studies reporting the economic impact of medication non-adherence in addition to total cost[11]. Cost outcome indicators that contributed the greatest proportion to total cost, formed the structure categorization of the framework. The MACE framework was developed to provide a streamlined approach to estimate the cost of medication non-adherence. Lack of such a system has resulted in the heterogeneous reporting of over 35 different cost outcome indicators, making the comparison of studies difficult and deficient. The consolidated framework will allow a more complete evaluation of the economic impact whilst simultaneously facilitating the comparison across studies and disease states. Use of the MACE framework (table 2) will enable understanding

of terms that appear to be different but incorporate the same cost components. Thus, it aids in the interpretation and comparison of studies that may have used different terminology to classify similar or the same cost outcome indicators. We attempted to minimize complexity by providing clear and concise category descriptions and examples. This resulted in an aggregated system containing two core categories, seven subcategories and an extensive list of examples of cost outcome indicators. The framework provides a guide to cost estimation and can be applied in its entirety or utilizing only those categories that are relevant to the study objectives. Additionally, validation of the framework is required to test and advance its viability. Applying the framework to both retrospective and intervention based studies across a range of disease states is required to ratify the proposed framework. Moving forward examining the application of the MACE framework across varying perspectives (e.g., government, healthcare, pharmaceutical industry and patient) may prove valuable in gaining a better understanding of the economic burden of medication non-adherence globally.

Assessment of study methodologies and identification of significant heterogeneity across classification of cost outcome indicators, in addition to a varied mix of reporting styles made the statistical analysis of data challenging [10]. Due to the substantial variation in cost outcome indicators reported, the missing data and lack of reported standard deviations of costs a weighted average cost analysis was chosen to report the findings. Analysis of cost outcome indicators revealed that three key cost components contributed the greatest percentage to overall total cost. These three cost outcome indicators were grouped into 'medical costs' of the proposed framework. While ideally all cost categories should be taken into consideration when determining the cost of medication non-adherence, it stems to reason that the most influential costs that need to be considered are medical costs; particularly inpatient, outpatient, pharmacy costs and medical expenses incurred in the community setting, for example, GP visits. These costs contribute to over 85% of the cost of medication non-adherence. While these costs make up the largest proportion of total cost, further investigation is required to determine the economic impact of indirect costs

on medication adherence, as many studies fail to evaluate these costs. However, Drummond et al stipulates that it is not worth investing time into the evaluation of costs that are so small they are unlikely to make a difference in the study results. It may be worthwhile identifying these cost categories, yet the estimation of them need not be pursued[7]. Depending upon the perspective of the economic evaluation it may be important to measure both direct and indirect costs.

Awareness of the different degrees and types of non-adherence are important when analyzing cost data[43]. The impact of non-adherence on, as well as the relevant levels of non-adherence for healthcare costs can vary across disease states with certain medications exhibiting greater 'forgiveness' than others[42,44]. The three dimensions of adherence; initiation, implementation and discontinuation should be taken into consideration when assessing costs associated with medication non-adherence[24]. Additionally, the differences in relevant costs from different perspectives emphasize the importance of specifying the point of view from which the cost calculation is performed[42]. Which costs and consequences count, and how they should be measured and valued, depends on what type of decision makers in healthcare are intended to be informed by the economic evaluation[7]. The most valid cost data in terms of real resource use is collated via measuring every single cost item in detail and valuing it according to market price[45]. However, this may not be feasible as many economic evaluations are conducted using summary data, such as costs in the literature from previously conducted studies. In this instance individual patient data is not available and how the data has been summarized will determine whether resource quantities can be separated from prices to conduct the analyses[7]. The MACE framework facilitates the analysis of both direct and indirect costs, some or all of the categories may be relevant depending on the perspective of the analyses being conducted. Reporting across the two core categories supports transparency in the data, allowing the reader to derive results that are relevant for their own purpose whilst simultaneously facilitating the establishment of comparisons between studies. Similarly, the condition for which the economic evaluation is being estimated is of significant importance with certain conditions

carrying a greater cost burden then others. In cancer direct costs have been reported to be the smallest portion of total costs per patient[46] while in diabetes one study conservatively estimates direct costs to account for 66% of total costs[47]. Alternatively, in Schizophrenia one study estimated non-medical costs to account for 65% of healthcare expenditure; 15% attributed to direct non-medical costs and 50% attributed to indirect/productivity costs[48]. These variations need to be taken into consideration when comparing studies utilising different cost outcome indicators and when comparing across conditions.

The medication non-adherence cost burden is multidimensional in nature traversing healthcare professional groups, governments and individuals. However the degree of visibility medication adherence occupies within the health policy context remains less than ideal, often being overshadowed by other health policy issues due to incongruence in demonstrating impact[49]. In order for funding or reimbursement for medication adherence to be introduced, convincing and comparable evidence on the cost and benefits of medication adherence support needs to be stipulated. This framework attempts to homogenise the cost findings, enabling clear communication with policymakers to stimulate concerted action to address the economic impact of medication non-adherence[49]. When used in conjunction with existing validated guidelines and frameworks for health outcomes research (e.g., ABC taxonomy, CHEERS, TIDier, EMERGE) it will provide evidence to evaluate the clinical and cost-effectiveness of interventions to address medication non-adherence, building a strong case for investment[8,24,28,49,50].

Conclusion

Economic evaluation can be used to assess the effectiveness of interventions and inform health policy. In order to guide policy makers on how to best allocate limited healthcare resources in the most efficient and effective manner, it is imperative that a comparable method be developed to accurately estimate the economic impact of medication non-adherence. The MACE framework streamlines the current disarray of cost outcomes that exists in the literature. It provides structure via building on the existing foundations to create a classification system taking into account direct and indirect costs, that can be used in its entirety or partially dependent upon the perspective of the intended audience. Moving forward, future research would be recommended to test, validate and advance the MACE framework. The adoption of this framework will help to standardize the cost outcome indicators utilized, hereby facilitating health policy decisions based on consistent evidence, terminology and reporting standards.

Summary Points

Background

- Medication non-adherence places significant economic and clinical burden on patients, governments and healthcare systems.
- Heterogeneity exists in the methods and cost outcome indicators used to report and measure the economic impact of medication non-adherence.
- The medication adherence cost estimation (MACE) framework is a newly proposed model to consolidate the monetary valuation of medication non-adherence through determination of the cost breakdown of related cost outcome indicators described in the literature.

Methods

- Secondary analysis of existing literature reported cost data was conducted to aggregate cost outcome indicators and their associated monetary value.
- A weighted-average cost analysis was performed to determine the proportion each indicator contributed to total cost. Indicators were ranked to determine their relative importance in relation to total cost and the MACE framework was developed through utilization of these rankings.

Results

- The MACE framework proposes that costs should be classified into two core categories: direct and indirect costs, with further subcategorization into hospital, primary care, medical test, pharmacy, direct non-medical, societal and productivity costs.
- The three most utilized categories to report the economic impact of medication non-adherence were hospital costs (68%), primary care costs (18%) and pharmacy costs (72%).

Conclusion

- The MACE framework streamlines the current disarray of cost outcomes that exists in the literature.
- The adoption of this framework will help to standardize the cost outcome indicators utilized, hereby facilitating health policy decisions based on consistent evidence, terminology and reporting standards.

Financial and competing interest disclosures

This research received no specific grant from any funding agency in the public, commercial or not-for-profit sectors. Naomi Van der Linden worked at the Centre for Health Economics Research and Evaluation while the work was performed. She currently works at AstraZeneca Netherlands.

Acknowledgements

RLC research is supported by an Australian Government Research Training Program Scholarship.

Author's contributions

RLC drafted the initial form and all revisions of this manuscript. All other authors (RLC, NVL, SIB, FFL, VGC) made significant contributions to the manuscript and read and modified the drafts. All the authors read and approved the final manuscript.

References

1. van Boven JF, Chavannes NH, van der Molen T, Rutten-van Molken MP, Postma MJ, Vegter S. Clinical and economic impact of non-adherence in COPD: a systematic review. *Respiratory medicine*, 108(1), 103-113 (2014).
2. Ho PM, Rumsfeld JS, Masoudi FA *et al.* Effect of medication nonadherence on hospitalization and mortality among patients with diabetes mellitus. *Archives of internal medicine*, 166(17), 1836-1841 (2006).
3. Ho PM, Bryson CL, Rumsfeld JS. Medication adherence: its importance in cardiovascular outcomes. *Circulation*, 119(23), 3028-3035 (2009).
4. Iuga AO, McGuire MJ. Adherence and health care costs. *Risk management and healthcare policy*, 7, 35-44 (2014).
5. New England Healthcare Institute.Thinking outside the pillbox: a system-wide approach to improving patient medication adherence for chronic disease (2009), http://www.nehi.net/publications/44/thinking_outside_the_pillbox_a_systemwide_approach_to_improving_patient_medication_adherence_for_chronic_disease.
6. World Health Organisation. Adherence to Long Term Therapies; Evidence for Action (2003) http://www.who.int/chp/knowledge/publications/adherence_full_report.pdf?ua=1

*** Provides a review on adherence to long-term therapies beyond inidividual diseases, through examination of the way health systems are structured, finianced and operated. Provides analysis, solutions and recommendations on further research requirements in addition to acknowledging current literature developments.**

7. Drummond MF, Sculpher MJ, Claxton K, Stoddart GL, Torrance GW. *Methods for the economic evaluation of health care programmes,* Oxford university press, New York, (2015).

**** Outlines key methodological principles relating to the economoc evaluation of health care programmes.**

8. Husereau D, Drummond M, Petrou S *et al.* Consolidated Health Economic Evaluation Reporting Standards (CHEERS)--explanation and elaboration: a report of the ISPOR Health Economic Evaluation Publication Guidelines Good Reporting Practices Task Force. *Value in health : the journal of the International Society for Pharmacoeconomics and Outcomes Research*, 16(2), 231-250 (2013).
9. Wang L, Si L, Cocker F, Palmer AJ, Sanderson K. A Systematic Review of Cost-of-Illness Studies of Multimorbidity. *Applied health economics and health policy*, 16(1), 15-29 (2018).
10. AJ OC, Hanly P, Skally M *et al.* Cost comparisons and methodological heterogeneity in cost-of-illness studies: the example of colorectal cancer. *Medical care*, 51(4), 339-350 (2013).
11. Cutler RL, Fernandez-Llimos F, Frommer M, Benrimoj C, Garcia-Cardenas V. Economic impact of medication non-adherence by disease groups: a systematic review. *BMJ open*, 8(1), e016982 (2018).

**** Systematic review analysing and reporting the economic impact of medication non-adherence.**

12. Lam WY, Fresco P. Medication Adherence Measures: An Overview. *BioMed research international*, 2015, 1-12 (2015).
13. Sokol MC, McGuigan KA, Verbrugge RR, Epstein RS. Impact of medication adherence on hospitalization risk and healthcare cost. *Medical care*, 43, 521-530 (2005).

14. Siris ES, Harris ST, Rosen CJ *et al.* Adherence to bisphosphonate therapy and fracture rates in osteoporotic women: relationship to vertebral and nonvertebral fractures from 2 US claims databases. *Mayo Clinic proceedings*, 81(8), 1013-1022 (2006).
15. Roebuck MC, Liberman JN, Gemmill-Toyama M, Brennan TA. Medication Adherence Leads To Lower Health Care Use And Costs Despite Increased Drug Spending. *Health affairs*, 30(1), 91-99 (2011).
16. Jha AK, Aubert RE, Yao J, Teagarden JR, Epstein RS. Greater adherence to diabetes drugs is linked to less hospital use and could save nearly $5 billion annually. *Health affairs (Project Hope)*, 31, 1836-1846 (2012).
17. Grabowski DC, Lakdawalla DN, Goldman DP *et al.* The large social value resulting from use of statins warrants steps to improve adherence and broaden treatment. *Health affairs*, 31(10), 2276-2285 (2012).
18. Dall TM, Blanchard TD, Gallo PD, Semilla AP. The economic impact of Medicare Part D on congestive heart failure. *The American journal of managed care*, 19(6 Suppl), s97-100 (2013).
19. Cutler DM, Long G, Berndt ER *et al.* The value of antihypertensive drugs: a perspective on medical innovation. *Health affairs*, 26(1), 97-110 (2007).
20. Burge R, Dawson-Hughes B, Solomon DH, Wong JB, King A, Tosteson A. Incidence and economic burden of osteoporosis-related fractures in the United States, 2005-2025. *Journal of bone and mineral research : the official journal of the American Society for Bone and Mineral Research*, 22(3), 465-475 (2007).
21. Behner P, Klink A, Visser S, Bocken J, Etgeton S. Unleashing the Potential of Therapy Adherence. High-Leverage Changes in Patient Behavior for Improved Health and Productivity. Bertelsmann Stiftung, Booz & Company, (2012).
22. P&S Market Research. Medication Adherence Market by Product (Software Centric, Hardware Centric), by Medication (Cardiovascular, CNS, Diabetes, Oncology, Respiratory, Gastrointestinal, Rheumatology), by Geography (U.S., Canada, Germany, France, U.K., Japan, China) – Global Market Size, Share, Development, Growth and Demand Forecast, 2013-2023, (2017). https://www.psmarketresearch.com/market-analysis/medical-adherence.
23. Agency for Healthcare Research and Quality. Medication Adherence Interventions: Comparative Effectiveness (Evidence Report), (2014). http://www.ahrq.gov/redirects/gapmedadtp.html.
24. Vrijens B, De Geest S, Hughes DA *et al.* A new taxonomy for describing and defining adherence to medications. *British journal of clinical pharmacology*, 73(5), 691-705 (2012).

*** Outlines and defines a standardised taxonomoy to define medication adherence.**

25. Fraser S. Concordance, compliance, preference or adherence. *Patient preference and adherence*, 4, 95-96 (2010).
26. Haynes RB, Ackloo E, Sahota N, McDonald HP, Yao X. Interventions for enhancing medication adherence. *The Cochrane database of systematic reviews*, (2), CD000011 (2008).
27. Centre for NHS Service Delivery and Organisation R & D (NCCSDO).Concordance, adherence and compliance in medicine taking. Report for the National Co-ordinating, (2005). http://www.netscc.ac.uk/hsdr/files/project/SDO_FR_08-1412-076_V01.pdf.
28. Helmy R, Zullig LL, Dunbar-Jacob J *et al.* ESPACOMP Medication Adherence Reporting Guidelines (EMERGE): a reactive-Delphi study protocol. *BMJ open*, 7(2), e013496 (2017).

29. De Geest S, Zullig LL, Dunbar-Jacob J *et al.* ESPACOMP Medication Adherence Reporting Guideline (EMERGE). *Annals of internal medicine*, 169(1), 30-35 (2018).
30. Hughes D, Cowell W, Koncz T, Cramer J. Methods for integrating medication compliance and persistence in pharmacoeconomic evaluations. *Value in health : the journal of the International Society for Pharmacoeconomics and Outcomes Research*, 10(6), 498-509 (2007).
31. Lakdawalla DN, Doshi JA, Garrison Jr LP, Phelps CE, Basu A, Danzon PM. Defining Elements of Value in Health Care—A Health Economics Approach: An ISPOR Special Task Force Report [3]. *Value in Health*, 21(2), 131-139 (2018).
32. Hiligsmann M, Boonen A, Rabenda V, Reginster JY. The importance of integrating medication adherence into pharmacoeconomic analyses: the example of osteoporosis. *Expert review of pharmacoeconomics & outcomes research*, 12(2), 159-166 (2012).
33. Hiligsmann M, Rabenda V, Bruyère O, Reginster J-Y. The clinical and economic burden of non-adherence with oral bisphosphonates in osteoporotic patients. *Health policy*, 96(2), 170-177 (2010).
34. Hughes DA, Bagust A, Haycox A, Walley T. The impact of non-compliance on the cost-effectiveness of pharmaceuticals: a review of the literature. *Health economics*, 10, 601-615 (2001).
35. Eisenberg JM. Clinical economics. A guide to the economic analysis of clinical practices. *Jama*, 262(20), 2879-2886 (1989).
36. Sherman EJ, Pfister DG, Ruchlin HS *et al.* The Collection of Indirect and Nonmedical Direct Costs (COIN) form: a new tool for collecting the invisible costs of androgen independent prostate carcinoma. *Cancer*, 91(4), 841-853 (2001).
37. Cantor SB, Levy LB, Cardenas-Turanzas M *et al.* Collecting direct non-health care and time cost data: application to screening and diagnosis of cervical cancer. *Medical decision making : an international journal of the Society for Medical Decision Making*, 26(3), 265-272 (2006).
38. King D, Knapp M, Patel A *et al.* The impact of non-adherence to medication in patients with schizophrenia on health, social care and societal costs. Analysis of the QUATRO study. *Epidemiol Psychiatr Sci*, 23(1), 61-70 (2014).
39. National Information Center on Health services Research and Health Crae Technology (NICHSR). Health Economic Resources: A Self-Study Course, (2018). https://www.nlm.nih.gov/nichsr/edu/healthecon/glossary.html.
40. Deloitte Access Economics. Asthma Australia and National Asthma Council Australia. The Hidden Cost of Asthma, (2015). https://www2.deloitte.com/content/dam/Deloitte/au/Documents/Economics/deloitte-au-economics-hidden-cost-asthma-241115.pdf.
41. Tamás K. Clinical and pharmacoeconomic impact of patient medication adherence. Dissertation, Semmelweis University, (2010).
42. Cleemput I, Kesteloot K, DeGeest S. A review of the literature on the economics of noncompliance. Room for methodological improvement. *Health policy*, 59(1), 65-94 (2002).
43. Geest SD, Abraham I, Dunbar-Jacob J, Vanhaecke J. Behavioral Strategies for Long-Term Survival of Transplant Recipients. In: *Drug Regimen Compliance.* (John Wiley & Sons, Ltd, 2002) 163-179.
44. Urquhart J. Patient non-compliance with drug regimens: measurement, clinical correlates, economic impact. *European heart journal*, 17 Suppl A, 8-15 (1996).
45. Gold MR. *Cost-effectiveness in health and medicine,* Oxford university press, (1996).

46. Pallis A, Tsiantou V, Simou E, Maniadakis N. Pharmacoeconomic considerations in the treatment of breast cancer. *ClinicoEconomics and outcomes research : CEOR*, 2, 47-61 (2010).
47. Centers for Disease Control and Prevention. National Diabetes Fact Sheet, (2007). http://www.cdc.gov/diabetes/pubs/pdf/ndfs_2007.pdf.
48. Wu EQ, Birnbaum HG, Shi L *et al.* The economic burden of schizophrenia in the United States in 2002. *The Journal of clinical psychiatry*, 66(9), 1122-1129 (2005).
49. Clyne W, McLachlan S. A mixed-methods study of the implementation of medication adherence policy solutions: how do European countries compare? *Patient preference and adherence*, 9, 1505-1515 (2015).
50. Hoffmann TC, Glasziou PP, Boutron I *et al.* Better reporting of interventions: template for intervention description and replication (TIDieR) checklist and guide. *BMJ : British Medical Journal*, 348 (2014).

Supplementary table 1: Cost outcome indicators reported and ABC taxonomy classification

Study	direct costs	indirect costs	total costs	total healthcare costs	medical costs	Hospital costs	inpatient costs	outpatient costs	emergency department visit costs	behavioural health inpatient costs	acute care costs	primary care costs	physician office visit costs	ancillary costs	services costs	medical services costs	external services costs	psychiatric assessment costs	targeted case management costs	interdisciplinary costs	institutional costs	medical test costs	laboratory costs	radiology costs	fracture costs	prescription medication costs	other pharmacy costs	direct non-medical costs	arrest costs	incarceration costs	short term disability costs	workers compensation costs	paid time off costs	total productivity costs	absenteeism costs	presenteeism costs	ABC Taxonomy Classification
Alvarez Payero M, Martinez Lopez de Castro N, Ucha Samartin M, Martin Vila A, Vazquez Lopez C, Pineiro Corrales G	X				X	X																															implementation discontinuation
An SY, Kim HJ, Chun KH, Kim TH, Jeon JY, Kim DJ, Han SJ, Kim YS, Woo JT, Ahn KJ, Park Y, Nam M, Baik SH, Lee KW	X		X		X	X		X																													implementation
Aubert RE, Yao J, Xia F, Garavaglia SB	X			X	X																																initiation implementation discontinuation

Bagalman E, Yu-Isenberg KS, Durden E, Crivera C, Dirani R, Bunn WB, 3rd	X	X	X		X																									X	X	X				implementation
Barnett PG, Chow A, Joyce VR, Bayoumi AM, Griffin SC, Nosyk B, Holodniy M, Brown ST, Sculpher M, Anis AH, Owens DK			X		X																															implementation
Becker MA, Young MS, Ochshorn E, Diamond RJ			X		X																															implementation
Briesacher BA, Andrade SE, Yood RA, Kahler KH	X		X		X	X	X	X																		X										initiation implementation
Buysman EK, Anderson A, Bacchus S, Ingham M	X				X																					X										implementation discontinuation

Candrilli SD, O'Brien SH, Ware RE, Nahata MC, Seiber EE, Balkrishnan R	X		X		X	X	X		X				X	X												X													initiation implementation
Carter CT, Waters HC, Smith DB	X				X	X																																		initiation implementation discontinuation
Casciano JP, Dotiwala ZJ, Martin BC, Kwong WJ	X		X		X	X	X	X																		X														initiation implementation discontinuation
Cooke CE, Lee HY, Xing S	X			X	X	X	X	X																		X														implementation
Curtis SE, Boye KS, Lage MJ, Garcia-Perez LE.	X		X		X	X		X			X															X														initiation implementation

Darkow T, Henk HJ, Thomas SK, Feng W, Baladi JF, Goldberg GA, Hatfield A, Cortes J	X			X	X	X	X	X	X																	X	X	X								initiation implementation discontinuation
Davis JR, Wu B, Kern DM, Tunceli O, Fox KM, Horton J, Legg R, Trudo F	X		X		X																					X										initiation implementation
Davis KL, Edin HM, Allen JK	X		X		X	X		X																		X										initiation implementation discontinuation
Davis KL, Candrilli SD, Edin HM	X		X		X																					X										initiation implementation
Delea TE, Stanford RH, Hagiwara M, Stempel DA	X		X		X	X		X	X																			X								initiation implementation

Delea TE, Thomas SK, Hagiwara M	X		X		X	X	X																		X		X									implementation
Diehl JL, Daw JR, Coley KC, Rayburg R	X		X		X										X											X										implementation discontinuation
Dilokthornsakul P, Chaiyakunapruk N, Nimpitakpong P, Jeanpeerapong N, Sruamsiri R	X			X	X	X	X	X																												initiation implementation
Dragomir A, Cote R, Roy L, Blais L, Lalonde L, Berard A, Perreault S	X			X	X	X																			X										initiation implementation
Dragomir A, Cote R, White M, Lalonde L, Blais L, Berard A, Perreault S	X			X	X	X																			X										initiation implementation

Eaddy M, Grogg A, Locklear J	X				X	X	X	X					X													X		X									initiation implementation discontinuation
Egede LE, Gebregziabher M, Dismuke CE, Lynch CP, Axon RN, Zhao Y, Mauldin PD	X				X	X	X	X																		X										implementation
Eisenberg DF, Placzek H, Gu T, Krishna A, Tulsi BB	X		X		X	X	X	X	X				X													X										initiation implementation discontinuation
Ettinger AB, Manjunath R, Candrilli SD, Davis KL	X		X		X	X	X		X				X	X												X	X									initiation implementation
Faught RE, Weiner JR, Guerin A, Cunnington MC, Duh MS	X		X		X	X	X	X	X																	X	X									initiation implementation discontinuation

Gentil L, Vasiliadis HM, Preville M, Berbiche D	X		X		X	X	X	X					X													X												implementation
Gilmer TP, Dolder CR, Lacro JP, Folsom DP, Lindamer L, Garcia P, Jeste DV	X		X		X	X		X																		X												implementation
Gosselin A, Luo R, Lohoues H, Toy E, Lewis B, Crawley J, Duh MS	X		X		X	X	X	X																		X												initiation implementation discontinuation
Hagen SE, Wright DW, Finch R, Talamonti WJ, Edington DW	X			X	X																					X					X							implementation
Halpern R, Becker L, Iqbal SU, Kazis LE, Macarios D, Badamgarav E	X				X																																	initiation implementation

Hansen RA, Farley JF, Droege M, Maciejewski ML	X			X	X	X	X	X																		X											implementation
Hazel-Fernandez L, Louder AM, Foster SA, Uribe CL, Burge RT	X			X	X	X	X	X	X																	X											initiation implementation discontinuation
Hong J, Reed C, Novick D, Haro JM, Aguado J	X		X	X	X	X	X																			X											implementation
Hong JS, Kang HC	X		X		X	X																															initiation implementation
Huybrechts KF, Ishak KJ, Caro JJ	X		X		X	X																X															initiation implementation discontinuation

Ivanova JI, Bergman RE, Birnbaum HG, Phillips AL, Stewart M, Meletiche DM	X	X	X	X	X	X	X	X	X																	X					X				X			implementation
Jha AK, Aubert RE, Yao J, Teagarden JR, Epstein RS	X		X		X	X			X																													implementation
Jiang Y, Ni W	X		X		X												X									X													initiation implementation discontinuation
Joe S and Lee JS			X		X																																		implementation discontinuation
Joshi AV, Madhavan SS, Ambegaonkar A, Smith M, Scott VG, Dedhia H		X			X																															X	X	X	implementation

Kane SV, Chao J, Mulani PM	X				X	X		X	X																	X											initiation implementation discontinuation
Kjellberg J, Jorgensen AD, Vestergaard P, Ibsen R, Gerstoft F, Modi A	X		X		X																																initiation implementation
Knapp M, King D, Pugner K, Lapuerta P	X		X		X	X	X										X																				implementation
Lee A, Song X, Khan I, Belozeroff V, Goodman W, Fulcher N, Diakun D	X		X		X	X	X	X	X																	X	X										initiation implementation discontinuation
Leider HL, Dhaliwal J, Davis EJ, Kulakodlu M, Buikema AR	X			X	X	X	X	X																		X											implementation

Miravitlles M, Sicras A, Crespo C, Cuesta M, Brosa M, Galera J, Lahoz R, Lleonart M, Riera MI	X				X	X			X			X	X							X		X	X	X		X											implementation
Mitra D, Hodgkins P, Yen L, Davis KL, Cohen RD	X				X	X	X	X	X					X												X											initiation implementation discontinuation
Modi A, Siris ES, Tang J, Sen S	X		X		X	X	X	X	X																	X		X									initiation implementation
Offord S, Lin J, Mirski D, Wong B	X		X		X	X		X																		X											initiation implementation discontinuation
Offord S, Lin J, Wong B, Mirski D, Baker RA	X				X	X	X																			X											initiation implementation

Olsen KR, Hansen C, Abrahamsen B	X				X																				X										initiation implementation
Pittman DG, Chen W, Bowlin SJ, Foody JM	X			X	X																					X									implementation
Pittman DG, Tao Z, Chen W, Stettin GD	X			X	X	X		X	X																	X									implementation
Pruitt Z, Robst J, Langland-Orban B, Brooks RG	X		X		X	X	X	X		X																X	X								initiation implementation
Quittner AL, Zhang J, Marynchenko M, Chopra PA, Signorovitch J, Yushkina Y, Riekert KA				X	X																													implementation

Rizzo JA and Simons WR				X	X																															initiation implementation
Robertson AG, Swanson JW, Van Dorn RA, Swartz MS	X		X			X	X	X	X									X	X							X			X	X						implementation
Robinson RL, Long SR, Chang S, Able S, Baser O, Obenchain RL, Swindle RW	X		X			X		X	X				X														X									initiation implementation
Ruetsch C, Tkacz J, Nadipelli VR, Brady BL, Ronquest N, Un H, Volpicelli J	X			X	X	X	X	X	X				X														X									initiation implementation discontinuation
Sokol MC, McGuigan KA, Verbrugge RR, Epstein RS	X		X		X																						X									implementation

Stroupe KT, Teal EY, Tu W, Weiner M, Murray MD	X			X		X	X	X																		X											implementation
Sunyecz JA, Mucha L, Baser O, Barr CE, Amonkar MM	X			X		X	X	X	X															X		X											initiation implementation discontinuation
Svarstad BL, Shireman TI, Sweeney JK	X					X																															implementation
Tan H, Cai Q, Agarwal S, Stephenson JJ, Kamat S	X				X																																initiation implementation
Tkacz J, Volpicelli J, Un H, Ruetsch C	X			X		X	X	X	X																	X											implementation

Wan GJ, Kozma CM, Slaton TL, Olson WH, Feagan BG	X		X	X		X	X	X	X																	X											initiation implementation discontinuation
Wei YJ, Palumbo FB, Simoni-Wastila L, Shulman LM, Stuart B, Beardsley R, Brown CH	X		X			X	X																			X											initiation implementation discontinuation
White TJ, Vanderplas A, Chang E, Dezii CM, Abrams GD	X		X		X																					X											implementation
White TJ, Vanderplas A, Ory C, Dezii CM, Chang E	X		X		X																					X											initiation implementation discontinuation
Wu EQ, Johnson S, Beaulieu N, Arana M, Bollu V, Guo A, Coombs J, Feng W, Cortes J	X		X			X	X	X	X																	X	X										initiation implementation

Wu J, Seiber E, Lacombe VA, Nahata MC, Balkrishnan R	X			X	X																				X											implementation
Wu N, Chen S, Boulanger L, Fraser K, Bledsoe SL, Zhao Y	X			X		X	X	X																	X											initiation implementation
Zhao Y, Chen SY, Wu N, Fraser KA, Boulanger L	X		X			X	X	X																	X											initiation implementation discontinuation
Zhao Y, Johnston SS, Smith DM, McMorrow D, Krege J, Krohn K	X			X		X	X	X																	X											initiation implementation
Zhao Y, Johnston SS, Smith DM, McMorrow D, Krohn K, Krege J	X			X		X	X	X																	X											initiation implementation

Zhao Y, Zabriski S, Bertram C	X			X	X																				X												initiation implementation

Supplementary table 2: Studies identified with medication non-adherence costs reported by cost outcome indicator and total cost

Author, Year, Country	Core cost outcome indicators	Subcategory cost outcome indicators	Economic impact of cost outcome indicator (USD, 2018)[2]
*An et al**[1]***	Direct costs	Hospital costs	Currency Year: USD, 2007
2014			Cost of Non-adherence†: TC:$1657.11 ($1986.66), OC: $1413.99
Korea			($1695.70), HC:$243.11 ($291.14)
*Aubert et al**[2]***	Direct costs	Primary Care Costs	Currency Year: USD, 2002
2010			Cost of Non-adherence: THC:$5289.61 ($7239.48), MC:$4908.09
US			($6717.23)
*Bagalman et al**[3]***	Indirect costs	Workplace costs	Currency Year: USD, 2005
2010			Cost of Non-adherence: TC:$6894 ($8723.70), STDC:$2134
US			($2700.38), WCC:$762 ($964.23), PTOC:$3998 ($5059.1)
*Candrilli et al**[4]***	Direct costs	Hospital costs	Currency Year: USD, 2008
2011		Pharmacy costs	Cost of Non-adherence:
US		Primary care costs	All cause:
			TC:$ 20436 ($23971.88), IC:$9780 ($11472.16), EDC:$837 ($981.81),
			PC:$2579 ($3025.22), POC:$3483 ($4085.63), AC:$3911 ($4587.69)
			Disease state specific:
			TC:$12097 ($14190.04), IC:$7315 ($8580.65), EDC:$552 ($647.50),
			PC:$158 ($185.33), POC:$1865 ($2187.68), AC:$2466 ($2892.67)
*Casciano et al**[5]***	Direct costs	Hospital costs	Currency Year: USD, 2005
2013		Pharmacy costs	Cost of Non-adherence†: TC:$16612.44 ($21021.5), IC:$9382.56
US		Primary Care costs	($11872.78), OC:$8605.92 ($10889.97), PC:$2388.24 ($3022.15),
			MC:$15235.80 ($19279.92)
*Cooke et al**[6]***	Direct costs	Hospital costs	Currency Year: USD, 2011
2014		Pharmacy costs	Cost of Non-adherence:
US			THC:$18868 ($21282.86),IC:$2700 ($3045.56),OC:$915 ($1032.11),
			PC:$15253 ($17205.19)

[2] Cost data adapted from "Economic impact of medication non-adherence by disease groups: a systematic review," by Cutler et al, 2018 *BMJ Open;*8:e016982. doi: 10.1136/bmjopen-2017-016982

*Curtis et al**[7]***	Direct costs	Hospital costs	Currency Year: USD, 2014
2017		Pharmacy costs	Cost of Non-adherence: TC:$38633 ($41143.25),OC:$16964 ($18066.3), PC:$9390 ($10000.13), ACC:$12153 ($12942.66)
US			
*Darkow et al**[8]***	Direct costs	Hospital costs	Currency Year: USD, 2004
2007		Pharmacy costs	Cost of Non-adherence:
US		Primary Care costs	≥95% adherence:
		Direct non-medical costs	THC:$42250 ($55178.33), IC:$1156 ($1509.72), OC:$9299 ($12144.45), EDC:$36 ($47.01), PC:$29056 ($37947.02), MC:$10731 ($14014.64), OtPC:$2462 ($3215.36), OtC:$241 ($314.742) 90-95% adherence: THC:$39236 ($51242.06), IC:$1362 ($1778.76), EDC:$568 ($741.81), OC:$11148 ($14559.25), PC:$23693 ($30942.96), MC:$13452 ($17568.25), OtPC:$2091 ($2730.843), OtC:$374 ($488.44) 50-90% adherence: THC:$54770 ($71529.4), IC:$19096 ($24939.3), OC:$14631 ($19108.02), EDC:$104 ($135.81), PC:$18330 ($23938.91), MC:$34202 ($44667.68), OtPC:$2238 ($2922.82), OtC:$371 ($484.52) <50% adherence: THC:$131357 ($171551.7), IC:$81572 ($106532.7), OC:$33956 ($44346.4), EDC:$183 ($238.99), PC:$8733 ($11405.26), MC:$116892 ($152660.5), OtPC:$5732 ($7485.967), OtC:$1181 ($1542.38)
*Davis et al**[9]***	Direct costs	Hospital costs	Currency Year: USD, 2014
2017		Pharmacy costs	Cost of Non-adherence†:
US			All cause, ≥80% adherence: TC:$22546 ($24011.32), OC:$7816 ($8323.85), PC:$7954 ($ 8470.83), HC:$6106 ($6503.09) All cause, 50-80% adherence: TC:$25545 ($27204.83), OC:$8225 ($8759.43), PC:$6862 ($7307.87), HC:$9391 ($10001.19) All cause, 30-50% adherence:

			TC:$24303 ($25882.13), OC:$8365 ($8908.52), PC:$5485 ($5841.4), HC:$9171 ($9766.90) All cause, <30% adherence: TC:$25148 ($26782.04), OC:$8857 ($9432.49), PC:$4395 ($4680.57), HC:$10849 ($11553.93) Disease state specific, ≥80% adherence: TC:$8075.33 ($8600.03), OC:$2194.33 ($2336.91), PC:$4464 (4754.05), HC:$1074.67 ($1144.50) Disease state specific, 50-80% adherence: TC:$7053 ($7511.28), OC:$1947 ($2073.51), PC:$3345 ($3562.35), HC:$1155 ($1230.04) Disease state specific, 30-50% adherence: TC:$6623 ($7053.34), OC:$1997 ($2126.76), PC:$2307 ($2456.90), HC:$1619 ($1724.1) Disease state specific, <30% adherence: TC:$5644 ($6010.72), OC:$2152 ($2291.82), PC:$1569 ($1670.94),HC:$1405 ($1496.29)
*Davis et al**[10]*** 2010 US	Direct costs	Pharmacy costs Primary Care costs	Currency Year: USD, 2001 Cost of Non-adherence: TC:$18511 ($25582.52), PC:$2684 ($3729.83), MC:$15827 ($21994.11)
*Delea et al**[11]*** 2008 US	Direct costs	Hospital costs Direct non-medical costs	Currency Year: USD, 2003 Cost of Non-adherence†: ≥75% adherence: TC:$1564 ($2098.56), OC:$1272 ($1706.76), EDC:$32 ($42.93), OtC:$292 ($391.80) 50-75% adherence: TC:$1128 ($1513.54), OC:$852 ($1143.20), EDC:$36 ($48.30), OtC:$276 ($370.33) 25-50% adherence: TC:$900 ($1207.61), OC:$600 ($805.07), EDC:$60 ($80.50), OtC:$300 ($402.54) <25% adherence:

			TC:$632 ($848.01), OC:$388 ($520.61), EDC:$48 ($64.40), OtC:$240 ($322.02)
*Delea et al**[12]*** 2011 US	Direct costs	Hospital costs Pharmacy costs Direct non-medical costs	Currency Year: USD, 2005 Cost of Non-adherence: Adjusted all cause: TC:$19686 ($24910.8), IC:$5954 ($7534.22), PC:$6391 ($8087.21), OtC:$8795 ($11129.26) Adjusted disease state specific: TC:$8574 ($10849.59), IC:$3705 ($4688.32), PC:$3850 ($4871.81), OtC:$1884 ($2384.02) Unadjusted all cause: TC:$19362 ($24500.8), IC:$5463 ($6912.91), PC:$6158 ($7792.37), OtC:$7740 ($9794.24) Unadjusted disease state specific: TC:$9156 ($11586.07), IC:$3238 ($4097.38), PC:$3789 ($4794.62), OtC:$2129 ($2694.05)
*Diehl et al**[13]*** 2010 US	Direct costs	Pharmacy costs Primary care costs	Currency Year: USD, 2007 Cost of Non-adherence: TC:$19093.46 ($22834.47), PC:$7647.40 ($9145.76), SC‡:$11604.03 ($13877.59)
*Dilokthornsakul et al**[14]*** 2012 Thailand	Direct costs	Hospital costs	Currency Year: USD, 2004 Cost of Non-adherence: THC:$1157 ($1511.03), IC:$1019 ($1330.80), OC:$138 ($180.23)
*Dragomir et al**[15]*** 2010 Canada	Direct Costs	Hospital costs Pharmacy costs Primary Care costs	Currency Year: CAD, 2006 Cost of Non-adherence: Unadjusted Disease state specific: THC:$7165 ($7276.36), PC: $1800 ($1827.97), MC: $1370 ($1391.29), HC: $3995 ($4057.09) Unadjusted Hospitalized patients: THC: $17397 ($17667.38), PC:$2685 ($2726.73), MC:$2608 ($2648.53), HC: $12104 ($12292.11) Predicted disease state specific: HC:$3877 ($3937.25) Predicted hospitalized patient: HC:$11715 ($11897.07)

*Dragomir et al**[16]***	Direct Costs	Hospital costs	Currency Year: CAD, 2005
2010		Pharmacy costs	Cost of Non-adherence:
Canada		Primary Care costs	Unadjusted Disease state specific: THC:$6243 ($6511.79), PC:$2506 ($2613.89), MC:$1241 ($1294.42), HC:$2496 ($2603.47) Unadjusted Hospitalized patients: THC:$14725 ($15358.99), PC:$3374 ($3519.26), MC:$2475 ($2581.55), HC:$8876 ($9258.15) Predicted disease state specific: HC:$2669 ($2783.91) Predicted hospitalized patient: HC$9214 ($9610.71)
*Eisenberg et a**[17]***	Direct costs	Hospital costs	Currency Year: USD, 2012
2015		Pharmacy costs	Cost of Non-adherence:
US		Primary care costs	all cause: TC:$7237 ($7961.57), IC:$1986 ($2184.83), OC:$2057 ($2262.94), EDC:$258 ($283.82), PC:$2197 ($2416.96), POC:$738 ($811.88) Disease state specific: TC:$674 ($741.48), IC:$334 ($367.44), OC:$77 ($84.71), EDC:$5 ($5.50), PC:$213 ($234.32), POC:$44 ($48.40)
*Ettinger et al**[18]***	Direct costs	Hospital costs	Currency Year: USD, 2003
2009		Pharmacy costs	Cost of Non-adherence: TC:$17817 ($23906.75), IC:$2714 ($3641.63), EDC:$526 ($705.78), PC:$347 ($465.60), POC:$3063 ($4109.91), AC:$8344 ($11195.94), OtPC:$2822 ($3786.54)
US		Primary care costs	
*Faught et al**[19]***	Direct costs	Hospital costs	Currency Year: USD, 2002
2009		Pharmacy costs	Cost of Non-adherence[†]: TC:$14417.64 ($19732.17), IC:$6682.28 ($7247.51), OC:$2172.40 ($2973.17), EDC:$405.96 ($555.60), PC:$822.40 ($1125.54), OtPC:$4334.60 ($5932.39)
US			
Gentil et al**[20]**	Direct costs	Hospital costs	Currency Year: CAD, 2010
2015		Pharmacy costs	Cost of Non-adherence:
Canada		Primary care costs	Adjusted all cause: TC:$11124 ($10352.92), IC:$7419 ($6904.74), OC: $2687 ($2500.74), PC: $504 ($469.06), POC:$513 ($477.43) Adjusted disease state specific:

			TC:$4477 ($4166.61), IC:$2836 ($2639.41), OC: $1518 ($1412.77), PC[¶]: $-444 ($-413.22), POC:$568 ($545.38) Unadjusted all cause: TC:$14979 ($13940.7), IC:$6351 ($5910.77), OC: $4058 ($3776.71), PC: $3503 ($3260.17), POC:$1066 ($992.1068) Unadjusted disease state specific: TC:$9008 ($8383.59), IC:$2854 ($2656.16), OC: $2654 ($2470.03), PC: $2498 ($2324.84), POC:$1002 ($932.54)
*Gilmer et al**[21]*** 2004 US	Direct costs	Hospital costs Pharmacy costs	Currency Year: USD, 1999 Cost of Non-adherence: TC:$8168 ($11874.51), OC:$3464 ($5035.91), PC:$1542 ($2241.73), HC:$3413 ($4961.76)
*Gosselin et al**[22]*** 2009 US	Direct costs	Hospital costs Pharmacy costs Primary Care costs	Currency Year: USD, 2003 Cost of Non-adherence: TC:$9497 ($12743.02), IC:$2116 ($2839.23), OC:$5458 ($7323.51), PC:$1922 ($2578.93), MC:$7575 ($10164.09)
*Hansen et al**[23]*** 2010 US	Direct costs	Hospital costs Pharmacy costs	Currency Year: USD, 2005 Cost of Non-adherence[§]: All cause: THC:$15448.50 ($19548.69), IC:$4242.33 ($5368.27), OC:$ 7377.83 ($9283.6), PC:$3828 ($4843.97) Disease state specific: THC:$3232.33 ($4090.22), IC:$873.50 ($1105.33), OC:$1545.67 ($1955.89), PC:$812.67 ($1028.35)
*Hazel-Fernandez et al**[24]*** 2013 US	Direct costs	Hospital costs Pharmacy costs	Currency Year: USD, 2010 Cost of Non-adherence[†]: ≥80% adherence: THC:$21033 ($24190.73), IC:$2198 ($2527.99), OC:$5151 ($5924.33), EDC:$211 ($242.67), PC:$13472 ($15494.58) 50-80% adherence: THC:$25574 ($29413.48), IC:$8448 ($9716.31), OC:$6439 ($7405.70), EDC:$330 ($379.54), PC:$10358 ($11913.07) <50% adherence:

			THC:$15528 ($17859.25), IC:$4897 ($5632.19), OC:$5806 ($6677.66), EDC:$465 ($534.80), PC:$4361 ($5015.72) Fracture related, ≥80% adherence: THC:$12670 ($14572.17), IC:$366 ($420.95), OC:$1048 ($1205.341), EDC:$6 ($6.89), PC:$10810 ($12432.93) Fracture related, 50-80% adherence: THC:$9292 ($10687.02), OC:$955 ($1098.381), IC:$830 ($954.61), EDC:$9 ($10.35), PC:$7420 ($8533.97) Fracture related, <50 adherence: THC:$4419 ($5082.43), IC:$1325 ($1523.92), OC:$767 ($882.15), EDC:$44 ($50.60), PC:$2068 ($2378.46)
*Hong et al**[25]*** 2011 UK	Direct costs	Hospital costs Pharmacy costs	Currency Year: GBP, 2008 Cost of Non-adherence†: TC:£5846.29 ($10506.27), IC:£2740.57 ($4925.03), OC:£1082.86 ($1945.99), PC:£1630.29 ($2929.76), HC:£337.14 ($605.86)
*Hong et al**[26]*** 2011 South Korea	Direct costs	Hospital costs	Currency Year: KRW, 2007 Cost of Non-adherence: TC:₩765453 ($1204.46), HC:₩397549 ($625.56)
*Huybrechts et al**[27]*** 2006 US	Direct costs	Primary care costs	Currency Year: USD, 2000 Cost of Non-adherence: TC:$7200 ($10234.59), MC:$1476 ($2098.11), InstC:$5736 ($8153.55)
*Ivanova et al**[28]*** 2012 US	Direct costs Indirect costs	Hospital costs Pharmacy costs Primary Care costs Workplace costs	Currency Year: USD, 2007 Cost of Non-adherence†: All cause: TC:$8079 ($9781.52), THC:$6022 ($7201.89), IC:$1030.50 ($1232.40), OC:$3231 ($3864.05), EDC:$143.50 ($171.61), PC:$1617 ($1933.82), MC:$4405.50 ($5268.67) Disease state specific: TC:$3005 ($3593.77), IC:$505 ($603.94), OC:$1710 ($2045.04),EDC:$37 ($44.25), PC:$753 ($900.54), MC:$2252 ($2693.24) Indirect:

			STDC:$1231 ($1472.19), AbC:$826 ($987.83)
*Jiang et al**[29]***	Direct costs	Pharmacy costs	Currency Year: USD, 2011
2015		Primary care costs	Cost of Non-adherence: TC:$14141 ($15307.29), PC:$3971 ($4298.51), MSC:$10170 ($11008.78)
US			
*Joshi et al**[30]***	Indirect costs	Workplace costs	Currency Year: USD, 2002
2006			Cost of Non-adherence¶:
US			High adherence:
			TPC:$1210.90 ($1657.25), AbC:$633.70 ($867.28), PrC:$577.20 ($789.96)
			Medium adherence:
			TPC:$1428.50 ($1955.05), AbC:$608.90 ($833.34), PrC:$819.60 ($1121.71)
			Low adherence:
			TPC:$1073.10 ($1468.65), AbC:$474.80 ($649.81), PrC:$598.30 ($818.84)
*Kjellberge al**[31]***	Direct costs	Primary Care costs	Currency Year: Euro, 2011
2016			Cost of Non-adherence:
Denmark			all cause:
			TC:€4933 ($6547.45), MC:€3471 ($4606.93)
			Disease state specific:
			TC:€754 ($1000.76), MC:€426 ($565.41)
*Lee et al**[32]***	Direct costs	Hospital costs	Currency Year: USD, 2010
2011		Pharmacy costs	Cost of Non-adherence: TC:$126996 ($146062.2), IC:$14844 ($17072.56), OC:$101854 ($117145.6), EDC:$734 ($844.19), PC:$3244 ($3731.02), OtPC:$9564 ($10999.87)
US			
*Leider et al**[33]***	Direct costs	Hospital costs	Currency Year: USD, 2008
2011		Pharmacy costs	Cost of Non-adherence: THC:$26433 ($31006.49), IC:$6361 ($7461.59), OC:$9734 ($11418.2), EDC:$421 ($493.84), PC:$7960 ($9337.26), MC:$1957 ($2295.60)
US		Primary Care costs	
*Modi et al**[34]***	Direct costs	Hospital costs	Currency Year: USD, 2011
2015		Pharmacy costs	Cost of Non-adherence:
US		Primary Care costs	all cause:

		Direct non-medical costs	TC:$11749 ($13163.41), IC:$8768 ($9823.53), OC:$3945 ($4419.91), EDC:$104 ($116.52), PC:$2981 ($3339.87), MC:$8768 ($9823.53), OtC:$997 ($1117.02) Disease state specific: TC:$630 ($705.84), IC:$443 ($496.33), OC:$158 ($177.02), EDC:$3 ($3.36), PC:$325 ($364.12), OtC:$26 ($29.13)
*Offord et al**[35]*** 2013 US	Direct costs	Hospital costs Pharmacy costs	Currency Year: USD, 2008 Cost of Non-adherence: all cause: TC:$15400 ($18064.54), OC:$5773 ($6771.85), PC:$3777 ($4430.50), HC:$5850 ($6862.17) Disease state specific: TC:$5358 ($6285.05), OC:$858 ($1006.45), PC:$1549 ($1817.01), HC:$2952 ($3462.76)
*Pittman et al**[36]*** 2011 US	Direct Costs	Pharmacy Costs Primary Care costs	Currency Year: USD, 2009 Cost of Non-adherence†: >80% adherence: THC:$6798.67 ($7914.05), PC:$1767.33 ($2057.27), MC:$4472.67 ($15750.57) 60-79% adherence: THC:$7072.67 ($8233.01), PC:$1789.33 ($2082.88), MC:$4840.67 ($5634.83) <59% adherence: THC:$7401.33 ($8615.59), PC:$1937.33 ($2255.16), MC:$5138.67 ($5981.72)
*Pittman et al**[37]*** 2010 US	Direct costs	Hospital costs Pharmacy Costs	Currency Year: USD, 2008 Cost of Non-adherence: Adjusted, >80% adherence: THC:$7261 ($8517.31), OC:$3390 ($3976.56), EDC:$101 ($118.47), PC:$2383 ($2795.30), HC:$1386 ($1625.80) Adjusted, 60-79% adherence:

			THC:$7530 ($8832.86), OC:$3705 ($4346.04), EDC:$134 ($157.18), PC:$1932 ($2266.27), HC:$1759 ($2063.34) Adjusted, <59% adherence: THC:$7370 ($8645.17), OC:$3776 ($4429.33), EDC:$172 ($201.76), PC:$1509 ($1770.09), HC:$1913 ($2243.98) Unadjusted, >80% adherence: THC:$7182 ($8424.64), OC:$3396 ($3983.57), EDC:$102 ($119.64), PC:$2317 ($2717.89), HC:$1366 ($1602.34) Unadjusted, 60-79% adherence: THC:$7560 ($8868.04), OC:$3635 ($4263.93), EDC:$131 ($153.67), PC:$2034 ($2385.92), HC:$1759 ($2063.34) Unadjusted, <59% adherence: THC:$7995 ($9378.30), OC:$3887 ($4559.541), EDC:$172 ($201.76), PC:$1880 ($2205.28), HC:$2057 ($2412.90)
*Pruitt et al**[38]*** 2015 US	Direct costs	Hospital costs Pharmacy costs	Currency Year: USD, 2009 Cost of Non-adherence†: HIV: TC:$15360 ($17880), IC:$3864 ($4497.86), OC:$3948 ($4595.67),PC:$4956 ($5769.11), OtPC:$1764 ($2053.44), BHIC:$840 ($977.81) AIDS: TC:$27648 ($32183.9), IC:$13008 ($15142.16), OC:$5880 ($6844.73), PC:$5640 ($6565.36), OtPC:$2580 ($3003.30), BHIC:$528 ($614.68)
*Robertson et al**[39]*** *2014* *US*	Direct costs Indirect costs	Hospital costs Pharmacy costs Primary care costs Societal costs	Currency Year: USD,2005 Cost of Non-adherence†: 60-91 days covered: TC:$28068 ($35318.22), IC:$12168 ($15311.11), OC:$6468 ($ 8138.74), EDC:$96 ($120.79), PC:$5316 ($6689.16), TCMC:$2100 ($2642.45), PAC:$240 ($301.99), ArC:$780 ($981.47), InC:$888 ($1117.38) 31-60 days covered:

			TC:$21720 ($27330.48), IC:$10068 ($12668.65), OC:$4152 ($5224.49), EDC:$108 ($135.89), PC:$3468 ($4363.82), TCMC:$1404 ($1766.66), PAC:$228 ($286.89), ArC:$1032 ($1298.57), InC:$1272 ($1600.56) 1-30 days covered: TC:$21084 ($26530.19), IC:$11376 ($14314.53), OC:$2916 ($3669.22), EDC:$144 ($181.20), PC:$2232 ($2808.54), TCMC:$1596 ($2008.26), PAC:$204 ($256.69), ArC:$1140 ($1434.47), InC:$1476 ($1857.26) 0 days covered: TC:$12516 ($15748.99), IC:$5592 ($7036.46), OC:$2136 ($2687.74), EDC:$84 ($105.69), PC:$984 ($1238.17), TCMC:$516 ($649.28), PAC:$156 ($196.29), ArC:$1200 ($1509.97), InC:$1860 ($2340.45)
*Robinson et al**[40]*** 2006 US	Direct costs	Hospital costs Pharmacy costs Primary care costs	Currency Year: USD, 2004 Cost of Non-adherence[†]: all cause: TC:$12658 ($16531.29), IC:$3006 ($3925.82), OC:$6118 ($7990.08), EDC:$334 ($436.19), PC:$3200 ($4179.18), POC:$178 ($232.46) Disease state specific: TC:$2028 ($2648.55), IC:$102 ($133.21), OC:$734 ($958.59), EDC:$18 ($23.50), PC:$1174 ($1533.24),POC:$120 ($156.71)
Ruetsch et al**[41]** 2017 US	Direct costs	Hospital costs Pharmacy costs Primary care costs	Currency Year: USD, 2013 Cost of Non-adherence: THC:$16555 ($17920.39),IC:$5657 ($6123.57), OC:$5594 ($58775.97), EDC:$1147 ($1241.60), PC:$2365 ($2560.06), POC:$1765 ($1910.57), MC:$14190 ($15360.34)
*Sokol et al**[42]*** 2005 US	Direct Costs	Pharmacy Costs Primary Care costs	Currency Year: USD, 1998 Cost of Non-adherence: All cause, diabetes 80-100%: TC:$8886 ($13102.76), PC:$2510 ($3701.09), MC:$6377 ($9403.141) All cause, diabetes 60-79%:

TC:$11484 ($16933.61), PC:$2121 ($3127.502), MC:$9363 ($13806.11)
All cause, diabetes 40-59%:
TC:$12978 ($19136.58), PC:$1970 ($2904.84), MC:$11008 ($16231.72)
All cause, diabetes 20-39%:
TC:$13077 ($19282.55), PC:$1877 ($2767.71), MC:$11200 ($16514.84)
All cause, diabetes 1-19%:
TC:$16498 ($24326.95), PC:$1312 ($1934.59), MC:$15186 ($22392.36)
All cause, hypertension 80-100%:
TC:$8386 ($11885.73), PC:$1817 ($2679.24), MC:$6570 ($9687.72)
All cause, hypertension 60-79%:
TC:$8929 ($13166.16), PC:$1271 ($1874.14), MC:$7658 ($11292.02)
All cause, hypertension 40-59%:
TC:$9491 ($13994.85), PC:$1123 ($1655.91), MC:$8368 ($12338.94)
All cause, hypertension 20-39%:
TC:$11238 ($16570.88), PC:$952 ($1403.76), MC:$10286 ($15167.12)
All cause, hypertension 1-19%:
TC:$9747 ($14372.33), PC:$916 ($1350.68), MC:$8831 ($13021.66)
All cause, hypercholesterolemia 80-100%:
TC:$6752 ($9956.08), PC:$1972 ($2907.79), MC:$4780 ($7048.30)
All cause, hypercholesterolemia 60-79%:
TC:$8412 ($12403.83), PC:$1736 ($2559.796, MC:$6676 ($9844.02)
All cause, hypercholesterolemia 40-59%:
TC:$6756 ($9961.99), PC:$1247 ($1838.74), MC:$5509 ($8123.23)
All cause, hypercholesterolemia 20-39%:
TC:$7982 ($11769.77), PC:$1152 ($1698.66), MC:$6830 ($10071.1)
All cause, hypercholesterolemia 1-19%:

TC:$10916 ($16096.07), PC:$1067 ($1573.33), MC:$9849 ($14522.73)
All cause, CHF 80-100%:
TC:$22164 ($32681.69), PC:$3107 ($4581.38), MC:$19056 ($28098.83)
All cause, CHF 60-79%:
TC:$29785 ($43919.15), PC:$3412 ($5031.12), MC:$26373 ($38888.02)
All cause, CHF 40-59%:
TC:$26311 ($38796.6), PC:$2208 ($3255.78), MC:$24103 ($35540.82)
All cause, CHF 20-39%:
TC:$19188 ($28293.46), PC:$2055 ($3030.18), MC:$17133 ($25263.28)
All cause, CHF 1-19%:
TC:$23964 ($35335.86), PC:$1961 ($2891.56), MC:$22003 ($32444.29)
Disease state specific, diabetes 80-100%:
TC:$4570 ($6738.64), PC:$763 ($1125.07), MC:$3808 ($5615.05)
Disease state specific, diabetes 60-79%:
TC:$6291 ($9276.32), PC:$404 ($595.71), MC:$5887 ($8680.61)
Disease state specific, diabetes 40-59%:
TC:$6522 ($9616.94), PC:$285 ($420.24), MC:$6237 ($9196.69)
Disease state specific, diabetes 20-39%:
TC:$7124 ($10456.5), PC:$165 ($243.29), MC:$6959 ($10261.32)
Disease state specific, diabetes 1-19%:
TC:$8867 ($13074.74), PC:$55 ($81.09), MC:$8812 ($12993.64)
Disease state specific, hypertension 80-100%:
TC:$4871 ($7182.48), PC:$489 ($721.04), MC:$4383 ($6462.90)
Disease state specific, hypertension 60-79%:
TC:$5262 ($7759.02), PC:$285 ($420.24), MC:$4977 ($7338.78)
Disease state specific, hypertension 40-59%:

			TC:$5297 ($7810.63), PC:$184 ($271.31), MC:$5113 ($7539.32) Disease state specific, hypertension 20-39%: TC:$6062 ($8938.66), PC:$89 ($131.23), MC:$5973 ($8807.41) Disease state specific, hypertension 1-19%: TC:$4878 ($7192.79), PC:$31 ($45.70), MC:$4847 ($7147.08) Disease state specific, hypercholesterolemia 80-100%: TC:$3924 ($5786.09), PC:$801 ($1181.11), MC:$3124 ($4606.46) Disease state specific, hypercholesterolemia 60-79%: TC:$5541 ($8170.41), PC:$603 ($889.14), MC:$4938 ($7281.27) Disease state specific, hypercholesterolemia 40-59%: TC:$3825 ($5640.11), PC:$373 ($550), MC:$3452 ($5090.11) Disease state specific, hypercholesterolemia 20-39%: TC:$4999 ($7371.22), PC:$213 ($314.07), MC:$4786 ($7057.14) Disease state specific, hypercholesterolemia 1-19%: TC:$6888 ($10156.62), PC:$78 ($115.01), MC:$6810 ($10041.61) Disease state specific, CHF 80-100%: TC:$12698 ($18755.33), PC:$437 ($644.37), MC:$12261 ($18079.33) Disease state specific, CHF 60-79%: TC:$13924 ($20531.49), PC:$158 ($232.9723), MC$13766 ($20298.51) Disease state specific, CHF 40-59%: TC:$11378 ($16777.31), PC:$134 ($197.58), MC:$11244 ($16579.72) Disease state specific, CHF 20-39%: TC:$7733 ($11402.61), PC:$90 ($132.70), MC:$7643 ($11269.9) Disease state specific, CHF 1-19%: TC:$9841 ($14510.94), PC:$15 ($22.12), MC:$9826 ($14488.82)
*Stroupe et al**[43]* 2006 US	Direct costs	Hospital costs Pharmacy Costs	Currency Year: USD, 2002 Cost of Non-adherence‡: THC:$6032.5 ($8256.16), IC:$2067 ($2828.92), OC:$3965 ($5426.55), PC:$130 ($177.92)
*Sunyecz et al**[44]* 2008 US	Direct costs	Hospital costs Pharmacy costs Medical test costs	Currency Year: USD, 2005 Cost of Non-adherence: All cause:

			THC:$23660 ($29939.52), IC:$18839 ($23839), OC:$10061 ($12731.26), EDC:$832 ($1042.27), PC:$6941 ($8783.18), RC:$1079 ($1365.36) Disease state specific: THC:$1602 ($2027.18), IC:$14074 ($17809.34), OC:$501 ($633.96), EDC:$452 ($571.96), PC:$918 ($1161.64), RC:$184 ($232.83)
*Tkacz et al**[45]*** 2014 US	Direct costs	Hospital costs Pharmacy costs	Currency Year: USD, 2010 Cost of Non-adherence: Adjusted: THC:$49051 ($56415.13), IC:$26470 ($30444), OC:$14570 ($16757.42), EDC:$4439 ($5105.44), PC:$3581 ($4118.62) Unadjusted: THC:$47868 ($55054.53), IC:$26043 ($29952.89), OC:$14173 ($16300.82), EDC:$4058 ($4667.23), PC:$3557 ($4091.02)
*Wan et al**[46]*** 2014 US	Direct costs	Hospital costs Pharmacy costs	Currency Year: USD, 2009 Cost of Non-adherence: All cause: TC:$47411 ($55189.26), THC:$32522 ($37857.57), IC:$17634 ($20527.04), OC:$10909 ($12698.74), EDC:$458 ($533.14), PC:$18410 ($21430.35) Disease state specific: TC:$33652 ($39172.96), THC:$18764 ($21842.43), IC:$12564 ($14625.25), OC:$5890 ($6856.31), EDC:$48 ($55.87), PC:$15150 ($17635.52)
*Wei et al**[47]*** 2014 US	Direct costs	Hospital costs Pharmacy costs	Currency Year: USD, 2007 Cost of Non-adherence: 90-100% adherence: TC:$36407 ($43540.29), IC:$15294 ($18290.58), OC:$10155 ($12144.69), PC:$10957 ($13103.82) 80-89% adherence: TC:$43417 ($51923.77), IC:$21603 ($25835.72), OC:$11838 ($14157.44), PC:$9976 ($11930.62)

			≤79% adherence: TC:$45867 ($54853.81), IC:$24727 ($29571.81), OC:$12889 ($15414.36), PC:$8251 ($9867.63)
*White et al**[48]*** 2003 US	Direct costs	Pharmacy costs Primary Care costs	Currency Year: USD, 1999 Cost of Non-adherence: TC:$11815 ($17176.47), PC:$1123 ($ 1632.59), MC:$10692 ($15543.87)
*White et al**[49]*** 2004 US	Direct costs	Pharmacy costs Primary Care costs	Currency Year: USD, 2000 Cost of Non-adherence: Adjusted ≥95% adherence: TC:$4835 ($6872.83), PC:$1429 ($2031.29), MC:$3406 ($4841.54) Adjusted 75-95% adherence: TC:$5314 ($7553.72), PC:$1157 ($1644.65), MC:$4157 ($5909.07) Adjusted <75% adherence: TC:$5706 ($8110.93), PC:$762 ($1083.16), MC:$4944 ($7027.77) Unadjusted ≥95% adherence: TC:$4809 ($6835.88), PC:$1402 ($1992.91), MC:$3407 ($4842.96) Unadjusted 75-95% adherence: TC:$5333 ($7580.72), PC:$1153 ($1638.95), MC:$4180 ($5941.77) Unadjusted <75% adherence: TC:$5605 ($7967.36), PC:$766 ($1088.84), MC:$4839 ($6878.52)
*Wu et al**[50]*** 2011 US	Direct Costs	Pharmacy Costs Primary Care costs	Currency Year: USD, 2005 Cost of Non-adherence: all cause: THC:$17807 ($22533.1), PC:$4915 ($6219.47) MC:$12892 ($16313.62) Disease state specific: THC:$2789 ($3529.22), PC:$489 ($618.78) MC:$2300 ($2910.44)
*Wu et al**[51]*** 2009 US	Direct costs	Hospital costs Pharmacy costs	Currency Year: USD, 2006 Cost of Non-adherence: adjusted all cause, commercial: THC:$32407 ($39785.38), IC:$12851 ($15492.2), OC:$11888 ($14594.64), PC$7667 ($9412.60)

			Adjusted all cause, medicare: THC:$24622 ($30227.9), IC:$ 6754 ($8291.73), OC:$10598 ($13010.94), PC:$7270 ($8925.22) Adjusted disease state specific, diabetes commercial: THC:$10024 ($12306.25), IC:$2232 ($2740.17), OC:$1989 ($2441.84), PC:$1451 ($1781.36) Adjusted disease state specific, diabetes medicare: THC:$5015 ($6156.80), IC:$2606 ($3199.32), OC:$1231 ($1511.26), PC:$1179 ($1447.43) Adjusted disease state specific, DPNP commercial: THC:$3565 ($4376.67), IC:$1739 ($2134.93), OC:$362 ($444.42), PC:$1464 ($1797.31) Adjusted disease state specific, DPNP medicare: THC:$2384 ($2926.78), IC:$1048 ($1286.60), OC:$181 ($222.20), PC:$1155 ($1417.97)
*Wu et al**[52]*** 2010 US	Direct costs	Hospital costs Pharmacy costs	Currency Year: USD, 2008 Cost of Non-adherence: TC:$107341 ($125913.4), IC:$44498 ($52197.14), OC:$34097 ($39996.54), EDC:$248 ($290.91), PC:$22846 ($26798.86), OtPC:$5652 ($6629.92)
*Zhao et al**[53]*** 2014 US	Direct Costs	Pharmacy Costs Primary Care costs	Currency Year: USD, 2010 Cost of Non-adherence: 96-100% adherence: THC:$6536.05 ($7517.32), PC:$449.86 ($517.4), MC:$3559.25 ($46270.09) 90-95% adherence: THC:$6493.80 ($7468.72), PC:$439.74 ($505.75), MC:$3666.81 ($4217.32) 85-89% adherence: THC:$6459.40 ($7429.16), PC:$458.83 ($527.71), MC:$3664 ($4214.08) 80-84% adherence:

			THC:$6227.47 ($7162.41), PC:$423.15 ($486.67), MC:$3586.58 ($4125.03) 70-79% adherence: THC:$5713.47 ($6571.24), PC:$356.74 ($410.30), MC:$3520.64 ($4049.20) 60-69% adherence: THC:$5875.26 ($6757.32), PC:$371.30 ($427.04), MC:$3551.99 ($4085.25) 40-59% adherence: THC:$5817.58 ($6690.98), PC:$279.21 ($321.13), MC:$3663.65 ($4213.68) <40% adherence: THC:$5249.12 ($6037.18), PC:$133.92 ($154.02), MC:$3499.95 ($4025.40)
*Zhao et al**[54]*** 2014 US	Direct costs	Hospital costs Pharmacy costs	Currency Year: USD, 2010 Cost of Non-adherence†: Adjusted, ≥80% adherence: THC:$34428 ($39596.76), IC:$7548 ($8681.18), OC:$9312 ($10710.08), PC:$18864 ($21696.13) Adjusted, 50-80% adherence: THC(50-80):$37956 ($43654.43), IC:$11520 ($1325.18), OC:$12816 ($14740.05), PC:$13116 ($15085.09) Adjusted, <50% adherence: THC:$31188 ($35870.34), IC:$11556 ($13290.91), OC:$13044 ($15002.34), PC:$7452 ($8570.72) Unadjusted, ≥80% adherence: THC:$37464 ($43088.59), IC:$7092 ($8156.72), OC:$9900 ($11386.26), PC:$20484 ($23559.28) Unadjusted, 50-80% adherence: THC:$35076 ($40342.01), IC:$11100 ($12766.44), OC:$11352 ($13056.32), PC:$12624 ($14519.25) Unadjusted, <50% adherence:

			THC:$29484 ($33910.52), IC:$10632 ($12228.18), OC:$11988 ($13787.79), PC:$6864 ($7894.55)
*Zhao et al**[55]*** 2013 US	Direct costs	Hospital costs Pharmacy costs	Currency Year: USD, 2010 Cost of Non-adherence[†]: Adjusted, ≥80% adherence: THC:$40212 ($46249.17), IC:$8136 ($9357.48), OC:$12924 ($14864.3), PC:$19392 ($22303.34) Adjusted, 50-80% adherence: THC:$40512 ($46594.21), IC:$12060 ($13870.54), OC:$14928 ($17169.16), PC:$13908 ($15995.98) Adjusted, <50% adherence: THC:$40128 ($46152.5), IC:$15444 ($17660.33), OC:$17568 ($20205.49), PC:$8700 ($10378.83) Unadjusted, ≥80% adherence: THC(≥80):$42768 ($49188.83), IC:$7620 ($8764.06), OC:$14580 ($16768.95), PC:$20568 ($23655.94) Unadjusted, 50-80% adherence: THC:$36780 ($42301.83), IC:$12228 ($14063.87), OC:$12108 ($13925.83), PC:$12444 ($14312.25) Unadjusted, <50% adherence: THC:$39792 ($45766.08), IC:$15768 ($18135.34), OC:$15324 ($17624.67),PC:$8700 ($10006.2)
*Zhao et al**[56]*** 2011 US	Direct costs	Hospital costs Pharmacy costs	Currency Year: USD, 2008 Cost of Non-adherence: Commercial: TC:$20323 ($23839.33),IC:$4808 ($5639.89), OC:$9822 ($11521.42), PC:$5693 ($6678.01) Medicare: TC:$25282 ($29656.35), IC:$8604 ($10092.68), OC:$10068 ($11809.98), PC:$6611 ($7754.85)

A: adherent, NA: non-adherent, MA: moderate adherence, LA: low adherence, NC: non-compliance, NE: no exposure, CHF: chronic heart failure, THC: total healthcare costs, TC: total costs, IC: inpatient costs, OC: outpatient costs, EDC: emergency department visit costs, HC: hospitalisation costs, BHIC: behavioural health inpatient costs, ACC: acute care costs, PC: prescription medication costs, OtPC: other pharmacy costs, MC: medical costs, POC: physician office visit costs, AC: ancillary costs, PAC: psychiatric assessment costs, TCMC: targeted case management

costs, SC: services costs, InstC: institutional costs, MSC: medical services costs, RC: radiology costs, STDC: short term disability costs, WCC: workers compensation costs, PTOC: paid time off costs, TPC: total productivity costs, AbC: absenteeism costs, PrC: presenteeism costs, ArC: arrest costs, InC: incarceration costs, OtC: other costs, USD: United States dollar, GBP: Great British Pound, EUR: Euro, CAD: Canadian dollar, KRW: South Korean won

†: extrapolated annual cost; ǂ: subgroups averaged; §: extrapolated annual cost and subgroups averaged; ¶: cost represents losses in workplace productivity; ₡: negative value as costs modelled against adherent group

1. An S-Y, Kim HJ, Chun KH *et al.* Clinical and economic outcomes in medication-adherent and -nonadherent patients with type 2 diabetes mellitus in the Republic of Korea. *Clinical therapeutics*, 36, 245-254 (2014).
2. Aubert RE, Yao J, Xia F, Garavaglia SB. Is there a relationship between early statin compliance and a reduction in healthcare utilization? *The American journal of managed care*, 16, 459-466 (2010).
3. Bagalman E, Yu-Isenberg KS, Durden E, Crivera C, Dirani R, Bunn WB. Indirect costs associated with nonadherence to treatment for bipolar disorder. *Journal of occupational and environmental medicine / American College of Occupational and Environmental Medicine*, 52, 478-485 (2010).
4. Candrilli SD, O'Brien SH, Ware RE, Nahata MC, Seiber EE, Balkrishnan R. Hydroxyurea adherence and associated outcomes among Medicaid enrollees with sickle cell disease. *American journal of hematology*, 86, 273-277 (2011).
5. Casciano JP, Dotiwala ZJ, Martin BC, Kwong WJ. The costs of warfarin underuse and nonadherence in patients with atrial fibrillation: a commercial insurer perspective. *Journal of managed care pharmacy : JMCP*, 19, 302-316 (2013).
6. Cooke CE, Lee HY, Xing S. Adherence to antiretroviral therapy in managed care members in the United States: a retrospective claims analysis. *Journal of managed care pharmacy : JMCP*, 20, 86-92 (2014).
7. Curtis SE, Boye KS, Lage MJ, Garcia-Perez LE. Medication adherence and improved outcomes among patients with type 2 diabetes. *The American journal of managed care*, 23(7), e208-e214 (2017).
8. Darkow T, Henk HJ, Thomas SK *et al.* Treatment interruptions and non-adherence with imatinib and associated healthcare costs: a retrospective analysis among managed care patients with chronic myelogenous leukaemia. *PharmacoEconomics*, 25, 481-496 (2007).
9. Davis JR, Wu B, Kern DM *et al.* Impact of Nonadherence to Inhaled Corticosteroid/LABA Therapy on COPD Exacerbation Rates and Healthcare Costs in a Commercially Insured US Population. *American health & drug benefits*, 10(2), 92-102 (2017).
10. Davis KL, Edin HM, Allen JK. Prevalence and cost of medication nonadherence in Parkinson's disease: evidence from administrative claims data. *Movement disorders : official journal of the Movement Disorder Society*, 25(4), 474-480 (2010).
11. Delea TE, Stanford RH, Hagiwara M, Stempel DA. Association between adherence with fixed dose combination fluticasone propionate/salmeterol on asthma outcomes and costs*. *Current medical research and opinion*, 24, 3435-3442 (2008).
12. Delea TE, Thomas SK, Hagiwara M. The association between adherence to levodopa/carbidopa/entacapone therapy and healthcare utilization and costs among patients with Parkinson's disease: a retrospective claims-based analysis. *CNS drugs*, 25, 53-66 (2011).
13. Diehl JL, Daw JR, Coley KC, Rayburg R. Medical utilization associated with palivizumab compliance in a commercial and managed medicaid health plan. *Journal of managed care pharmacy : JMCP*, 16, 23-31 (2010).
14. Dilokthornsakul P, Chaiyakunapruk N, Nimpitakpong P, Jeanpeerapong N, Sruamsiri R. The Effects of Medication Supply on Hospitalizations and Health-Care Costs in Patients with Chronic Heart Failure. *Value in Health*, 15, S9-S14 (2012).
15. Dragomir A, Côté R, Roy L *et al.* Impact of adherence to antihypertensive agents on clinical outcomes and hospitalization costs. *Medical care*, 48, 418-425 (2010).
16. Dragomir A, Cote R, White M *et al.* Relationship between adherence level to statins, clinical issues and health-care costs in real-life clinical setting. *Value in health : the journal of the International Society for Pharmacoeconomics and Outcomes Research*, 13(1), 87-94 (2010).

17. Eisenberg DF, Placzek H, Gu T, Krishna A, Tulsi BB. Cost and consequences of noncompliance to oral bisphosphonate treatment. *Journal of managed care & specialty pharmacy*, 21(1), 56-65 (2015).
18. Ettinger AB, Manjunath R, Candrilli SD, Davis KL. Prevalence and cost of nonadherence to antiepileptic drugs in elderly patients with epilepsy. *Epilepsy & behavior : E&B*, 14, 324-329 (2009).
19. Faught RE, Weiner JR, Guérin A, Cunnington MC, Duh MS. Impact of nonadherence to antiepileptic drugs on health care utilization and costs: findings from the RANSOM study. *Epilepsia*, 50, 501-509 (2009).
20. Gentil L, Vasiliadis HM, Preville M, Berbiche D. Adherence to Oral Antihyperglycemic Agents Among Older Adults With Mental Disorders and Its Effect on Health Care Costs, Quebec, Canada, 2005-2008. *Preventing chronic disease*, 12, E230 (2015).
21. Gilmer TP, Dolder CR, Lacro JP *et al.* Adherence to treatment with antipsychotic medication and health care costs among Medicaid beneficiaries with schizophrenia. *The American journal of psychiatry*, 161, 692-699 (2004).
22. Gosselin A, Luo R, Lohoues H *et al.* The impact of proton pump inhibitor compliance on health-care resource utilization and costs in patients with gastroesophageal reflux disease. *Value in health : the journal of the International Society for Pharmacoeconomics and Outcomes Research*, 12, 34-39 (2009).
23. Hansen RA, Farley JF, Droege M, Maciejewski ML. A retrospective cohort study of economic outcomes and adherence to monotherapy with metformin, pioglitazone, or a sulfonylurea among patients with type 2 diabetes mellitus in the United States from 2003 to 2005. *Clinical therapeutics*, 32, 1308-1319 (2010).
24. Hazel-Fernandez L, Louder AM, Foster SA, Uribe CL, Burge RT. Association of teriparatide adherence and persistence with clinical and economic outcomes in Medicare Part D recipients: a retrospective cohort study. *BMC musculoskeletal disorders*, 14, 4 (2013).
25. Hong J, Reed C, Novick D, Haro JM, Aguado J. Clinical and economic consequences of medication non-adherence in the treatment of patients with a manic/mixed episode of bipolar disorder: results from the European Mania in Bipolar Longitudinal Evaluation of Medication (EMBLEM) study. *Psychiatry research*, 190, 110-114 (2011).
26. Hong JS, Kang HC. Relationship between oral antihyperglycemic medication adherence and hospitalization, mortality, and healthcare costs in adult ambulatory care patients with type 2 diabetes in South Korea. *Medical care*, 49, 378-384 (2011).
27. Huybrechts KF, Ishak KJ, Caro JJ. Assessment of compliance with osteoporosis treatment and its consequences in a managed care population. *Bone*, 38, 922-928 (2006).
28. Ivanova JI, Bergman RE, Birnbaum HG, Phillips AL, Stewart M, Meletiche DM. Impact of medication adherence to disease-modifying drugs on severe relapse, and direct and indirect costs among employees with multiple sclerosis in the US. *Journal of medical economics*, 15, 601-609 (2012).
29. Jiang Y, Ni W. Estimating the Impact of Adherence to and Persistence with Atypical Antipsychotic Therapy on Health Care Costs and Risk of Hospitalization. *Pharmacotherapy*, 35(9), 813-822 (2015).
30. Joshi AV, Madhavan SS, Ambegaonkar A, Smith M, Scott VG, Dedhia H. Association of medication adherence with workplace productivity and health-related quality of life in patients with asthma. *The Journal of asthma : official journal of the Association for the Care of Asthma*, 43, 521-526 (2006).
31. Kjellberg J, Jorgensen AD, Vestergaard P, Ibsen R, Gerstoft F, Modi A. Cost and health care resource use associated with noncompliance with oral bisphosphonate therapy: an analysis using Danish health registries. *Osteoporosis International*, 27(12), 3535-3541 (2016).

32. Lee A, Song X, Khan I *et al.* Association of cinacalcet adherence and costs in patients on dialysis. *Journal of medical economics*, 14, 798-804 (2011).
33. Leider HL, Dhaliwal J, Davis EJ, Kulakodlu M, Buikema AR. Healthcare costs and nonadherence among chronic opioid users. *The American journal of managed care*, 17, 32-40 (2011).
34. Modi A, Siris ES, Tang J, Sen S. Cost and consequences of noncompliance with osteoporosis treatment among women initiating therapy. *Current medical research and opinion*, 31(4), 757-765 (2015).
35. Offord S, Lin J, Mirski D, Wong B. Impact of early nonadherence to oral antipsychotics on clinical and economic outcomes among patients with schizophrenia. *Advances in therapy*, 30, 286-297 (2013).
36. Pittman DG, Chen W, Bowlin SJ, Foody JM. Adherence to statins, subsequent healthcare costs, and cardiovascular hospitalizations. *The American journal of cardiology*, 107, 1662-1666 (2011).
37. Pittman DG, Tao Z, Chen W, Stettin GD. Antihypertensive medication adherence and subsequent healthcare utilization and costs. *The American journal of managed care*, 16, 568-576 (2010).
38. Pruitt Z, Robst J, Langland-Orban B, Brooks RG. Healthcare costs associated with antiretroviral adherence among medicaid patients. *Applied health economics and health policy*, 13, 69-80 (2015).
39. Robertson AG, Swanson JW, Van Dorn RA, Swartz MS. Treatment participation and medication adherence: effects on criminal justice costs of persons with mental illness. *Psychiatric services (Washington, D.C.)*, 65(10), 1189-1191 (2014).
40. Robinson RL, Long SR, Chang S *et al.* Higher costs and therapeutic factors associated with adherence to NCQA HEDIS antidepressant medication management measures: analysis of administrative claims. *Journal of managed care pharmacy : JMCP*, 12, 43-54 (2006).
41. Ruetsch C, Tkacz J, Nadipelli VR *et al.* Heterogeneity of nonadherent buprenorphine patients: subgroup characteristics and outcomes. *The American journal of managed care*, 23(6), e172-e179 (2017).
42. Sokol MC, McGuigan KA, Verbrugge RR, Epstein RS. Impact of medication adherence on hospitalization risk and healthcare cost. *Medical care*, 43, 521-530 (2005).
43. Stroupe KT, Teal EY, Tu W, Weiner M, Murray MD. Association of Refill Adherence and Health Care Use Among Adults with Hypertension in an Urban Health Care System. *Pharmacotherapy*, 26, 779-789 (2006).
44. Sunyecz JA, Mucha L, Baser O, Barr CE, Amonkar MM. Impact of compliance and persistence with bisphosphonate therapy on health care costs and utilization. *Osteoporosis international : a journal established as result of cooperation between the European Foundation for Osteoporosis and the National Osteoporosis Foundation of the USA*, 19, 1421-1429 (2008).
45. Tkacz J, Volpicelli J, Un H, Ruetsch C. Relationship between buprenorphine adherence and health service utilization and costs among opioid dependent patients. *Journal of substance abuse treatment*, 46, 456-462 (2014).
46. Wan GJ, Kozma CM, Slaton TL, Olson WH, Feagan BG. Inflammatory bowel disease: healthcare costs for patients who are adherent or non-adherent with infliximab therapy. *Journal of medical economics*, 17, 384-393 (2014).
47. Wei Y-J, Palumbo FB, Simoni-Wastila L *et al.* Antiparkinson drug adherence and its association with health care utilization and economic outcomes in a Medicare Part D population. *Value in health : the journal of the International Society for Pharmacoeconomics and Outcomes Research*, 17, 196-204 (2014).

48. White TJV, Ann; Ory, Caron; Dezii, Christopher M.; Chang, Eunice. Economic Impact of Patient Adherence with Antidepressant Therapy Within a Managed Care Organization. *Disease Management & Health Outcomes*, 11(12), 817-822 (2003).
49. White TJV, Ann; Chang, Eunice; Dezii, Christopher M.; Abrams, Geoffrey D. The Costs of Non-Adherence to Oral Antihyperglycemic Medication in Individuals with Diabetes Mellitus and Concomitant Diabetes Mellitus and Cardiovascular Disease in a Managed Care Environment. *Disease Management & Health Outcomes*, 12(3), 181-188 (2004).
50. Wu J, Seiber E, Lacombe VA, Nahata MC, Balkrishnan R. Medical utilization and costs associated with statin adherence in Medicaid enrollees with type 2 diabetes. *The Annals of pharmacotherapy*, 45, 342-349 (2011).
51. Wu N, Chen S, Boulanger L, Fraser K, Bledsoe SL, Zhao Y. Duloxetine compliance and its association with healthcare costs among patients with diabetic peripheral neuropathic pain. *Journal of medical economics*, 12, 192-202 (2009).
52. Wu EQ, Johnson S, Beaulieu N *et al.* Healthcare resource utilization and costs associated with non-adherence to imatinib treatment in chronic myeloid leukemia patients. *Current medical research and opinion*, 26, 61-69 (2010).
53. Zhao Y, Zabriski S, Bertram C. Associations between statin adherence level, health care costs, and utilization. *Journal of managed care & specialty pharmacy*, 20, 703-713 (2014).
54. Zhao Y, Johnston SS, Smith DM, McMorrow D, Krege J, Krohn K. Association between teriparatide adherence and healthcare utilization and costs among hip fracture patients in the United States. *Bone*, 60, 221-226 (2014).
55. Zhao Y, Johnston SS, Smith DM, McMorrow D, Krohn K, Krege J. Association between teriparatide adherence and healthcare utilization and costs in real-world US kyphoplasty/vertebroplasty patients. *Osteoporosis International*, 24, 2525-2533 (2013).
56. Zhao Y, Chen S-Y, Wu N, Fraser KA, Boulanger L. Medication Adherence and Healthcare Costs among Fibromyalgia Patients Treated with Duloxetine. *Pain Practice*, 11, 381-391 (2011).

This page is intentionally left blank

Chapter 5

Pharmacist-led medication non-adherence intervention: reducing the economic burden placed on the Australian health care system

Cutler, R.L., Torres-Robles, A., Wiecek, E., Drake, B., Van der Linden, N., Benrimoj, S.I. & Garcia-Cardenas, V. 2019, 'Pharmacist led medication non-adherence intervention: reducing the economic burden placed on the Australian health care system', *Patient Preference and Adherence*, vol. 13, pp. 853

This page is intentionally left blank

Abstract

Background: Scarcity of prospective medication non-adherence cost measurements for the Australian population with no directly measured estimates makes determining the burden medication non-adherence places on the Australian health care system difficult. This study aims to indirectly estimate the national cost of medication non-adherence in Australia comparing the cost prior to and following a community pharmacy led intervention.

Methods: Retrospective observational study. A de-identified database of dispensing data from 20,335 patients (n= 11,257 on rosuvastatin, n= 6,797 on irbesartan, and n= 2,281 on desvenlafaxine) was analysed and average adherence rate determined through calculation of PDC. Included patients received a pharmacist led medication adherence intervention and had twelve months dispensing records; six months before and six months after the intervention. The national cost estimate of medication non-adherence in hypertension, dyslipidaemia and depression pre and post intervention was determined through utilisation of disease prevalence and comorbidity, non-adherence rates and per patient disease specific adherence related costs.

Results: The total national cost of medication non-adherence across three prevalent conditions, hypertension, dyslipidaemia and depression was $10.4 billion equating to $517 per adult. Following enrollment in the pharmacist led intervention medication non-adherence costs per adult decreased $95 saving the Australian health care system and patients $1.9 billion annually.

Conclusion: In the absence of a directly measured national cost of medication non-adherence this estimate demonstrates that pharmacists are ideally placed to improve patient adherence and reduce financial burden placed on the health care system due to non-adherence. Funding of medication adherence programs should be considered by policy and decision makers to ease the current burden and improve patient health outcomes moving forward.

Keywords: medication adherence, community pharmacy, big data, dispensing records, health economics

Introduction

Appropriate use of medications remains sub-optimal despite their proven effectiveness in preventing and managing chronic conditions[1]. In an outpatient setting medication non-adherence is one of the principal obstacles in successful pharmacotherapy, yet often fails to be clinically recognised[1]. The high prevalence of medication non-adherence is associated with increased morbidity and mortality, disease progression and increased utilisation of health care resources and accompanying expenditure[2,3]. Nevertheless, medication non-adherence remains a neglected element of patient therapeutic management.

Internationally the economic impact of medication non-adherence has been examined at the macro-level in a number of studies, independent reports and grey literature findings. Heterogeneity exists in the reported costs with limited information available to determine how these values were calculated. The 2013 IMS "Avoidable Costs in US Healthcare" report stipulates that annually US$105.4 billion or 3.9% of the nation's health care spending would be avoidable if medication non-adherence were addressed [4]. Furthermore, while the "Advancing the responsible use of medicines" report specifies that medication non-adherence contributes 57% of the world's total avoidable cost due to suboptimal medicines use[5]. The quantification of cost avoidance and the research substantiating these analyses implies that better use of medicines can improve quality of life through reduced hospitalisations and improved health outcomes such as morbidity and mortality. Figure One presents a timeline of the global predictive annual economic burden attributed to medication non-adherence reported in the grey literature, highlighting the tendency of medication non-adherence costs to increase over time.

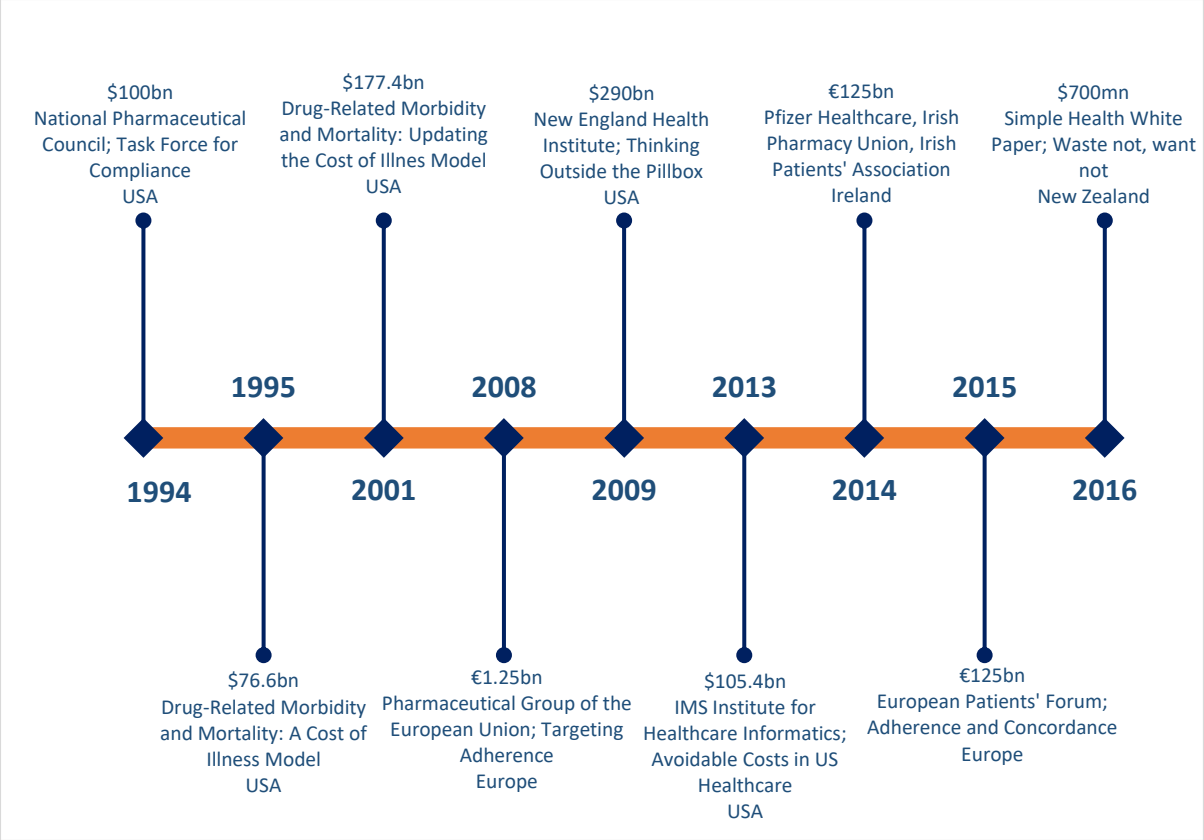

Figure 1: Timeline of macro-level medication non-adherence costs

Grey literature reports data demonstrating the increasing costs associated with medication non-adherence over time. **Note**: Costs in $ are expressed in US$.

The micro-level economic examination of medication non-adherence within single disease state studies supports the determination that non-adherence is largely associated with higher health care costs[2,6-9] and solidifies big data international projections.[4,10] A recent systematic review reported the annual adjusted disease specific economic cost of non-adherence to range from US$949 to $44,190 per person. Costs associated with non-adherence to cancer treatment ($114,101) were substantially higher than costs associated with non-adherence to treatment for cardiovascular disease ($16,124), mental health ($16,110) or osteoporosis ($43,240).[11] These micro costing studies however are limited as they only report for a specific population and fail to take into consideration recent changes in disease prevalence. Additionally the majority of the studies are conducted in the United States (US) where health care is generally more expensive, and the health insurance system differs significantly between the US and Australia. Scarcity of prospective medication non-adherence cost measurements for the Australian population with no directly measured estimates reported

makes the generalisability of these results limited in their pertinence to extrapolating national cost estimates of medication non-adherence.

In Australia inappropriate use of medicines costs the Australian public hospital system AUD$1.2 billion per year representing 2-3% of all hospital admissions, with this figure rising to 20-30% of all admissions in the population aged 65 years and over.[12] It is estimated that 4.7% of total Australian health expenditure is avoidable due to suboptimal medicines use[5] extrapolating to AUD$8 billion annually.[13] These costs however do not directly estimate medication non-adherence and take into consideration a number of confounding factors that contribute to inappropriate medication use. In addition to medication non-adherence these avoidable costs arise when patients fail to receive the right medications at the right time or in the right way, or receive them but fail to take them. Medication non-adherence has been identified as an "opportunity cost" to reclaim current health care spending wastage.[4] Targeted analysis is required to accurately estimate the associated cost of medication non-adherence in Australia, which is thought to be significantly underestimated. [14-16]

Improvements in health care in conjunction with prolonged life expectancy has resulted in a rise in the prevalence of chronic conditions ultimately increasing the burden placed on health care systems and subsequently leading to a higher number of prescription medications and budgetary spending allocations to manage these conditions. [17] Most illnesses and deaths in Australia are caused by chronic conditions with an estimated 1 in 2 Australians (50%) suffering from at least one chronic condition.[18] Cardiovascular disease and mental health conditions are two of the most prevalent chronic conditions, with 1 in 5 (18%) Australians experiencing one of these.[18] Suboptimal adherence to commonly prescribed medications in cardiovascular disease and mental health contribute significantly to disease progression and mortality, [19-22] increasing the budget impact on the Australian health care system. Increased availability of large prescription data sets enhances the analysis and evaluation of patient medication adherence, enabling a cost-effective approach to estimate the economic impact of medication non-adherence. [23,24]

With up to 30% of prescriptions never being filled and approximately 50% of people with chronic conditions stopping their medications within the first twelve months,[25] the negative financial implications of medication non-adherence are of paramount concern. Evidence

supports that community pharmacists are ideally situated to deliver medication adherence interventions,[26] however further examination is necessary to determine the broader economic impact pharmacist medication adherence interventions have in cost savings to the Australian health care system. In the absence of a directly measured national cost of medication non-adherence, this study aims to indirectly estimate the national cost of medication non-adherence in Australia comparing the cost prior to and following a community pharmacy led intervention. Utilising population based and pharmacy claims data a transparent and replicable model will be developed to determine the national estimate of medication non-adherence in hypertension, dyslipidaemia and depression[27] prior to and following a community pharmacy based intervention through examining medication use of three molecules rosuvastatin, irbesartan and desvenlafaxine.

Methods

Study design and data sources

A retrospective analysis of de-identified patient pharmacy dispensing data from the GuildLink Pty Ltd database was conducted. GuildLink Pty Ltd is a wholly owned subsidiary of the Pharmacy Guild of Australia, which focuses on providing software solutions to community pharmacies to aid in the provision and documentation of pharmacy services.

The MedScreen Compliance program was utilised to identify patients receiving an educational based intervention to enhance medication adherence from community pharmacies across Australia. This program is designed to help ensure that quality use of medicine is achieved and adherence to prescribed therapy is maintained or improved. The service targets non-adherent patients when a calculated medication possession ratio (MPR) is below 70%. The clinical service consists of 1) identifying patient specific barriers and facilitators to medication adherence 2) engaging patients in a brief pharmacist educational interaction regarding adherence and quality use of medicines, this includes provision of either oral or written communication to enhance patient understanding and emphasise the importance of adherence 3) goal setting for patient treatment targets 4) recording the interaction and making patient specific notes.[28] Patients could receive one or multiple interventions across

time periods depending on the calculated MPR, alerting the pharmacist to invite the patient to the intervention if they remain below the 70% adherence threshold.

The unique patient identifier allowed patients enrolled in the MedScreen Compliance intervention to be anonymously identified and their medication adherence rates tracked. One year dispensing history was analysed for each patient who completed the intervention; six months prior to the adherence intervention and six months following the intervention. Process indicators to validate the fidelity of the intervention were not available.

Medication adherence

Descriptive outcomes included adherence measures in patients with a dispensing history during the six months prior to the MedScreen Compliance intervention (pre-intervention/baseline), when the intervention was performed and six months following the intervention (post-intervention). For this analysis adherence to three molecules rosuvastatin, irbesartan and/or desvenlafaxine was determined using the proportion of days covered (PDC). The three molecules modelled disease state prevalence. PDC was defined as the total number of days supplied with the medication during the six month period before and after the intervention divided by the total number of days in the fixed period. Analysis was conducted per trimesters, 6 months before and 6 months after the first pharmacist intervention, calculating the average PDC (%) and standard deviation (SD) for all patients in each period using descriptive statistics. [29] Adherence was defined as a PDC of 80% or greater, the most common threshold for adequate adherence to chronic medications.[30] The number of non-adherent patients for each condition was determined by multiplying the rate of non-adherence pre and post intervention with the Australian adult population with the disease. This indicator was selected instead of MPR as it does not overestimate adherence, provides a conservative estimate and accounts for overlapping days supply.[31]

Estimates of the Australian population and number of patients with hypertension, dyslipidaemia and depression were collected from the Australian Bureau of Statistics. [18,32-35] The steps and sources of data used in the cost estimation are depicted in Figure 2 adapted from Nasseh et al,[27] data input values are presented in Table 1.The prevalence rates of the conditions were multiplied by the total Australian population to determine national estimates.

Cost calculations

Monetary values attributed to medication non-adherence for hypertension, dyslipidaemia and depression were identified from the literature.[11] All costs were converted to Australian dollars (2018 values) using the Cochrane Economics Methods Group - Evidence for Policy and Practice Information and Coordinating -Centre Cost Converter tool.[36] The most conservative non-adherence cost estimate (minimum reported value) was utilised to extrapolate national expenditure attributed to non-adherence across each disease, radical estimates represented the maximum reported value in the literature. Comorbidity risk adjustment was undertaken to prevent duplication of non-adherence costs across multiple conditions. Within the non-adherent hypertension, dyslipidaemia and depression population estimations were made for the number of patients with only 1 of the conditions and all combinations of 2 or 3 of the comorbid conditions. The national non-adherence cost estimate was further evaluated in terms of the cost outcome indicators that contributed to the total cost through application of the MACE framework [37] examining national hospital cost data,[38] and the Pharmaceutical Benefits Scheme expenditure data.[39]

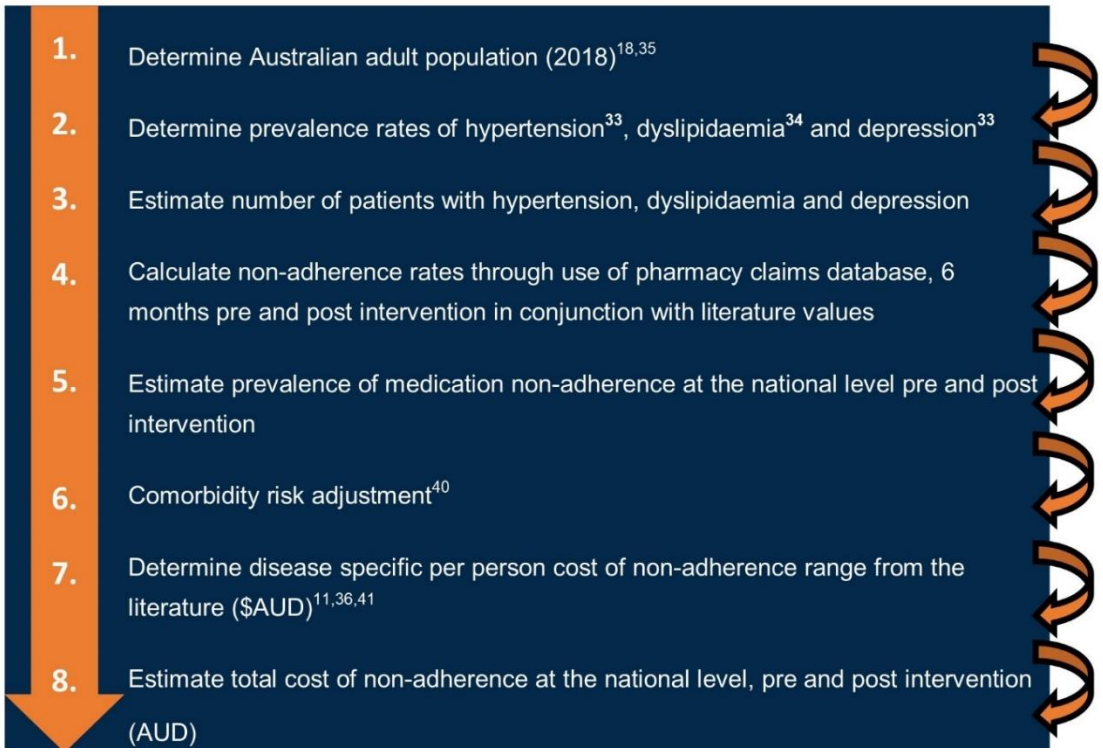

Figure 2: Derivation of the cost of medication non-adherence
Note: Stepwise approach in the methodology (adapted from Nasseh et al[27]) undertaken to estimate the national cost of medication non-adherence in Australia pre- and post- community pharmacist led intervention

Table 1: Derivation of cost process

Outlines data input values to determine the national cost estimate of medication non-adherence in Australia

Derivation of cost process	Reported Findings					
Australian adult population (2018)[18,35]	20,160,000					
	Hypertension[33]		**Dyslipidaemia**[34]		**Depression**[33]	
Prevalence rates of conditions (%)	34%		32.8%		17.5%	
Prevalence rates of conditions (number of patients)	6,854,400		6,612,480		3,528,000	
Average PDC 6 months pre and post intervention (%)	Pre	45.5%	Pre	45.6%	Pre	52%
	Post	37.1%	Post	37.6%	Post	40.5%
National prevalence of medication non-adherence	Pre	3,118,752	Pre	3,015,290	Pre	1,834,560
	Post	2,542,982	Post	2,486,292	Post	1,428,840
Disease specific non-adherence cost ($AUD)[11,36,41]	Min	$2,386	Min	$8,125	Min	$3,812
	Max	$13,493	Max	$14,631	Max	$24,717
Conservative national estimate ($AUD)	Pre	$1,994,279,728	Pre	$6,565,793,975	Pre	$1,874,215,848
	Post	$1,626,104,753	Post	$5,413,900,830	Post	$1,459,725,805
Radical national estimate ($AUD)	Pre	$11,277,793,957	Pre	$11,823,277,741	Pre	$12,152,411,631
	Post	$9,195,738,241	Post	$9,749,019,451	Post	$9,464,859,059

Abbreviations: PDC, proportion of days covered; Pre, pre-adherence intervention; Post, post-adherence intervention

Sensitivity Analysis

A sensitivity analysis was conducted to quantify the changes in estimated total cost of non-adherence when varying adherence thresholds and cost inputs. As varying evidence exists quantifying the range of medication non-adherence rates, we conducted a sensitivity analysis using various adherence thresholds. For this sensitivity analysis in accordance with Meichenbaum et al thresholds of 0.30, 0.40, 0.50, 0.60 in addition to pre-intervention and post-intervention thresholds identified in this study, were analysed holding all other inputs fixed.[40] Additional analyses were conducted to examine the effects of conservative versus radical cost inputs to estimations at 30% and 50% non-adherence rates.

Ethical Considerations

Ethics approval was granted by the University of Technology Sydney Human Research Ethics Committee (approval number ETH18-2312).

Results

Study Population

The GuildLink Pty Ltd database comprised prescription dispensing histories and intervention offerings for 2,530,562 million patients serviced through 3, 318 pharmacies across Australia, providing in excess of 22 million dispensing records. A total of 20,335 patients (n=11,257 rosuvastatin, n=6,797 irbesartan and n=2,281 desvenlafaxine) from 1,805 pharmacies across Australia, were included in the analysis. The average number of patients per pharmacy was 11.27 (SD: 3.77) compared to 8.59 (SD: 5.14) across the entire database as patients visited multiple pharmacies.

The average age was highest in patients taking irbesartan 67 (SD: 12.42), followed by 65 (SD: 11.76) in rosuvastatin and 50 (SD: 15.70) for desvenlafaxine. Female patients represented a higher proportion of the population with the distribution of gender following a similar trend across molecules. For patients taking rosuvastatin 56% were

female and 44% male, irbesartan 61% female and 39% male and desvenlafaxine 70% female and 30% male.

Medication Adherence

The MedScreen Compliance intervention increased average PDC from 52.3% at baseline (SD: 31.4) by 9.3% to 61.6% (SD: 31.7), while from the intervention time point average PDC increased from 49.3% (SD: 30) by 12% to 61.6% (SD: 31.7). Desvenlafaxine displayed the overall lowest average PDC of the three molecules at baseline (48%, SD: 30.3) and post intervention (59.5%, SD: 30.6) however simultaneously demonstrated the greatest proportional increase in adherence over time following the intervention (PDC 11.5%, SD: 29.3). Similar results were established between rosuvastatin and irbesartan with PDC over time increasing on average 8% (SD: 30.8) and 8.4% (SD: 31) respectively. Across all three molecules there was a trend for medication adherence to decrease from baseline to the intervention, peak in the trimester following the intervention before slowly decreasing and plateauing (rosuvastatin PDC 62.4% (SD: 31.7), irbesartan PDC 62.9% (SD: 32) and desvenlafaxine PDC 59.5% (SD: 30.6)).

Cost estimation

The total national cost of medication non-adherence across three prevalent disease states in 2018 prior to a community pharmacy led intervention was $10.4 billion equating to approximately $517 per adult in Australia. Following enrollment in the MedScreen Compliance intervention medication non-adherence costs per adult decreased $95 saving the Australian health care system and patients $1.9 billion annually. Figure 3 depicts the national cost range of medication non-adherence pre and post adherence intervention. Significant reductions in cost expenditure were demonstrated across all three conditions with depression exhibiting the greatest saving as a proportion of the original expenditure (22%). Dyslipidaemia demonstrated the largest dollar figure saving ($1.1 billion), however was the smallest as a proportion of the original expenditure (17.5%). The same trends were demonstrated when applying the conservative and radical approach.

With over 85% of non-adherence costs attributed to medical related expenses, application of the MACE framework[37] to the conservative extrapolated costs facilitates the estimation of the proportion of costs attributed to various cost outcome indicators. Of the $8.4 billion annual non-adherence cost post intervention; $2.1 billion arose from the outpatient setting, $1.9 billion from inpatient related expenses, $1.8 billion on prescription medications and $1.6 billion was attributed to medical related costs such as general practitioner visits. If no adherence intervention is received the baseline non-adherence cost of $10 billion can be broken down into $2.6 billion outpatient costs, $2.3 billion inpatient costs, $2.2 billion prescription medication and $1.9 billion medical expenses.

Sensitivity Analysis

Similar results were seen when cost estimation was performed using different adherence thresholds. Non-adherence costs decreased across all three molecules as adherence thresholds increased. Application of the conservative estimation across 30% and 50% non-adherence thresholds resulted in a total cost range varying between $6.7 billion ($333 per adult) to $11.1 billion ($555 per adult) annually. When applying the radical costing assumption to estimate disease specific costs, the estimated national cost of medication non-adherence rose substantially ranging from $22.2 billion ($1,102 per adult) to $37 billion ($1,837 per adult).

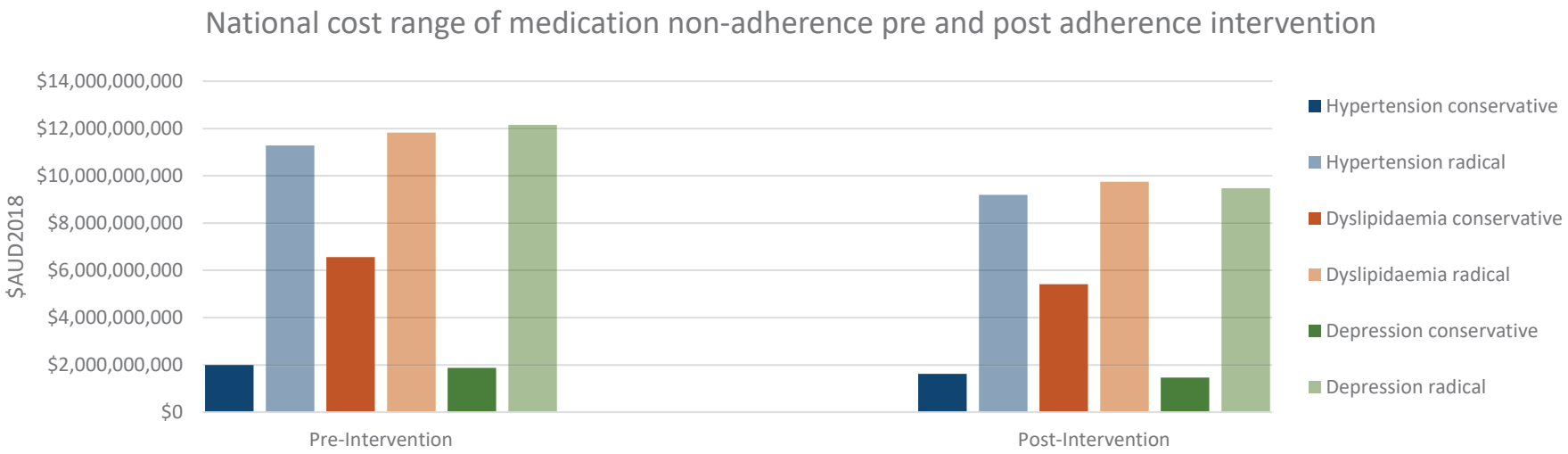

Figure 3: National cost range of medication non-adherence pre and post adherence intervention

Bars represent the conservative and radical cost associated with medication non-adherence across three chronic conditions hypertension, dyslipidaemia and depression. Chart comparison demonstrates Australian national cost range pre and post community pharmacist-led medication adherence intervention

Discussion

The Australian national cost estimate of medication non-adherence across three highly prevalent chronic conditions prior to a community pharmacy led intervention was $10.4 billion or $517 per adult. Aitken et al[5] approximated that 4.7% of total Australian health expenditure is avoidable due to suboptimal medicines use extrapolating to $8 billion annually.[13] This estimate did not directly measure medication non-adherence but rather examined inappropriate medication use. The extrapolated estimate although 25% higher than the value predicted by Aitken et al provides a more accurate evaluation utilising pharmacy claims data, literature values and current disease prevalence to determine the cost of medication non-adherence in Australia. This cost reduced to $8.4 billion or $421 per adult following the MedScreen Compliance intervention.

Sustainability of the Australian health care system presents a major challenge and concern, with current levels of funding set to create significant financial burden for governments in the future.[41] The emergence of new health challenges, the ageing population and the increase in risk factors for chronic conditions in combination with the expectation of the Australian population to provide higher standards of care and subsidisation fuel this situation. While Australia has a good health system by international standards, it is estimated that spending on health care by government as a percentage of gross domestic product will nearly double by 2050.[42] There are fears that the current level of funding is not sustainable and new models need to be considered.[41] Subsidisation of the Pharmaceutical Benefits Scheme represents 30% of funds administered by the Department of Health and the Medical Benefits Scheme 52%.[43] Funding of strategies including pharmacist led services to improve medication adherence, removes wastage and inefficient usage of the current system, resulting in more sustainable, cost effective resource allocation.

Interventions to improve medication adherence have consistently demonstrated an improvement in health care outcomes and a reduction in total health care costs.[44] A recent systematic review conducted by Milosavljevic et al[45] found that overwhelmingly community pharmacist led intervention improved patients'

adherence contributing to better blood pressure control, cholesterol management, chronic obstructive pulmonary disease and asthma control. However, studies in the review, did not report statistically significant effects of interventions on diabetes or depression control,[45] challenging the results found from improvements demonstrated with the MedScreen compliance intervention in depression. Data from the GuildLink Pty Ltd database supports the improvement of patient adherence rates in hypertension, dyslipidaemia and depression measured through calculation of PDC increasing on average 9.3% from baseline and 12% from intervention date. Accompanying cost extrapolation data further harnesses these findings with a $1.9 billion annual cost saving attributable to the MedScreen Compliance intervention across the three molecules. While the intervention demonstrates improvements in medication adherence rates in the six months ensuing, sustaining improvements long term requires further investigation and represents an obstacle in reducing future preventable health care expenditure.

The low number of studies directly comparing adherence interventions thwarts the determination of the most effective intervention. A recent network meta-analysis likening the effect of all interventions in one single model ranks interventions containing an economic component followed by technical component with the best results. Educational or attitudinal components were ranked next, with standard care always considered the worst option.[46] The GuildLink adherence intervention relies on educational components to enhance medication adherence. Moving forward incorporating attitudinal and technical components into this intervention would improve results. Evidence suggests that only 20% of national health interventions produce sufficient savings to be at or near budget neutrality.[47] A balance between intervention costs and achievable savings attributable to the intervention needs to be obtained. Financial incentives or rewards are not necessarily a viable long-term solution for a national health strategy. While exhibiting some success in improving processes in primary care, limited evidence of improved health outcomes or cost savings exists with interventions containing economic motivation, often eroding the potential economic gain.[48-50] Medication adherence intervention programs

represent an opportunistic national policy initiative to increase utilisation of prescription medication to reduce the preventable burden currently placed on the Australian health care system. Pharmacists are ideally placed to implement, modify and sustain clearly defined adherence enhancing interventions across a dynamic population. This way they can minimise negative therapeutic outcomes due to non-adherence, while increasing prescription volumes.[51]

The strategy developed to quantify the economic impact of medication non-adherence in Australia was conceptual. To date there has been no specific estimate of the cost medication non-adherence poses to the Australian population. This study improves upon previous international estimates, despite its limitations. Actual medical condition prevalence estimates were applied from latest available population statistics.[33,34] A national representative sample of non-adherent Australian adults were utilised to determine average medication adherence rates from prescription dispensing histories. Disease specific per person cost of non-adherence were derived from the literature employing a 'conservative' and 'radical' approach. This analysis attempted to make estimates within a conceptual model that can be further tested and refined. Nonetheless, estimates from this study relied on data in the literature and on tertiary health statistics summaries. Moving forward the strategy should be tested in a real-life setting incorporating the determination of actual costs associated with this health problem. Prospective measurement of resource use in patients who receive the MedScreen Compliance intervention versus those who do not would address this. Furthermore the current cost estimates only take into consideration three chronic conditions: hypertension, dyslipidaemia and depression. For a more holistic outlook on the burden medication non-adherence places on the Australian health care system additional conditions should be examined. Additionally, it would be beneficial to examine the offset of costs associated with delivering the service compared to cost saving potential. Currently costs associated with delivering the service have not been considered. Despite these limitations, analysis of the economic impact of medication non-adherence across three highly prevalent conditions, utilising real life data demonstrated the positive

impact pharmacist led intervention can provide. Even when a conservative approach is employed.

Conclusion

Medication non-adherence across hypertension, dyslipidaemia and depression costs $10.4 billion annually, significantly contributing to avoidable health care costs in Australia. Community pharmacist led medication adherence interventions have been demonstrated to improve adherence rates by 9.3% over a twelve month period, reducing the burden incurred by non-adherence by $1.9 billion. Given these findings policy and decision makers should consider funding medication adherence programs to improve patient health outcomes and save money. Actively encouraging medication adherence through pharmacist led intervention should be a top priority.

Contributors: RLC drafted the initial form and all revisions of this manuscript. All other authors (RLC, ATB, EW, BD, NVDL, SB, and VGC) made significant contributions to the manuscript and read and modified the drafts. All authors read and approved the final manuscript.

Funding: This research received no specific grant from any funding agency in the public, commercial or not-for-profit sectors.

Competing interests: Naomi Van der Linden currently works at AstraZeneca Netherlands.

Data sharing statement: All data is available in paper.

Acknowledgement: RLC research is supported by an Australian Government Research Training Program Scholarship.

References

1. Sabaté E. *Adherence to long-term therapies: evidence for action.* World Health Organization; 2003.
2. Sokol MC, McGuigan KA, Verbrugge RR, Epstein RS. Impact of medication adherence on hospitalization risk and healthcare cost. *Medical care.* 2005;43:521-530.
3. DiMatteo MR, Giordani PJ, Lepper HS, Croghan TW. Patient adherence and medical treatment outcomes: a meta-analysis. *Medical care.* 2002;40(9):794-811.
4. Aitken M, Valkova S. Avoidable costs in US healthcare: the $200 billion opportunity from using medicines more responsibly. *IMS Institute for Healthcare Informatics.* 2013:20-21.
5. Aitken M, Gorokhovich L. Advancing the responsible use of medicines: applying levers for change. 2012.
6. Pittman DG, Chen W, Bowlin SJ, Foody JM. Adherence to statins, subsequent healthcare costs, and cardiovascular hospitalizations. *The American journal of cardiology.* 2011;107(11):1662-1666.
7. Iuga AO, McGuire MJ. Adherence and health care costs. *Risk management and healthcare policy.* 2014;7:35-44.
8. Egede LE, Gebregziabher M, Dismuke CE, et al. Medication nonadherence in diabetes: longitudinal effects on costs and potential cost savings from improvement. *Diabetes care.* 2012;35(12):2533-2539.
9. Cantrell CR, Eaddy MT, Shah MB, Regan TS, Sokol MC. Methods for evaluating patient adherence to antidepressant therapy: a real-world comparison of adherence and economic outcomes. *Medical care.* 2006;44(4):300-303.
10. NEHI. NEHI. *Thinking outside the pillbox: a system-wide approach to improving patient medication adherence for chronic disease.* New England Health Care Institute.;2009.
11. Cutler RL, Fernandez-Llimos F, Frommer M, Benrimoj C, Garcia-Cardenas V. Economic impact of medication non-adherence by disease groups: a systematic review. *BMJ open.* 2018;8(1):e016982.
12. Roughead L, Semple S, Rosenfeld E. Literature review: medication safety in Australia. *Australian Commission on Safety and Quality in Health Care.* 2013.
13. Australian Institute of Health and Welfare. *Health expenditure Australia 2015–16.* Health and welfare expenditure series. 2017; no. 58. Cat. no. HWE 68. Canberra: AIHW 2017.
14. Ye S, Krupka D, Davidson K. Diagnosing Medication Non-Adherence in a Patient with Myocardial Infarction. *Frontiers in Psychology.* 2012;3(267).
15. Laba T, Lung T, Jan S, et al. Medication non adherence in a cohort of chronically ill Australians. *Australian Journal for General Practitioners.* 2018;47:556-562.
16. Australian Government Department of Health PBS. Compliance to Medicines Working Group (CMWG) Report to Pharmaceutical Benefits Advisory Committee (PBAC). 2016; http://www.pbs.gov.au/info/publication/factsheets/shared/cmwg-report-to-pbac. Accessed 27 January, 2019.
17. Zweifel P, Felder S, Meiers M. Ageing of population and health care expenditure: a red herring? *Health economics.* 1999;8(6):485-496.
18. Australian Institute of Health and Welfare. *Australia's health 2018.* Australia's health series no. 16. AUS 221. Canberra: AIHW2018.

19. Krivoy A, Balicer RD, Feldman B, et al. Adherence to antidepressant therapy and mortality rates in ischaemic heart disease: cohort study. *The British journal of psychiatry : the journal of mental science.* 2015;206(4):297-301.
20. Shoval G, Stubbs B, Balicer RD, et al. Low adherence to antidepressants is associated with increased mortality in Parkinson disease patients. *Parkinsonism & related disorders.* 2017;43:92-96.
21. Chowdhury R, Khan H, Heydon E, et al. Adherence to cardiovascular therapy: a meta-analysis of prevalence and clinical consequences. *European heart journal.* 2013;34(38):2940-2948.
22. Ford ES, Ajani UA, Croft JB, et al. Explaining the decrease in U.S. deaths from coronary disease, 1980-2000. *The New England journal of medicine.* 2007;356(23):2388-2398.
23. Vik SA, Maxwell CJ, Hogan DB. Measurement, correlates, and health outcomes of medication adherence among seniors. *The Annals of pharmacotherapy.* 2004;38(2):303-312.
24. Raebel MA, Schmittdiel J, Karter AJ, Konieczny JL, Steiner JF. Standardizing terminology and definitions of medication adherence and persistence in research employing electronic databases. *Medical care.* 2013;51(8 Suppl 3):S11-21.
25. Ho PM, Bryson CL, Rumsfeld JS. Medication adherence: its importance in cardiovascular outcomes. *Circulation.* 2009;119(23):3028-3035.
26. Pringle J, Coley KC. Improving medication adherence: a framework for community pharmacy-based interventions. *Integr Pharm Res Pract.* 2015;4:175-183.
27. Nasseh K, Frazee SG, Visaria J, Vlahiotis A, Tian Y. Cost of medication nonadherence associated with diabetes, hypertension, and dyslipidemia. *Am J Pharm Benefits.* 2012;4(2):e41-e47.
28. GuildLink Pty. Ltd. *GuildCare MedScreen Compliance Protocol.* 2015.
29. Torres-Robles A, Wiecek E, Cutler R, et al. Using Dispensing Data to Evaluate Adherence Implementation Rates in Community Pharmacy. *Frontiers in pharmacology.* 2019;10(130).
30. Sattler EL, Lee JS, Perri M, 3rd. Medication (re)fill adherence measures derived from pharmacy claims data in older Americans: a review of the literature. *Drugs & aging.* 2013;30(6):383-399.
31. Pillittere-Dugan D, Nau DP, McDonough K, Pierre Z. Development and testing of performance measures for pharmacy services. *Journal of the American Pharmacists Association : JAPhA.* 2009;49(2):212-219.
32. Australian Bureau of Statistics. *Australian Demographic Statistics* Canberra 2018.
33. Australian Bureau of Statistics. *National Health Survey 2014-15 Australia.* Canberra 2015.
34. Australian Bureau of Statistics. *Australian Health Survey 2011/12.* Canberra 2012.
35. Australian Bureau of Statistics. Australian Social Trends: Population Growth: Australia's child population. 1997; http://www.abs.gov.au/AUSSTATS/abs@.nsf/2f762f95845417aeca25706c00834efa/f757d567b9b9b9eeca2570ec001b074e!OpenDocument. Accessed 11 September, 2018.
36. Shemilt I, Thomas J, Morciano M. A web-based tool for adjusting costs to a specific target currency and price year. *Evidence & Policy: A Journal of Research, Debate and Practice.* 2010;6(1):51-59.
37. Cutler RL, Van der Linden N, Benrimoj SI, Fernandez-Llimos F, Garcia-Cardenas V. An evidence based model to consolidate Medication Adherence Cost Estimation:

the medication adherence cost estimation framework In. *Journal of Comparative Effectiveness Research*. 2019;8(8):555-567.
38. Independent Hospital Pricing Authority. *National Hospital Cost Data Collection Cost Report: Round 20 Financial Year 2015-16.* 2018.
39. PBS Information Management Section; Pricing and Policy Branch; Technology Assessment and Access Division. *Expenditure and Prescriptions Twelve Months to 30 June 2017.* Australia 2017.
40. Meichenbaum D, Turk DC. *Facilitating treatment adherence: A practitioner's guidebook.* Plenum Press; 1987.
41. Taylor N. CEDA overview: Reform or ration. *Healthcare: Reform or ration.* 2013:10.
42. Australian Treasury, Swan W. *Australia to 2050: future challenges.* Commonwealth of Australia, Canberra; 2010.
43. Australian Government Department of Health. *Department of Health Annual Report 2016-17.* Commonwealth of Australia, Canberra, Australia 2017.
44. Roebuck MC, Liberman JN, Gemmill-Toyama M, Brennan TA. Medication Adherence Leads To Lower Health Care Use And Costs Despite Increased Drug Spending. *Health affairs.* 2011;30(1):91-99.
45. Milosavljevic A, Aspden T, Harrison J. Community pharmacist-led interventions and their impact on patients' medication adherence and other health outcomes: a systematic review. *The International journal of pharmacy practice.* 2018;26(5):387-397.
46. Tonin FS, Wiecek E, Torres-Robles A, et al. An innovative and comprehensive technique to evaluate different measures of medication adherence: The network meta-analysis. *Research in social & administrative pharmacy : RSAP.* 2018.
47. Bott DM, Kapp MC, Johnson LB, Magno LM. Disease management for chronically ill beneficiaries in traditional Medicare. *Health affairs.* 2009;28(1):86-98.
48. Scott A, Connelly LB. Financial incentives and the health workforce. *Australian health review : a publication of the Australian Hospital Association.* 2011;35(3):273-277.
49. Flodgren G, Eccles MP, Shepperd S, Scott A, Parmelli E, Beyer FR. An overview of reviews evaluating the effectiveness of financial incentives in changing healthcare professional behaviours and patient outcomes. *The Cochrane database of systematic reviews.* 2011(7):CD009255.
50. de Bruin SR, Baan CA, Struijs JN. Pay-for-performance in disease management: a systematic review of the literature. *BMC health services research.* 2011;11:272.
51. Johnson JA, Bootman JL. Drug-related morbidity and mortality. A cost-of-illness model. *Archives of internal medicine.* 1995;155(18):1949-1956.

Chapter 6

Discussion and conclusions

This page is intentionally left blank

Discussion

This thesis has explored, analysed and quantified the economic burden that medication non-adherence places on health care systems. The body of work emphasises the need for a standardised approach to appraise the cost outcome indicators used to estimate the economic burden of non-adherence and proposes a framework to overcome the existing heterogeneity within the literature. Internationally medication non-adherence is posed as a substantial health care challenge, however the lack of research within the Australian health care landscape highlighted the need to determine the cost of medication non-adherence nationally. Additionally, exploration of the measures available to reduce this cost were explored through pharmacist intervention. A series of recommendations developed from the compilation of work presented in this thesis are proposed moving forward.

Medication non-adherence is an increasingly costly health problem associated with higher health care costs than remaining adherent (Aubert et al. 2010; Bagalman et al. 2010; Cutler et al. 2018; Davis, Edin & Allen 2010; Diehl et al. 2010; Ivanova et al. 2012; Knapp et al. 2004; Leider et al. 2011). Moreover, as chronic diseases continue to grow worldwide so too does the economic, clinical and humanistic impacts of medication non-adherence (Pages-Puigdemont et al. 2016). As the prevalence of patients with comorbidities increases, so does the negative consequences on both patients and providers, such as loss of treatment effectiveness and increases in health care costs attributed to the rising incidence of medication non-adherence (Simpson et al. 2006). Across the broad scope of non-adherence studies there has remained a tendency to focus on the impact of single disease states thus resulting in a failure of the true magnitude of non-adherence to be captured (Pages-Puigdemont et al. 2016). Of the seventy nine included studies in the systematic review, Sokol et al was the only study to assess the economic impact of non-adherence across multiple comorbidities (Sokol et al. 2005). While demonstrating significant financial burden, the study was limited to four conditions (diabetes, hypertension, hypercholesterolemia and congestive heart failure). Analysis from the systematic review supports Sokol et al findings, with generally medication non-adherence costs

being higher for all inputs other than pharmacy related expenses; however, goes further to demonstrate the economic burden across multiple disease groups providing a holistic overview of the current non-adherence challenge. Fragmented analysis of the broader economic implications associated with medication non-adherence exists, resulting in a somewhat disintegrated view of the non-adherence landscape and an inclination of the problem to be significantly underestimated due to a number of contributing factors such as failure to assess primary non-adherence, lack of utilisation of ICD classification for non-adherence and heterogenous analysis techniques (Baines et al. 2015; Egede et al. 2012; Lee et al. 2018). In order for a global picture of the non-adherence problem to be determined examination of the cost of non-adherence was required across disease states and countries (chapter 3), the MACE framework can be applied internationally across adherence research to minimise heterogeneity in methodological approaches and determine the economic impact of non-adherence through use of its costing categories.

Analysis of non-adherence studies across 14 disease groups (cardiovascular, mental health, diabetes mellitus, osteoporosis, respiratory, gastrointestinal, HIV/AIDS, parkinson's, musculoskeletal, cancer, addiction, metabolic and blood conditions) and 19 countries revealed that the annual adjusted economic impact of medication non-adherence per person ranged from $949 to $44,190, while the unadjusted cost ranged from $949 to $162,699 ($US2015). Wide scoping cost variation was attributed to a range of methodological limitations in adherence research including; no consistent approach in the estimation of costs, variation in the metric classification used to estimate medication non-adherence and the source of data e.g. health care claims databases, patient self-report and observational report. Cancer exhibited more than double the cost variation of all other disease groups ($114,101) most likely due to supportive care costs associated with the condition, while direct costs had greater economic bearing than indirect costs across all disease groups. These conclusions highlight the scope and weight of the non-adherence problem and provide sound basis for the need of inclusion in national health policies moving forward. Although this systematic review effectively quantified the reported burden

of non-adherence among the literature, the existing heterogeneity in the literature restricted the applicability of the results to sufficiently inform health care decision making. Application of the MACE framework moving forward will minimise existing disparity in costing inputs to generate comparable cost outcome findings enabling the potential inclusion of medication adherence initiatives in national health policy. Quantification of medication non-adherence among disease groups proves both beneficial and problematic at the same time. These findings support the need for more effective utilisation of health care budgetary allocations to minimise the economic impact of medication non-adherence yet substantial variation in the differential cost of non-adherence among disease groups proves challenging due to the varying scope of their inclusions, with high cost conditions such as cancer always going to incur a greater cost burden due to the enhanced reliance on the health care system and resultant increase in both direct and indirect costs associated with the condition. Exploration of adherence initiatives such as utilising the role of the community pharmacist to improve medication taking behaviour require further analysis to determine the cost saving potential, they can provide to the health care system.

A number of sources of heterogeneity in the papers included in the systematic review were identified, including: 1) measures of adherence, 2) cost outcome indicator/s used to estimate non-adherence, 3) definition/s of what was included in cost calculations and 4) costing methodology. This resultant heterogeneity limits the ability to truly estimate costs attributed to non-adherence until a streamlining of the processes is developed. Despite, the existing heterogeneity medication non-adherence incurs greater costs for all cost outcome indicators other than pharmacy costs as patients require greater utilisation of health care resources to manage the complications associated with non-adherence. While individual studies cannot independently inform health policy, the scope and breadth of the combined literature from the systematic review demonstrates the need for policy intervention in this domain to combat the rising economic encumbrance medication non-adherence is placing on health care systems globally. Achieving the optimal level of

adherence to medication is more nuanced than strictly raising adherence rates, policy makers should focus on technologies or programs, such as personalised medicine that facilitate the inclusion of patients in the decision making process to drive optimal adherence behaviour (Philipson 2015).

Improving medication non-adherence represents an opportunity to enhance health outcomes and health system efficiency, especially given the proportion of the population who do not adhere to their medications. Analysis of the existing literature examining the economic impact of medication non-adherence revealed that substantial work is still to be done in the field in terms of strengthening methodological rigour. Consequently, the disparity of cost outcome indicators reported in the systematic review, were standardised and collated into a single costing framework reported in chapter 4.

Recommendation 1:

Standardisation of methodological processes in medication adherence costing studies is required to better inform health policy initiatives.

Increasingly the cost effectiveness of interventions and overall health care gain to the population are important to determine the allocation of competing resources (Tamás 2010). Economic evaluations are being used to aid decision making, with evaluations providing evidence of the feasibility of intervention scalability and sustainability and the determination of the costs and benefits of public health interventions providing data for health professionals and decision makers to choose which interventions are effective, efficient, equitable, scalable and sustainable (Rabarison et al. 2015). However, in many instances the input parameters being used within the interventions are not comparable, with studies utilising a disjointed combination of direct and/or indirect costs, leading to a "cookie-cutter" outcome effect and ultimately resulting in rationing and potential allocative inefficiency

(Cutler et al. 2018). Decision making bodies need to consider how best to allocate resources in a cost effective manner, so as to aid the improvement of the overall populations health. Although the arguments given for using average estimates in health care research have been widely accepted, they are essentially pragmatic and should rather motivate further methodological development on the estimation streamlining of cost outcome indicators (Basu 2009). Decisions based on the average might adopt one particular intervention for the whole population, while decisions considering heterogeneity can deny the intervention in some patients where it is not cost effective (Espinoza 2012). Adequate estimation of cost inputs are imperative to be made prior to economic evaluations being conducted. This will facilitate clearly reported methodologies in terms of cost outcome indicators, in addition to outcomes, analysis perspective, time horizon, robustness of the findings, limitations and generalisability aspects, of the findings. This ensures that comparable findings can be incorporated into economic evaluations to achieve evidence based results that effectively inform decision making.

Failure to address the issue of heterogeneity across medication non-adherence costing studies leads to potentially misinformed decision making in terms of resource allocation. Varied methodologies leads to differing cost estimates, even in similar settings and across similar time horizons. For example Modi et al estimated all cause total costs associated with medication non-adherence in US 2011 dollars as $11,749, whereas Eisenberg et al using 2012 dollars, put these costs at $7,237 (a difference of over 62%) (Eisenberg et al. 2015; Modi et al. 2015). As regards the major drivers of heterogeneity, descriptions of the epidemiological approach for the majority were not explicit, with differences existing even when studies ostensibly adopted similar methodological approaches. For example Offord et al in one study utilised time to discontinuation as the measure of adherence and reported on total costs, outpatient costs, pharmacy costs and hospitalisation costs in measuring antipsychotic adherence (Offord, Lin, Mirski, et al. 2013) yet another study on adherence in schizophrenia patients, utilised MPR and only measured inpatient costs and pharmacy costs (Offord, Lin, Wong, et al. 2013). Such diversity makes it difficult to

compare costs between settings or over time within a single setting, thus hindering comparability and leading to a lack of generalisability of study findings (O. Ceilleachair et al. 2013). This problem is unlikely to be confined solely to medication adherence literature and is a problem with the methodology used to interrogate cost data across cost of illness studies.

In addressing recommendation one, the MACE framework was developed to assist costing of medication non-adherence studies by providing guidance on choices about the available cost outcome indicators that are required to be included in an economic impact study (chapter 4). The framework utilises core concepts central to cost of illness studies presented through the works of Rice and colleagues in 1967 (Rice 1967) and subsequently revised (Cooper & Rice 1976; Rice, Hodgson & Kopstein 1985). It is the first study to classify cost categories in adherence research and propose a new methodological approach moving forward.

The motivation behind the production of the MACE framework stemmed from the identification of 35 different cost outcome indicators across 79 studies. The heterogeneous reporting of cost outcome indicators in economic impact studies questioned the methodological integrity of existing literature and consequently the policy value they provide. A consolidated framework was proposed with clear and concise category descriptions and examples. The aggregated system contains two core categories; direct and indirect costs, seven subcategories; hospital, primary care, medical test, pharmacy, non-medical, societal and productivity costs and an extensive list of cost outcome indicators. It is anticipated that the MACE framework will encourage future economic impact studies to be more precise about what cost outcome indicators are included, classified and analysed to determine the economic impact of medication non-adherence.

Economic assessment is a way of informing the importance of a particular phenomenon such as medication non-adherence with a primary purpose of informing decision makers through descriptive indicators of the magnitude of the problem. Additionally, it is a way of estimating avoidable costs that can inform policy perspective. The MACE framework incorporates direct and indirect costs. There is no

single perspective or measurement focus, instead a menu-based set of considerations are presented, determining the approach to costing that is selected. The framework can be adopted in its entirety or partially dependent upon the perspective of the study. Further inclusion of medication adherence into pharmacoeconomic evaluations is required. The standardisation of the costing approach used to estimate the economic impact of medication non-adherence through the MACE framework will enable current limitations in methodological rigour to be overcome and facilitate a more seamless inclusion of adherence into economic modelling considerations. Additionally, the MACE framework will benefit decision makers, national governments and academic institutions through presentation of a uniform framework for assessing the economic impact of medication non-adherence. It is hoped that the MACE framework will contribute to improve the standards of methodological design, increasing the degree of comparability and uniformity between studies to facilitate discussion in the field and allocation of funding from health care budgets to counteract the current economic burden non-adherence places on health care systems.

The medication non-adherence cost burden is multi-dimensional in nature traversing health care professional groups, governments and individuals. However, the degree of visibility medication adherence occupies within the health policy context remains less than ideal, often being overshadowed by other health policy issues due to incongruence in demonstrating impact (Clyne & McLachlan 2015). Despite the diminished health status of the population resultant from medication non-adherence (Kim et al. 2016; Morello & Hirsch 2017; Sabaté 2003) the lack of convincing and comparable evidence on the costs and benefits of medication adherence restrict the true magnitude of the problem being revealed. When used in conjunction with existing and validated guidelines and frameworks for health outcomes research the MACE framework will provide evidence to evaluate the clinical and cost-effectiveness of interventions to address medication non-adherence, ultimately shedding light on the economic burden attributed to medication non-adherence and building a strong

case for investment (Clyne & McLachlan 2015; Helmy et al. 2017; Hoffmann et al. 2014; Husereau et al. 2013; Vrijens et al. 2012).

Recommendation 2:

The MACE framework should be applied in conjunction with existing guidelines and frameworks to evaluate the clinical and cost-effectiveness of interventions to address medication non-adherence.

The examination of the economic impact of medication non-adherence continues to be reported through cost of illness studies and grey literature findings, despite the prevailing methodological heterogeneity. On an international scale grey literature reports equate medication non-adherence to cost $100-$290 billion in the USA (New England Healthcare Institute 2009), €125 billion in Europe (Pharmaceutical Group of the European Union 2018) and $700 million in New Zealand (SimplHealth 2016). These reports lack transparency and methodological rigour, making it difficult to replicate the findings. In Australia, there has been no directly estimated cost of non-adherence. With the rising burden of medication non-adherence highlighted as having a significant economic impact on health care systems, it calls to question why budgetary allocations within the Australian landscape have not yet considered the financial impact this is causing.

Rising health care costs and burden of chronic disease among the Australian population is placing significant strain on the health care system, with the viability of current levels of funding being scrutinised (Taylor 2013). Subsidisation of the Medicare Benefits Schedule (MBS); the list of medical services which the Australian Government subsidises and the Pharmaceutical Benefits Scheme (PBS); the list of medications which the Australian Government subsidises, in 2018-19 is estimated to cost $35.3 billion (Australian Government Department of Health 2018). Evaluation of the effectiveness of this allocation of funding is required if projected medication

adherence rates for chronic conditions average 50% (Brown & Bussell 2011; Haynes et al. 2002; Sackett et al. 1978), in addition to consideration as to what other measures should be funded to curb the rising rate of non-adherence and the associated economic complications.

Cost of illness studies provide a useful framework to assess the economic burden of medication non-adherence to society. While medication non-adherence is not classified as an illness or disease it provides substantial strain on budgets and health care systems. To identify the economic impact of medication non-adherence at a national level would help policy makers and managers to analyse the inputs that encompass the cost to determine inefficient and/or ineffective functions. Thus facilitating the reassessment of the best method to reduce medication non-adherence through evidence based practices.

Analysis of whether there is a relationship between cost variability and variables such as health care team and system related, condition related, therapy related, patient related or social and economic related factors allows policy makers to feed the planning process with more accurate information as to the future provision of services (Sabaté 2003). Knowing the cost drivers that explain at least partially the consumption pattern of resources can be useful when planning the provision of health services (Tarricone 2006). For example, the total national cost of medication non-adherence across hypertension, dyslipidaemia and depression was $10.4 billion annually in Australia. With over 85% of non-adherence costs attributed to medical related expenses, application of the MACE framework demonstrated that of the $10.4 billion cost; $2.6 billion arises from outpatient costs, $2.3 billion from inpatient costs, $2.2 billion from prescription medications and $1.9 billion from medical expenses. Strategies to enhance adherence need to consider the overall impact on health care costs, weighing increased medication expenditure against cost saving potential. The majority of costs attributed to medication non-adherence arise from avoidable hospitalisations and outpatient health care utilisation. Policy makers need to examine whether increasing adherence across all conditions and non-adherent patients is worthwhile or if they should focus on specific conditions. Increasing

adherence in mild illnesses may not make substantial savings, if the cost of the medication is relatively high, while the baseline rate of hospitalisations and ED visits is low, total health care costs may increase with better adherence (Herndon et al. 2012; Mattke et al. 2010). Focusing on higher severity patients may shift the balance towards cost savings (Iuga & McGuire 2014).

Cost analysis is an important building block for more complex economic evaluations, such as cost effectiveness analyses (Byford, Torgerson & Raftery 2000; Drummond et al. 2015; Tarricone 2006), and has the potential to be of value in the rapidly emerging area of comparative effectiveness research (Meyer et al. 2012; Sox et al. 2010). Collection and analysis of costs associated with medication non-adherence provides useful information on primary health needs in addition to indicating the amount of funding likely to be required to manage non-adherence through provision of primary health services. Specifically cost analysis facilitates 1) accountability, 2) assessing efficiency, 3) assessing equity, 4) assessing priorities, 5) ability to make cost projections and 6) considerations for cost recovery (Creese & Parker 1994). Identifying and measuring costs of the alternative options is a key step in cost effectiveness research, with economic costs needing to be determined to enable the assessment of true economic efficiency. The MACE framework can be utilised to streamline the cost inputs utilised in adherence cost analysis to facilitate the comparison of alternative courses of action through cost effectiveness research.

Recommendation 3:

Cost estimates of medication non-adherence magnitude should be determined through utilisation of the MACE framework and used as building blocks to inform more complex economic evaluations.

Medication taking behaviour is complex and involves a number of interplaying factors that influence the outcome. Multiple interventions strategies have been

developed to tackle the non-adherence problem and can be categorised into six categories of intervention strategies: patient education, medication regimen management, pharmacist led interventions, cognitive behavioural therapies, medication taking reminders and incentives to promote adherence (Kini & Ho 2018). Selection of the most appropriate intervention type is dependent upon a patient's individual barriers to adherence (Kini & Ho 2018). Intervention effectiveness is dependent upon the availability and feasibility within a given health care system. Reasons for medication non-adherence are complex and rather it may be more appropriate to address non-adherence across multiple elements of the health care system instead of acting in isolation. Improving adherence is about implementing a behavioural change, while there may be different reasons underlying non-adherent behaviour, understanding these varying reasons is important when changing patient's behaviour. The $10.4 billion burden that medication non-adherence places on the Australian health care system across hypertension, dyslipidaemia and depression represents 13% of Commonwealth health funding budgetary expenditure in 2018-19 (Australian Government Department of Health 2018). The existence of interventions to improve medication non-adherence have consistently demonstrated an improvement in health care outcomes and a reduction in total health care costs (Roebuck et al. 2011). Exploration of the potential benefit pharmacist led intervention can demonstrate in improving medication adherence liberated $1.9 billion across the three conditions over a six month period, highlighting the valuable efforts pharmacists can sustain when included in the holistic approach to managing medication non-adherence.

The delivered pharmacist adherence intervention included knowledge (education), self-efficacy (motivation) and awareness functionalities to improve patient's medication taking behaviour (Vrijens, Urquhart & White 2014). Educational interventions such as the MedScreen compliance intervention reflect pedagogic interventions, verbal or written, with a knowledge based emphasis designed to convey information, educate and motivate patients based on the concept that patients who understand their condition and its treatment will be more informed,

more empowered and more likely to adhere (Demonceau et al. 2013; Roter et al. 1998; Sapkota et al. 2015). They are the predominant type of adherence intervention utilised in research studies (Thoopputra et al. 2015). These interventions are relatively inexpensive and easy to implement in the community pharmacy setting, demonstrating somewhat effective outcomes due to positive influences on patient satisfaction and knowledge (Eussen et al. 2010; Raynor 1992). Despite this predominance, emerging evidence suggests that multicomponent and targeted and personalised interventions demonstrate the greatest effectiveness compared to standard care with additive effect displayed in longer follow up periods (Torres-Robles et al. 2018; Wiecek et al 2019; Zedler et al. 2011). Multicomponent interventions incorporate elements of a variety of intervention designs (e.g. educational, attitudinal, technical, reward) into a single service offering. Educational interventions while demonstrating greater effect in improving medication adherence compared to standard care ranks lower in effect than interventions involving economic and technical components or educational, attitudinal and technical or economic components (Torres-Robles et al. 2018; Wiecek et al 2019). Nonetheless, the educational intervention delivered in this study improved medication adherence across all three conditions increasing PDC on average by 9.3% from baseline and 12% from the intervention time point and resulted in a $1.9 billion cost saving. Examination of the cost of implementing the intervention compared to the cost saving potential must be considered to ensure the cost effectiveness of the program. While economic components including financial incentives or rewards may reap the greatest improvement in adherence rates, they may not be a sustainable long term solution to a national health strategy. Generally, implementation and service costs erode the potential economic gain (de Bruin, Baan & Struijs 2011; Flodgren et al. 2011; Scott & Connelly 2011). It would prove useful in the future to determine the added cost saving potential multicomponent community pharmacist led interventions have across these conditions and whether the cost saving potential outweighs the cost of implementing these services when compared to educational interventions. The MedScreen compliance intervention proved effective in improving adherence rates, however they only averaged 61.6% post intervention, highlighting

the inquiry as to what potential multicomponent interventions have to increase this rate further. Even so, medication adherence interventions should be integrated into community pharmacy practice, as all interventions prove valuable compared to standard care (Tonin et al. 2018; Torres-Robles et al. 2018; Wiecek et al 2019).

Community pharmacist led interventions contribute to improved medication adherence and better disease control. The implementation of pharmacy services targeting medication non-adherence represent an opportune national health policy initiative to provide a cost effective service to minimise the conservative $10.4 billion burden attributable to non-adherence in Australia. While pharmacists have been reported as being their own barrier to the effective implementation of pharmacy services (Blenkinsopp et al. 2000) this can be overcome through effective pharmacist training, policy development and providing sufficient remuneration for the services provided (Mossialos, Naci & Courtin 2013). Investigation of barriers and facilitators for change relating to the delivery of community pharmacy services by Hossain et al demonstrates that engagement of key stakeholders throughout the development, implementation and evaluation of health services is crucial to ensure the initiatives are effective and successfully implemented (Hossain et al. 2017). The study additionally provides an extensive list of barriers and/or facilitators identified by pharmacists, patients, GPs and nurses that can be used to assist pharmacy service planners and researchers to identify elements that may enable or hinder the implementation of community pharmacy services (Hossain et al. 2017).

Equipping community pharmacists with patient centred responsibilities is justified on the grounds of pressing system wide challenges that span demographic, economic and public health issues (Mossialos, Naci & Courtin 2013). Community pharmacists have the potential to improve patient health outcomes and reduce costs of care through an expanded patient-centred role with the expectation that these activities will encourage coordinated care delivery across the health care system (Malet-Larrea et al. 2016; Smith, Giuliano & Starkowski 2011). Development of such a system will require organisational and functional changes in addition to a national policy agenda to align the roles, objectives and incentives of health professionals (Mossialos, Naci

& Courtin 2013). Moving forward, expansion of the role of the pharmacist within the Australian health landscape is required to help ease the burden on the health care system and better utilise their skillset to enhance efficiency of the system. This fits with the international trend of a more clinical role for pharmacists (Mossialos et al. 2015). However, increasing the health providing role of pharmacists, might affect the physician's role, thus increased collaboration between pharmacists, physicians and other health care providers are suggested when implementing adherence enhancing interventions in the community pharmacy setting (Nkansah et al. 2010). Inclusion of pharmacists as a member of a patient's health care team, can help to improve adherence holistically instead of acting in isolation. Integration of care offers advantages for both the patient through better health outcomes and the health care system through better utilisation of health resources and cost saving. Expansion of the role community pharmacists hold within the health care sector will help to bridge the divide, enhancing continuity of care for patients; implementation of medication adherence interventions in community pharmacy is just one example of many as to how the pharmacist's role can be expanded.

Recommendation 4:

Expansion of the role of community pharmacists is required to enhance patient continuity of care and generate cost savings to the health care system.

Recommendation 5:

Medication adherence interventions should be integrated into pharmacy practice to improve medication adherence rates.

Methodological Strengths and Limitations

This thesis examined the economic impact of medication non-adherence across a global and national scale. Multiple methodologies were employed to assess, determine and analyse the magnitude of the non-adherence problem while simultaneously streamlining and strengthening the costing approach used to estimate the burden.

The synthesis of costs associated with medication non-adherence across disease states and major health care systems presented a gap in adherence literature. To attain an overview of the current economic impact of medication non-adherence a systematic review methodology was employed (chapter 3). This presented a novel attempt to use existing studies to broaden the scope of knowledge associated with the economic impact of non-adherence via quantifying the cost of medication non-adherence across disease groups. An advantage of the systematic approach over other methodologies is its ability to synthesise the results from all available studies in a particular area addressing a focused, clearly formulated question through systematic and explicit methods, thus minimising the likelihood of bias relating to selection, interpretation of results and conclusions (Cook, Mulrow & Haynes 1997; Pae 2015). No other systematic review within the adherence literature has attempted to encompass all costs and health care systems to provide a global picture of the scale of the medication non-adherence epidemic. Limited by the quality of research that had already been conducted, accurate estimate of costs attributed to non-adherence proved difficult to determine as a multitude of cost outcome indicators were utilised. Additionally, the majority of included studies were conducted in the USA where health care is generally more expensive. Comparing costs across health care systems proves difficult as no two systems are the same and sources of funding and reimbursement differ significantly. In order to minimise this shortcoming all costs were converted and reported in US dollars and analysis was undertaken to compare studies within the USA to other countries. Generally, there was an overall agreement that medication non-adherence incurs greater costs for all cost outcome indicators other than pharmacy costs despite the health care system.

The central theme underpinning this thesis was the concern over the existing heterogeneity in medication adherence studies regarding the cost outcome indicators utilised to quantify economic burden. Specifically, the lack of reliable data has thwarted policy initiatives to support improvements in adherence and resulted in an absence of acknowledgement as a global health concern in the health policy agenda. Looking across the body of literature, it was apparent that a considerable degree of methodological heterogeneity existed and that studies suffered from a range of conceptual deficiencies. In light of these methodological shortcomings, as well as the strong continuing demand for economic impact studies, a costing framework was developed to appropriately estimate the economic impact of medication non-adherence, with the view to enhancing the consistency and coherence of studies (chapter 4). The MACE framework consolidates and streamlines the inputs that should be included when estimating the cost of medication non-adherence. It facilitates a more complete evaluation of the economic impact while enabling the comparison across studies and disease states. Validation of this framework is required to further test and advance its viability. Application of the MACE framework to retrospective and intervention studies will improve the methodological rigour moving forward and facilitate the inclusion of medication adherence into health policy dialogue.

Rigorous research methods were conducted as a strategy for increasing validity of data and strengthening evaluation of research findings. Quantitative methodologies were used to inform the development of the MACE framework (chapter 4) and then apply the framework to a retrospective pharmacy dispensing database (chapter 5). Additionally, the analysis of big data enabled the utilisation of quality performance measurements across various means. The use of prescription refill data facilitates the analysis of large datasets increasing the reliability of medication adherence analyses and provides a viable and economic approach for estimation in real time (Raebel et al. 2013; Vik, Maxwell & Hogan 2004). While big data is not sufficient alone, it is imperative that rich data is available to inform complex logical deductions from large population estimates. The source of data in this case contained over 22 million

dispensing records across a national sample, capturing dispense date, quantity supplied, medication utilisation and patient specific characteristics thus facilitating appropriate calculations of medication adherence rate. Within the adherence field, there has been limited use of big data to inform economic, clinical and humanistic measures. This study presents emerging techniques to analyse the economic impact of non-adherence, paving the way for future research.

Globally, the economic impact of medication non-adherence has been quantified through macroeconomic and microeconomic studies and reports. However up until completion of this body of work the economic impact of medication non-adherence in Australia had only been projected through inclusion in suboptimal medicine use as a proportion of GDP. A novel approach was used to extrapolate the economic burden of non-adherence across hypertension, dyslipidaemia and depression given the constraints on available data (chapter 5). While traditionally this approach focuses attention on one problem without acknowledging that resources saved will likely be balanced by increased spending on alternate illnesses, improving medication adherence is different (Kennelly 2017). While improving adherence increases the spending on prescription medications studies have demonstrated that the net saving on reduced health care utilisation (e.g. hospitalisations) substantially outweighs increased prescription spending. Quantitative analysis of the role community pharmacist led intervention can contribute to reducing the burden further strengthened this study. This is the first study within the Australian landscape to quantify the economic impact of medication non-adherence and demonstrate the cost saving potential of pharmacist led intervention. Pharmacists are ideally placed to provide medication adherence pharmacy services as demonstrated through a resultant 12% increase in adherence post intervention and potential cost saving of $1.9 billion across three disease states. The analyses provided in this study estimate a projected cost of non-adherence across three disease states with the strategy developed to quantify the cost being conceptual. Utilisation of Australian national health data and literature estimates permitted estimates within the model to be made. To strengthen the model moving forward it would benefit from the

incorporation of real time costs through utilisation of MBS and PBS data and incorporation of all molecules within a disease state to determine the true prevalence of disease.

Finally, the works have a shared limitation in the data collection, synthesis and analysis, in that all studies were conducted by a single researcher. Procedures were put in place to minimise the impact and ensure rigour: 1) systematic review definitions were developed in consultation with co-authors, with uncertainty discussed among two adherence experts and resolved via consensus; 2) in development of the MACE framework independent review of data was undertaken by a health economist in addition to providing consultation and discussion around the feasibility and applicability of the framework; 3) existing research methodology was employed to extrapolate the national cost of medication non-adherence, where uncertainty existed in the methodology contact with the original author was sought for clarification.

Implications and recommendations for future research

Public health professionals are interested in improving the health outcomes of the population whilst simultaneously minimising costs. In order to complete this feat, evidence based research is integral to their decision making process. Existing and long term heterogeneity within the adherence literature prevents decision makers from exploring public policy options to curb the rising economic burden of non-adherence. Consistent and comparable economic evidence can provide insight into the value of public health investments to the overall health system. With evidence suggesting that increased investment in preventable activities and improvements in patient health practices can produce measurable and sustainable health gains.

Medication adherence research has lamented the lack of a standardised approach to quantify the economic impact of medication non-adherence. The development of the MACE framework has taken steps to address this issue. In order to test the reliability

and validity of the framework application to both retrospective and intervention based studies across a range of disease states is required for ratification purposes. Through streamlining the processes taken to estimate the burden, it will provide an opportunity for the evolution of evidence based research that can be utilised in economic evaluations to build a strong case for the need of public health intervention and health system funding.

Resulting estimates from this body of work highlight the diminished health status of non-adherent patients and the subsequent increased utilisation of health care resources. This information can usefully inform decision makers about the overall magnitude of economic losses and their distribution across a number of key health care settings. Although insufficient as a basis for setting priorities and allocating resources in health- for which data on effectiveness is also needed, it identifies possible strategies for reducing the cost of non-adherence through community pharmacist led intervention. Non-adherence cost estimates should be used as a source of information within economic evaluations and cost effectiveness studies. Additional economic evaluations incorporating the streamlined costing process are required to be undertaken to explore the economic impact of medication non-adherence.

Community pharmacist led intervention has been demonstrated as providing additional care benefits that increase the health of the population and decrease the cost burden on the health care system. Additional exploration into the expansion of the role community pharmacists play within the health care system is required, as well as effective models of remuneration. Expansion of the medication adherence intervention from solely educational to a multicomponent intervention may result in greater adherence improvements and cost saving potential.

The research in this thesis provides a platform to enhance future medication adherence study design. The findings suggest there remains room for improvement in the methodological evidence base of current costing estimates. Further research with longitudinal studies examining the economic impact of non-adherence through

use of patient linked health data would be beneficial to more accurately estimate the true magnitude of the problem on a national and global scale.

Conclusions

- Medication non-adherence places a significant cost burden on health care systems. Current research assessing the economic impact of medication non-adherence is fragmented and of varying quality, failing to provide adaptable data to influence health policy.
- A framework to streamline the current disarray of cost outcomes that exist in the literature has been developed. The MACE framework provides a basis for the methodological design of medication adherence costing studies and a foundation to support comparable future economic evaluations.
- The estimated economic burden of medication non-adherence in Australia across three highly prevalent conditions is $10.4 billion. Implementation of a community pharmacist led adherence intervention resulted in a cost saving of $1.9 billion. Models of remuneration and expansion of the role pharmacists play in managing health care is required.

References

Abdulsalim, S., Unnikrishnan, M.K., Manu, M.K., Alrasheedy, A.A., Godman, B. & Morisky, D.E. 2018, 'Structured pharmacist-led intervention programme to improve medication adherence in COPD patients: A randomized controlled study', *Research in Social and Administrative Pharmacy*, vol. 14, no. 10, pp. 909-14.

Agency for Healthcare Research and Quality. 2014, *Medication Adherence Interventions: Comparative Effectiveness (Evidence Report)*, viewed 4 April 2018, <http://www.ahrq.gov/redirects/gapmedadtp.html>.

Aguiar, P.M., Balisa-Rocha, B.J., Brito, G.C. & Lyra, D.P., Jr. 2012, 'Pharmaceutical care program for elderly patients with uncontrolled hypertension', *J Am Pharm Assoc (2003)*, vol. 52, no. 4, pp. 515-8, 1 p following 8.

Aitken, M. & Valkova, S. 2013, 'Avoidable costs in US healthcare: the $200 billion opportunity from using medicines more responsibly', *IMS Institute for Healthcare Informatics*, pp. 20-1.

Arnet, I., Abraham, I., Messerli, M. & Hersberger, K.E. 2014, 'A method for calculating adherence to polypharmacy from dispensing data records', *International journal of clinical pharmacy*, vol. 36, no. 1, pp. 192-201.

Aubert, R.E., Yao, J., Xia, F. & Garavaglia, S.B. 2010, 'Is there a relationship between early statin compliance and a reduction in healthcare utilization?', *The American journal of managed care*, vol. 16, pp. 459-66.

Australian Government Department of Health. 2017, *Chronic Conditions*, Commonwealth of Australia, Canberra, Australia, viewed 15 January 2019, <http://www.health.gov.au/internet/main/publishing.nsf/content/chronic-disease>.

Australian Government Department of Health 2017, *Department of Health Annual Report 2016-17*, Commonwealth of Australia, Canberra, Australia

Australian Government Department of Health 2018, *Guaranteeing the essential services Australians rely on*, Commonwealth of Australia, Canberra, Australia, viewed 15 January 2019, <https://www.budget.gov.au/2018-19/content/essentials.html>.

Australian Institute of Health and Welfare 2014, *Australia's health 2014*, Australia's health series no. 14. Cat no. AUS 178. Canberra: AIHW.

Australian Institute of Health and Welfare 2016, *Health expenditure Australia 2014–15.* Health and welfare expenditure series no. 57. Cat. no. HWE 67. Canberra: AIHW.

Australian Institute of Health and Welfare 2017, *Health expenditure Australia 2015–16*, Health and welfare expenditure series. 2017; no. 58. Cat. no. HWE 68. Canberra: AIHW

Australian Institute of Health and Welfare 2018, *Australia's health 2018*, Australia's health series no. 16. AUS 221. Canberra: AIHW.

Australian Treasury & Swan, W. 2010, *Australia to 2050: future challenges*, Commonwealth of Australia, Canberra.

Bagalman, E., Yu-Isenberg, K.S., Durden, E., Crivera, C., Dirani, R. & Bunn, W.B. 2010, 'Indirect costs associated with nonadherence to treatment for bipolar disorder.', *Journal of occupational and environmental medicine / American College of Occupational and Environmental Medicine*, vol. 52, pp. 478-85.

Baines, L.S., Little, D.J., Nee, R. & Jindal, R.M. 2015, 'Non-Adherence Codes in the New ICD-10: Need for Prospective Trials', *American Journal of Nephrology*, vol. 42, no. 2, pp. 148-50.

Balkrishnan, R. & Christensen, D.B. 2000, 'Inhaled corticosteroid use and associated outcomes in elderly patients with moderate to severe chronic pulmonary disease', *Clin Ther*, vol. 22, no. 4, pp. 452-69.

Basu, A. 2009, 'Individualization at the heart of comparative effectiveness research: the time for i-CER has come', *Med Decis Making*, vol. 29, no. 6, pp. Np9-np11.

Blenkinsopp, A., Phelan, M., Bourne, J. & Dakhil, N. 2000, 'Extended adherence support by community pharmacists for patients with hypertension: a randomised controlled trial', *International Journal of Pharmacy Practice*, vol. 8, no. 3, pp. 165-75.

Brown, M.T. & Bussell, J.K. 2011, 'Medication adherence: WHO cares?', *Mayo Clin Proc*, vol. 86, no. 4, pp. 304-14.

Buysman, E.K., Anderson, A., Bacchus, S. & Ingham, M. 2017, 'Retrospective Study on the Impact of Adherence in Achieving Glycemic Goals in Type 2 Diabetes Mellitus Patients Receiving Canagliflozin', *Adv Ther*, vol. 34, no. 4, pp. 937-53.

Byford, S., Torgerson, D.J. & Raftery, J. 2000, 'Economic note: cost of illness studies', *BMJ (Clinical research ed.)*, vol. 320, no. 7245, pp. 1335-.

Carpenter, A., Elshaug, A., Turnbull, F., Wilson, A. & Jan, S. 2014, *Health Policy, Administration and Expenditure*, Canberra.

Centre for Business Innovation Medical Adherence Consortium 2018, *Encouraging adherence initiatives: aligning indivdiual, commercial, and social value*, viewed 20 November 2018, <https://www.cfbi.com/CfBI%20Medical%20Adherence%20Consortium%20Position%20Paper.pdf>.

Chowdhury, R., Khan, H., Heydon, E., Shroufi, A., Fahimi, S., Moore, C., Stricker, B., Mendis, S., Hofman, A., Mant, J. & Franco, O.H. 2013, 'Adherence to cardiovascular therapy: a meta-analysis of prevalence and clinical consequences', *European Heart Journal*, vol. 34, no. 38, pp. 2940-8.

Clifford, S., Barber, N., Elliott, R., Hartley, E. & Horne, R. 2006, 'Patient-centred advice is effective in improving adherence to medicines', *Pharm World Sci*, vol. 28, no. 3, pp. 165-70.

Clyne, W. & McLachlan, S. 2015, 'A mixed-methods study of the implementation of medication adherence policy solutions: how do European countries compare?', *Patient Prefer Adherence*, vol. 9, pp. 1505-15.

Congressional Budget Office 2012, *Offsetting effects of prescription drug use on medicare's spending for medical services.*, viewed 10 August 2017, <http://www.cbo.gov/sites/default/files/cbofiles/attachments/43741-MedicalOffsets-11-29-12.pdf.>.

Cook, D.J., Mulrow, C.D. & Haynes, R.B. 1997, 'Systematic reviews: synthesis of best evidence for clinical decisions', *Ann Intern Med*, vol. 126, no. 5, pp. 376-80.

Cooper, B.S. & Rice, D.P. 1976, 'The economic cost of illness revisited', *Soc Secur Bull*, vol. 39, no. 2, pp. 21-36.

Cramer, J.A. 2004, 'A Systematic Review of Adherence With Medications for Diabetes', *Diabetes Care*, vol. 27, no. 5, p. 1218.

Creese, A. & Parker, D. 1994, *Cost Analysis in Primary Health Care. A Training Manual for Programme Managers*, ERIC.

Cutler, R.L., Fernandez-Llimos, F., Frommer, M., Benrimoj, C. & Garcia-Cardenas, V. 2018, 'Economic impact of medication non-adherence by disease groups: a systematic review', *BMJ Open*, vol. 8, no. 1.

Davis, K.L., Edin, H.M. & Allen, J.K. 2010, 'Prevalence and cost of medication nonadherence in Parkinson's disease: evidence from administrative claims data', *Mov Disord*, vol. 25, no. 4, pp. 474-80.

de Bruin, S.R., Baan, C.A. & Struijs, J.N. 2011, 'Pay-for-performance in disease management: a systematic review of the literature', *BMC Health Serv Res*, vol. 11, p. 272.
De Geest, S., Zullig, L.L., Dunbar-Jacob, J., Helmy, R., Hughes, D.A., Wilson, I.B. & Vrijens, B. 2018, 'ESPACOMP Medication Adherence Reporting Guideline (EMERGE)', *Ann Intern Med*, vol. 169, no. 1, pp. 30-5.
Delea, T.E., Thomas, S.K. & Hagiwara, M. 2011, 'The association between adherence to levodopa/carbidopa/entacapone therapy and healthcare utilization and costs among patients with Parkinson's disease: a retrospective claims-based analysis.', *CNS drugs*, vol. 25, pp. 53-66.
Demonceau, J., Ruppar, T., Kristanto, P., Hughes, D.A., Fargher, E., Kardas, P., De Geest, S., Dobbels, F., Lewek, P., Urquhart, J. & Vrijens, B. 2013, 'Identification and assessment of adherence-enhancing interventions in studies assessing medication adherence through electronically compiled drug dosing histories: a systematic literature review and meta-analysis', *Drugs*, vol. 73, no. 6, pp. 545-62.
Diehl, J.L., Daw, J.R., Coley, K.C. & Rayburg, R. 2010, 'Medical utilization associated with palivizumab compliance in a commercial and managed medicaid health plan.', *Journal of managed care pharmacy : JMCP*, vol. 16, pp. 23-31.
DiMatteo, M.R. 2004, 'Variations in patients' adherence to medical recommendations: a quantitative review of 50 years of research', *Med Care*, vol. 42, no. 3, pp. 200-9.
DiMatteo, M.R., Giordani, P.J., Lepper, H.S. & Croghan, T.W. 2002, 'Patient adherence and medical treatment outcomes: a meta-analysis', *Med Care*, vol. 40, no. 9, pp. 794-811.
Drummond, M.F., Sculpher, M.J., Claxton, K., Stoddart, G.L. & Torrance, G.W. 2015, *Methods for the economic evaluation of health care programmes*, Oxford university press.
Egede, L.E., Gebregziabher, M., Dismuke, C.E., Lynch, C.P., Axon, R.N., Zhao, Y. & Mauldin, P.D. 2012, 'Medication Nonadherence in Diabetes', *Diabetes Care*, vol. 35, no. 12, p. 2533.
Eisenberg, D.F., Placzek, H., Gu, T., Krishna, A. & Tulsi, B.B. 2015, 'Cost and consequences of noncompliance to oral bisphosphonate treatment', *J Manag Care Spec Pharm*, vol. 21, no. 1, pp. 56-65.
Elliott, R. 2013, 'Nonadherence to medicines: the scale of the problem', *Prescriber*, vol. 24, no. 17, pp. 47-50.
Elliott, R.A., Barber, N., Clifford, S., Horne, R. & Hartley, E. 2008, 'The cost effectiveness of a telephone-based pharmacy advisory service to improve adherence to newly prescribed medicines', *Pharm World Sci*, vol. 30, no. 1, pp. 17-23.
Espinoza, M.A. 2012, 'Cost effectiveness analysis: methods to explore the value of subgroups and individualized care in a collectively funded health system', University of York.
Eussen, S.R., van der Elst, M.E., Klungel, O.H., Rompelberg, C.J., Garssen, J., Oosterveld, M.H., de Boer, A., de Gier, J.J. & Bouvy, M.L. 2010, 'A pharmaceutical care program to improve adherence to statin therapy: a randomized controlled trial', *Ann Pharmacother*, vol. 44, no. 12, pp. 1905-13.
Fischer, M.A., Stedman, M.R., Lii, J., Vogeli, C., Shrank, W.H., Brookhart, M.A. & Weissman, J.S. 2010, 'Primary medication non-adherence: analysis of 195,930 electronic prescriptions', *Journal of general internal medicine*, vol. 25, no. 4, pp. 284-90.
Flodgren, G., Eccles, M.P., Shepperd, S., Scott, A., Parmelli, E. & Beyer, F.R. 2011, 'An overview of reviews evaluating the effectiveness of financial incentives in changing healthcare professional behaviours and patient outcomes', *Cochrane Database Syst Rev*, no. 7, p. CD009255.

Ford, E.S., Ajani, U.A., Croft, J.B., Critchley, J.A., Labarthe, D.R., Kottke, T.E., Giles, W.H. & Capewell, S. 2007, 'Explaining the decrease in U.S. deaths from coronary disease, 1980-2000', *N Engl J Med*, vol. 356, no. 23, pp. 2388-98.

Fraser, S. 2010, 'Concordance, compliance, preference or adherence', *Patient Prefer Adherence*, vol. 4, pp. 95-6.

Gatwood, J. & Bailey, J.E. 2014, 'Improving medication adherence in hypercholesterolemia: challenges and solutions', *Vasc Health Risk Manag*, vol. 10, pp. 615-25.

Gehi, A., Haas, D., Pipkin, S. & Whooley, M.A. 2005, 'Depression and medication adherence in outpatients with coronary heart disease: findings from the Heart and Soul Study', *Arch Intern Med*, vol. 165, no. 21, pp. 2508-13.

Gonzalez, J.S., Peyrot, M., McCarl, L.A., Collins, E.M., Serpa, L., Mimiaga, M.J. & Safren, S.A. 2008, 'Depression and diabetes treatment nonadherence: a meta-analysis', *Diabetes care*, vol. 31, no. 12, pp. 2398-403.

Haynes, R.B., Ackloo, E., Sahota, N., McDonald, H.P. & Yao, X. 2008, 'Interventions for enhancing medication adherence', *Cochrane Database Syst Rev*, no. 2, p. CD000011.

Haynes, R.B., McDonald, H., Garg, A.X. & Montague, P. 2002, 'Interventions for helping patients to follow prescriptions for medications', *Cochrane Database Syst Rev*, vol. 2, no. 11, pp. 7.9-1.4.

Heaney, L. 2013, *Clinical Focus Series: Difficult Asthma*, JP Medical Ltd.

Helmy, R., Zullig, L.L., Dunbar-Jacob, J., Hughes, D.A., Vrijens, B., Wilson, I.B. & De Geest, S. 2017, 'ESPACOMP Medication Adherence Reporting Guidelines (EMERGE): a reactive-Delphi study protocol', *BMJ Open*, vol. 7, no. 2, p. e013496.

Herndon, J.B., Mattke, S., Evans Cuellar, A., Hong, S.Y. & Shenkman, E.A. 2012, 'Anti-inflammatory medication adherence, healthcare utilization and expenditures among Medicaid and children's health insurance program enrollees with asthma', *Pharmacoeconomics*, vol. 30, no. 5, pp. 397-412.

Hiligsmann, M., McGowan, B., Bennett, K., Barry, M. & Reginster, J.Y. 2012, 'The clinical and economic burden of poor adherence and persistence with osteoporosis medications in Ireland', *Value Health*, vol. 15, no. 5, pp. 604-12.

Hoffmann, T.C., Glasziou, P.P., Boutron, I., Milne, R., Perera, R., Moher, D., Altman, D.G., Barbour, V., Macdonald, H., Johnston, M., Lamb, S.E., Dixon-Woods, M., McCulloch, P., Wyatt, J.C., Chan, A.-W. & Michie, S. 2014, 'Better reporting of interventions: template for intervention description and replication (TIDieR) checklist and guide', *BMJ : British Medical Journal*, vol. 348.

Horne, R., Chapman, S.C., Parham, R., Freemantle, N., Forbes, A. & Cooper, V. 2013, 'Understanding patients' adherence-related beliefs about medicines prescribed for long-term conditions: a meta-analytic review of the Necessity-Concerns Framework', *PLoS One*, vol. 8, no. 12, p. e80633.

Hossain, L.N., Fernandez-Llimos, F., Luckett, T., Moullin, J.C., Durks, D., Franco-Trigo, L., Benrimoj, S.I. & Sabater-Hernández, D. 2017, 'Qualitative meta-synthesis of barriers and facilitators that influence the implementation of community pharmacy services: perspectives of patients, nurses and general medical practitioners', *BMJ open*, vol. 7, no. 9, p. e015471.

Hughes, D.A., Bagust, A., Haycox, A. & Walley, T. 2001, 'Accounting for noncompliance in pharmacoeconomic evaluations', *Pharmacoeconomics*, vol. 19, no. 12, pp. 1185-97.

Husereau, D., Drummond, M., Petrou, S., Carswell, C., Moher, D., Greenberg, D., Augustovski, F., Briggs, A.H., Mauskopf, J., Loder, E. & Force, Ispor Health Economic Evaluation Publication Guidelines- CHEERS Good Reporting Practices Task Force. 2013, 'Consolidated Health Economic Evaluation Reporting Standards (CHEERS)--

explanation and elaboration: a report of the ISPOR Health Economic Evaluation Publication Guidelines Good Reporting Practices Task Force', *Value Health*, vol. 16, no. 2, pp. 231-50.

Institute for Healthcare Informatics. 2012, *Advancing the responsible use of medicines; applying levers for change.*, viewed 10 March 2016, <http://pharmanalyses.fr/wp-content/uploads/2012/10/Advancing-Responsible-Use-of-Meds-Report-01-10-12.pdf>.

Iuga, A.O. & McGuire, M.J. 2014, 'Adherence and health care costs', *Risk Manag Healthc Policy*, vol. 7, pp. 35-44.

Ivanova, J.I., Bergman, R.E., Birnbaum, H.G., Phillips, A.L., Stewart, M. & Meletiche, D.M. 2012, 'Impact of medication adherence to disease-modifying drugs on severe relapse, and direct and indirect costs among employees with multiple sclerosis in the US.', *Journal of medical economics*, vol. 15, pp. 601-9.

Jaam, M., Awaisu, A., Mohamed Ibrahim, M.I. & Kheir, N. 2018, 'A holistic conceptual framework model to describe medication adherence in and guide interventions in diabetes mellitus', *Res Social Adm Pharm*, vol. 14, no. 4, pp. 391-7.

Jimmy, B. & Jose, J. 2011, 'Patient medication adherence: measures in daily practice', *Oman Med J*, vol. 26, no. 3, pp. 155-9.

Joshi, A.V., Madhavan, S.S., Ambegaonkar, A., Smith, M., Scott, V.G. & Dedhia, H. 2006, 'Association of medication adherence with workplace productivity and health-related quality of life in patients with asthma.', *The Journal of asthma : official journal of the Association for the Care of Asthma*, vol. 43, pp. 521-6.

Kardas, P., Lewek, P. & Matyjaszczyk, M. 2013, 'Determinants of patient adherence: a review of systematic reviews', *Front Pharmacol*, vol. 4, p. 91.

Kennelly, B. 2017, 'How should cost-of-illness studies be interpreted?', *The Lancet Psychiatry*, vol. 4, no. 10, pp. 735-6.

Khan, R. & Socha-Dietrich, K. 2018, 'Investing in medication adherence improves health outcomes and health system efficiency'.

Kim, H.J., Yoon, S.J., Oh, I.H., Lim, J.H. & Kim, Y.A. 2016, 'Medication Adherence and the Occurrence of Complications in Patients with Newly Diagnosed Hypertension', *Korean Circ J*, vol. 46, no. 3, pp. 384-93.

Kini, V. & Ho, P.M. 2018, 'Interventions to Improve Medication Adherence: A Review', *Jama*, vol. 320, no. 23, pp. 2461-73.

Knapp, M., King, D., Pugner, K. & Lapuerta, P. 2004, 'Non-adherence to antipsychotic medication regimens: associations with resource use and costs.', *The British journal of psychiatry : the journal of mental science*, vol. 184, pp. 509-16.

Krivoy, A., Balicer, R.D., Feldman, B., Hoshen, M., Zalsman, G., Weizman, A. & Shoval, G. 2015, 'Adherence to antidepressant therapy and mortality rates in ischaemic heart disease: cohort study', *Br J Psychiatry*, vol. 206, no. 4, pp. 297-301.

Lam, W.Y. & Fresco, P. 2015, 'Medication Adherence Measures: An Overview', *Biomed Res Int*, vol. 2015, p. 217047.

Lee, S.-Q., Raamkumar, A.S., Li, J., Cao, Y., Witedwittayanusat, K., Chen, L. & Theng, Y.-L. 2018, 'Reasons for Primary Medication Nonadherence: A Systematic Review and Metric Analysis', *Journal of Managed Care & Specialty Pharmacy*, vol. 24, no. 8, pp. 778-94.

Leider, H.L., Dhaliwal, J., Davis, E.J., Kulakodlu, M. & Buikema, A.R. 2011, 'Healthcare costs and nonadherence among chronic opioid users.', *The American journal of managed care*, vol. 17, pp. 32-40.

Li, Y.C. & Huang, W.L. 2015, 'Effects of Adherence to Statin Therapy on Health Care Outcomes and Utilizations in Taiwan: A Population-Based Study', *Biomed Res Int*, vol. 2015, p. 149573.

Loeppke, R., Taitel, M., Haufle, V., Parry, T., Kessler, R.C. & Jinnett, K. 2009, 'Health and productivity as a business strategy: a multiemployer study', *J Occup Environ Med*, vol. 51, no. 4, pp. 411-28.

Malet-Larrea, A., Garcia-Cardenas, V., Saez-Benito, L., Benrimoj, S.I., Calvo, B. & Goyenechea, E. 2016, 'Cost-effectiveness of professional pharmacy services in community pharmacy: a systematic review', *Expert Rev Pharmacoecon Outcomes Res*, vol. 16, no. 6, pp. 747-58.

Marie-Schneider, P. & Aslani, P. 2010, 'Adherence policy, education and practice - an international perspective', *Pharmacy practice*, vol. 8, no. 4, pp. 209-12.

Mattke, S., Martorell, F., Hong, S.Y., Sharma, P., Cuellar, A. & Lurie, N. 2010, 'Anti-inflammatory medication adherence and cost and utilization of asthma care in a commercially insured population', *J Asthma*, vol. 47, no. 3, pp. 323-9.

McCarthy, R. 1998, 'The price you pay for the drug not taken*', Business and health*, vol. 16, no. 10, pp. 27-33.

McGinnis, J.M., Grossmann, C. & Olsen, L. 2011, *Learning what works: infrastructure required for comparative effectiveness research: workshop summary*, National Academies Press.

Mes, M.A., Katzer, C.B., Chan, A.H.Y., Wileman, V., Taylor, S.J.C. & Horne, R. 2018, 'Pharmacists and medication adherence in asthma: a systematic review and meta-analysis', *European Respiratory Journal*, p. 1800485.

Meyer, A.M., Carpenter, W.R., Abernethy, A.P., Sturmer, T. & Kosorok, M.R. 2012, 'Data for cancer comparative effectiveness research: past, present, and future potential', *Cancer*, vol. 118, no. 21, pp. 5186-97.

Milosavljevic, A., Aspden, T. & Harrison, J. 2018, 'Community pharmacist-led interventions and their impact on patients' medication adherence and other health outcomes: a systematic review', *Int J Pharm Pract*, vol. 26, no. 5, pp. 387-97.

Modi, A., Siris, E.S., Tang, J. & Sen, S. 2015, 'Cost and consequences of noncompliance with osteoporosis treatment among women initiating therapy', *Curr Med Res Opin*, vol. 31, no. 4, pp. 757-65.

Morello, C. & Hirsch, J. 2017, 'Strategies for addressing the cost of nonadherence in diabetes', *The American journal of managed care*, vol. 23, no. 13 Suppl, pp. S247-S52.

Morgan, S.G. & Lee, A. 2017, 'Cost-related non-adherence to prescribed medicines among older adults: a cross-sectional analysis of a survey in 11 developed countries', *BMJ open*, vol. 7, no. 1, pp. e014287-e.

Mossialos, E., Courtin, E., Naci, H., Benrimoj, S., Bouvy, M., Farris, K., Noyce, P. & Sketris, I. 2015, 'From "retailers" to health care providers: Transforming the role of community pharmacists in chronic disease management', *Health Policy*, vol. 119, no. 5, pp. 628-39.

Mossialos, E., Naci, H. & Courtin, E. 2013, 'Expanding the role of community pharmacists: policymaking in the absence of policy-relevant evidence?', *Health Policy*, vol. 111, no. 2, pp. 135-48.

Nasseh, K., Frazee, S.G., Visaria, J., Vlahiotis, A. & Tian, Y. 2012, 'Cost of medication nonadherence associated with diabetes, hypertension, and dyslipidemia', *Am J Pharm Benefits*, vol. 4, no. 2, pp. e41-e7.

National Council on Patient Information and Education 2013, *Accelerating Progress in Prescription Medicine Adherence: The Adherence Action Agenda*, United States.

National Pharmaceutical Council 1992, *Noncompliance with medicine regimens. An economic tragedy. Emerging issues in pharmaceutical cost containing*, Washington DC.

Nau, D.P. 2011, *Proportion of Days Covered (PDC) as a Preferred Method of Measuring Medication Adherence*, viewed 22 November 2018, <http://www.pqaalliance.org/images/uploads/files/PQA%20PDC%20vs%20%20MPR.pdf>.

New England Health Care Institute. 2009, *Thinking outside the pillbox: a system-wide approach to improving patient medication adherence for chronic disease*, New England Health Care Institute.

Nieuwlaat, R., Wilczynski, N., Navarro, T., Hobson, N., Jeffery, R., Keepanasseril, A., Agoritsas, T., Mistry, N., Iorio, A., Jack, S., Sivaramalingam, B., Iserman, E., Mustafa, R.A., Jedraszewski, D., Cotoi, C. & Haynes, R.B. 2014, 'Interventions for enhancing medication adherence', *Cochrane Database Syst Rev*, no. 11, p. CD000011.

Nkansah, N., Mostovetsky, O., Yu, C., Chheng, T., Beney, J., Bond, C.M. & Bero, L. 2010, 'Effect of outpatient pharmacists' non-dispensing roles on patient outcomes and prescribing patterns', *Cochrane Database Syst Rev*, no. 7, p. Cd000336.

O. Ceilleachair, A.J., Hanly, P., Skally, M., O'Neill, C., Fitzpatrick, P., Kapur, K., Staines, A. & Sharp, L. 2013, 'Cost comparisons and methodological heterogeneity in cost-of-illness studies: the example of colorectal cancer', *Med Care*, vol. 51, no. 4, pp. 339-50.

Offord, S., Lin, J., Mirski, D. & Wong, B. 2013, 'Impact of early nonadherence to oral antipsychotics on clinical and economic outcomes among patients with schizophrenia.', *Advances in therapy*, vol. 30, pp. 286-97.

Offord, S., Lin, J., Wong, B., Mirski, D. & Baker, R.A. 2013, 'Impact of oral antipsychotic medication adherence on healthcare resource utilization among schizophrenia patients with Medicare coverage.', *Community mental health journal*, vol. 49, pp. 625-9.

Osterberg , L. & Blaschke , T. 2005, 'Adherence to Medication', *New England Journal of Medicine*, vol. 353, no. 5, pp. 487-97.

Pae, C.-U. 2015, 'Why Systematic Review rather than Narrative Review?', *Psychiatry investigation*, vol. 12, no. 3, pp. 417-9.

Pages-Puigdemont, N., Mangues, M.A., Masip, M., Gabriele, G., Fernandez-Maldonado, L., Blancafort, S. & Tuneu, L. 2016, 'Patients' Perspective of Medication Adherence in Chronic Conditions: A Qualitative Study', *Adv Ther*, vol. 33, no. 10, pp. 1740-54.

Pednekar, P., Malmenas, M., Agh, T., Bennett, B. & Peterson, A. 2017, 'Measuring Multiple Medication Adherence–Which Measure When?', *Value and Outcomes Spotlight*, vol. 3, no. 6, pp. 17-20.

Peterson, A.M.T., L.; Finley, R. 2003, 'Meta-analysis of trials of interventions to improve medication adherence', *Am J Health Syst Pharm*, vol. 60, no. 7, pp. 657-65.

Pharmaceutical Group of the European Union. 2008, *Targeting adherence. Improving patient outcomes in Europe through community pharmacists' intervention*, viewed 28 January 2016, < http://www.pgeu.eu/policy/5-adherence.html>.

Pharmaceutical Group of the European Union. 2018, *Adherence*, viewed 10 June 2018, <https://www.pgeu.eu/en/policy/5-adherence.html>.

Philipson, T. 2015, 'Non-Adherence in Health Care: Are patients or policy makers ill-informed?', *Forbes*, viewed 22 January 2019, <https://www.forbes.com/sites/tomasphilipson/2015/05/08/non-adherence-in-health-care-are-patients-or-policy-makers-ill-informed/#6ee4e7874c4a>.

Pringle, J. & Coley, K.C. 2015, 'Improving medication adherence: a framework for community pharmacy-based interventions', *Integr Pharm Res Pract*, vol. 4, pp. 175-83.
Psaty, B.M., Koepsell, T.D., Wagner, E.H., LoGerfo, J.P. & Inui, T.S. 1990, 'The relative risk of incident coronary heart disease associated with recently stopping the use of beta-blockers', *JAMA*, vol. 263, no. 12, pp. 1653-7.
Rabarison, K.M., Bish, C.L., Massoudi, M.S. & Giles, W.H. 2015, 'Economic Evaluation Enhances Public Health Decision Making', *Front Public Health*, vol. 3, p. 164.
Raebel, M.A., Schmittdiel, J., Karter, A.J., Konieczny, J.L. & Steiner, J.F. 2013, 'Standardizing terminology and definitions of medication adherence and persistence in research employing electronic databases', *Med Care*, vol. 51, no. 8 Suppl 3, pp. S11-21.
Raynor, D.K. 1992, 'Patient compliance: the pharmacist's role', *International Journal of Pharmacy Practice*, vol. 1, no. 3, pp. 126-35.
Rice, D.P. 1967, 'Estimating the cost of illness', *Am J Public Health Nations Health*, vol. 57, no. 3, pp. 424-40.
Rice, D.P., Hodgson, T.A. & Kopstein, A.N. 1985, 'The economic costs of illness: a replication and update', *Health Care Financ Rev*, vol. 7, no. 1, pp. 61-80.
Roebuck, M.C., Liberman, J.N., Gemmill-Toyama, M. & Brennan, T.A. 2011, 'Medication adherence leads to lower health care use and costs despite increased drug spending.', *Health affairs (Project Hope)*, vol. 30, pp. 91-9.
Roter, D.L., Hall, J.A., Merisca, R., Nordstrom, B., Cretin, D. & Svarstad, B. 1998, 'Effectiveness of interventions to improve patient compliance: a meta-analysis', *Med Care*, vol. 36, no. 8, pp. 1138-61.
Roughead, L., Semple, S. & Rosenfeld, E. 2013, 'Literature review: medication safety in Australia', *Australian Commission on Safety and Quality in Health Care*.
Ruetsch, C., Tkacz, J., Nadipelli, V.R., Brady, B.L., Ronquest, N., Un, H. & Volpicelli, J. 2017, 'Heterogeneity of nonadherent buprenorphine patients: subgroup characteristics and outcomes', *Am J Manag Care*, vol. 23, no. 6, pp. e172-e9.
Sabaté, E. 2003, *Adherence to long-term therapies: evidence for action*, World Health Organization.
Sackett, D.L., Haynes, R.B., Gibson, E.S., Taylor, D.W., Roberts, R.S. & Johnson, A.L. 1978, 'Patient compliance with antihypertensive regimens', *Patient counselling and health education*, vol. 1, no. 1, pp. 18-21.
Sapkota, S., Brien, J.A., Greenfield, J. & Aslani, P. 2015, 'A systematic review of interventions addressing adherence to anti-diabetic medications in patients with type 2 diabetes--impact on adherence', *PLoS One*, vol. 10, no. 2, p. e0118296.
Scott, A. & Connelly, L.B. 2011, 'Financial incentives and the health workforce', *Aust Health Rev*, vol. 35, no. 3, pp. 273-7.
Shemilt, I., Thomas, J. & Morciano, M. 2010, 'A web-based tool for adjusting costs to a specific target currency and price year', *Evidence & Policy: A Journal of Research, Debate and Practice*, vol. 6, no. 1, pp. 51-9.
Shoval, G., Stubbs, B., Balicer, R.D., Feldman, B., Hoshen, M., Zalsman, G., Sagy, R., Hochman, E., Weizman, A. & Krivoy, A. 2017, 'Low adherence to antidepressants is associated with increased mortality in Parkinson disease patients', *Parkinsonism Relat Disord*, vol. 43, pp. 92-6.
Simoni-Wastila, L., Wei, Y.-J., Qian, J., Zuckerman, I.H., Stuart, B., Shaffer, T., Dalal, A.A. & Bryant-Comstock, L. 2012, 'Association of Chronic Obstructive Pulmonary Disease Maintenance Medication Adherence With All-Cause Hospitalization and Spending in a Medicare Population', *The American Journal of Geriatric Pharmacotherapy*, vol. 10, no. 3, pp. 201-10.

SimplHealth. 2016, *Waste not, want not*, New Zealand, viewed 22 January 2019, <http://innovation.health.nz/media/documents/Waste_Not_Want_Not_Whitepaper_June_16.pdf>
Simpson, S.H., Eurich, D.T., Majumdar, S.R., Padwal, R.S., Tsuyuki, R.T., Varney, J. & Johnson, J.A. 2006, 'A meta-analysis of the association between adherence to drug therapy and mortality', *Bmj*, vol. 333, no. 7557, p. 15.
Smith, M., Giuliano, M.R. & Starkowski, M.P. 2011, 'In Connecticut: improving patient medication management in primary care', *Health Aff (Millwood)*, vol. 30, no. 4, pp. 646-54.
Sokol, M.C., McGuigan, K.A., Verbrugge, R.R. & Epstein, R.S. 2005, 'Impact of medication adherence on hospitalization risk and healthcare cost', *Med Care*, vol. 43, no. 6, pp. 521-30.
Sox, H.C., Helfand, M., Grimshaw, J., Dickersin, K., Tovey, D., Knottnerus, J.A. & Tugwell, P. 2010, 'Comparative effectiveness research: challenges for medical journals', *Croatian medical journal*, vol. 51, no. 3, pp. 191-4.
Sperber, C.M., Samarasinghe, S.R. & Lomax, G.P. 2017, 'An upper and lower bound of the Medication Possession Ratio', *Patient preference and adherence*, vol. 11, pp. 1469-78.
Sturgess, I.K., McElnay, J.C., Hughes, C.M. & Crealey, G. 2003, 'Community pharmacy based provision of pharmaceutical care to older patients', *Pharm World Sci*, vol. 25, no. 5, pp. 218-26.
Svarstad, B.L., Kotchen, J.M., Shireman, T.I., Brown, R.L., Crawford, S.Y., Mount, J.K., Palmer, P.A., Vivian, E.M. & Wilson, D.A. 2013, 'Improving refill adherence and hypertension control in black patients: Wisconsin TEAM trial', *J Am Pharm Assoc (2003)*, vol. 53, no. 5, pp. 520-9.
Tamás, K. 2010, 'Clinical and pharmacoeconomic impact of patient medication adherence', Dissertation, Semmelweis University.
Tarricone, R. 2006, 'Cost-of-illness analysis: What room in health economics?', *Health Policy*, vol. 77, no. 1, pp. 51-63.
Taylor, N. 2013, 'CEDA overview: Reform or ration', *Healthcare: Reform or ration*, p. 10.
The Pharmacy Guild of Australia 2010, *Medication Adherence Programs*, viewed 4 January 2019, <https://www.guild.org.au/__data/assets/pdf_file/0021/5655/medication-adherence-programs.pdf>.
Thoopputra, T., Newby, D., Schneider, J. & Li, S.C. 2015, 'Interventions in chronic disease management: a review of the literature on the role of community pharmacists', *American Journal of Pharmacy and Health Research*, vol. 3, no. 1, pp. 82-117.
Tkacz, J., Volpicelli, J., Un, H. & Ruetsch, C. 2014, 'Relationship between buprenorphine adherence and health service utilization and costs among opioid dependent patients.', *Journal of substance abuse treatment*, vol. 46, pp. 456-62.
Tommelein, E., Mehuys, E., Van Hees, T., Adriaens, E., Van Bortel, L., Christiaens, T., Van Tongelen, I., Remon, J.P., Boussery, K. & Brusselle, G. 2014, 'Effectiveness of pharmaceutical care for patients with chronic obstructive pulmonary disease (PHARMACOP): a randomized controlled trial', *Br J Clin Pharmacol*, vol. 77, no. 5, pp. 756-66.
Tonin, F.S., Wiecek, E., Torres-Robles, A., Pontarolo, R., Benrimoj, S.I., Fernandez-Llimos, F. & Garcia-Cardenas, V. 2018, 'An innovative and comprehensive technique to evaluate different measures of medication adherence: The network meta-analysis', *Research in Social and Administrative Pharmacy*.
Torres-Robles, A., Wiecek, E., Tonin, F.S., Benrimoj, S.I., Fernandez-Llimos, F. & Garcia-Cardenas, V. 2018, 'Comparison of Interventions to Improve Long-Term Medication

Adherence Across Different Clinical Conditions: A Systematic Review With Network Meta-Analysis', *Frontiers in Pharmacology*, vol. 9, no. 1454.

Velligan, D.I., Wang, M., Diamond, P., Glahn, D.C., Castillo, D., Bendle, S., Lam, Y.W., Ereshefsky, L. & Miller, A.L. 2007, 'Relationships among subjective and objective measures of adherence to oral antipsychotic medications', *Psychiatr Serv*, vol. 58, no. 9, pp. 1187-92.

Vik, S.A., Maxwell, C.J. & Hogan, D.B. 2004, 'Measurement, correlates, and health outcomes of medication adherence among seniors', *Ann Pharmacother*, vol. 38, no. 2, pp. 303-12.

Viswanathan, M., Golin, C.E., Jones, C.D., Ashok, M., Cocker-Schwimmer, E.J.L., Grodensky, C.A., Rosen, D.L., Yuen, A., Sista, P. & Lohr, K.N. 2012, *Medication Adherence Interventions: Comparative Effectiveness. Closing the Quality Gap: Revisiting the State of Science.*, Agency for Healthcare Research and Quality, Evidence Report No. 208.

Vrijens, B., De Geest, S., Hughes, D.A., Przemyslaw, K., Demonceau, J., Ruppar, T., Dobbels, F., Fargher, E., Morrison, V., Lewek, P., Matyjaszczyk, M., Mshelia, C., Clyne, W., Aronson, J.K., Urquhart, J. & Team, A.B.C.P. 2012, 'A new taxonomy for describing and defining adherence to medications', *Br J Clin Pharmacol*, vol. 73, no. 5, pp. 691-705.

Vrijens, B., Urquhart, J. & White, D. 2014, 'Electronically monitored dosing histories can be used to develop a medication-taking habit and manage patient adherence', *Expert Rev Clin Pharmacol*, vol. 7, no. 5, pp. 633-44.

Wei, Y.-J., Palumbo, F.B., Simoni-Wastila, L., Shulman, L.M., Stuart, B., Beardsley, R. & Brown, C.H. 2014, 'Antiparkinson drug adherence and its association with health care utilization and economic outcomes in a Medicare Part D population.', *Value in health : the journal of the International Society for Pharmacoeconomics and Outcomes Research*, vol. 17, pp. 196-204.

Whalley Buono, E., Vrijens, B., Bosworth, H.B., Liu, L.Z., Zullig, L.L. & Granger, B.B. 2017, 'Coming full circle in the measurement of medication adherence: opportunities and implications for health care', *Patient Prefer Adherence*, vol. 11, pp. 1009-17.

White, T.J.V., Ann; Ory, Caron; Dezii, Christopher M.; Chang, Eunice 2003, 'Economic Impact of Patient Adherence with Antidepressant Therapy Within a Managed Care Organization', *Disease Management & Health Outcomes*, vol. 11, no. 12, pp. 817-22.

Wiecek, E.K., V. Garcia-Cardenas, A. Torres-Robles, F. S. Tonin, F. Fernandez-Llimos, and S. I. Benrimoj. 2019, 'Temporal effectiveness of interventions to improve medication adherence: A network meta-analysis', *PloS One,* vol. 14, no. 3, e0213432

Williams, A.B., Amico, K.R., Bova, C. & Womack, J.A. 2013, 'A proposal for quality standards for measuring medication adherence in research', *AIDS and behavior*, vol. 17, no. 1, pp. 284-97.

Zedler, B.K., Kakad, P., Colilla, S., Murrelle, L. & Shah, N.R. 2011, 'Does packaging with a calendar feature improve adherence to self-administered medication for long-term use? A systematic review', *Clin Ther*, vol. 33, no. 1, pp. 62-73.

Appendices

A. Negligible Risk Ethics Approval

Dear Applicant

Project title: Analysis of retrospective medication adherence data

You have declared your research as Nil/Negligible Risk and that it DOES NOT include any of the following:
* Establishment of a register or databank for possible use in future research projects
* Collection, transfer and/or banking of human biospecimens
* Any significant alteration to routine care or health service provided to participants
* Interventions and therapies, including clinical and non-clinical trials, and innovations
* Targeted recruitment or analysis of data from any of the participant groups listed in Chapter 4 of the National Statement (or where any of these participants are likely to be significantly over-represented in the group being studied) including:
  - Women who are pregnant and the human fetus
  - Children and young people (under 18 years)
  - People in dependent or unequal relationships
  - People highly dependent on medical care who may be unable to give consent
  - People with a cognitive impairment, an intellectual disability, or a mental illness
  - People who may be involved in illegal activities (including those affected)
  - Aboriginal and Torres Strait Islander Peoples
* Collection, use or disclosure of personal information (except where expert opinion is being canvased with full disclosure, consent and identification for use in the public domain)
* Collection, use or disclosure of health information
* Collection, use or disclosure of sensitive information
* Covert observation, active concealment, or planned deception of participants
* Activity that potentially infringes the privacy or professional reputation of participants, providers or organisations (except where expert opinion is being canvased with full disclosure, consent and identification for use in the public domain)
* Potential for participants to experience harm (e.g. physical, psychological, social, economic and/or legal)
* Direct contact with UTS staff/students, patients, consumers or members of the public (except where expert opinion is being canvased with full disclosure, consent and identification for use in the public domain)
* Participants who have a pre-existing relationship with the researcher (except where expert opinion is being canvased with full disclosure, consent and identification for use in the public domain)
* People unable to give free informed consent due to difficulties in understanding the Information Sheet or Consent Form
* People in other countries

PLEASE NOTE: If at any time, the scope of your research changes to include one or more of the above categories, you are immediately required to submit a new application.
To access the National Statement on Ethical Conduct in Human Research, visit the NHMRC webpage: https://www.nhmrc.gov.au/guidelines-publications/e72

Please keep a copy of your Declaration form on file to show you have considered the risks associated with your research. You should **consider this your official letter of approval**.

For tracking purposes, you have been provided with an ethics application number, which is UTS HREC ETH18-2312N.

I also refer you to the AVCC guidelines relating to the storage of data, which require that data be kept for a minimum of 5 years after publication of research. However, in NSW, longer retention requirements are required for research on human subjects with potential long-term effects, research with long-term environmental effects, or research considered of national or international significance, importance, or controversy. If the data from this research project falls into one of these categories, contact University Records for advice on long-term retention.

Instructions for saving the declaration form can be downloaded from:
https://staff.uts.edu.au/howdoi/Pages/Researching/Research%20ethics%20and%20Integrity/Human%20research%20ethics/submit-my-human-research-ethics-application.aspx

To access this application, please follow the URLs below:
* if accessing within the UTS network: https://rm.uts.edu.au
* if accessing outside of UTS network: https://vpn.uts.edu.au, and click on ""RM6 - Production"" after logging in.

If you have any queries about this approval, please do not hesitate to contact your local research office or Research.Ethics@uts.edu.au.

Kind regards

UTS HREC Ethics Secretariat
C/- Research & Innovation Office
University of Technology Sydney
E: Research.Ethics@uts.edu.au
https://staff.uts.edu.au/topichub/Pages/Researching/Research%20Ethics%20and%20Integrity/Human%20research%20ethics/human-research-ethics.aspx
PO Box 123, BROADWAY NSW 2007
[Level 14, Building 1, Broadway Campus]

REF: Ethics 2 -Neg Risk approved (c)