UTS UNIVERSITY OF TECHNOLOGY SYDNEY

Economic Evaluation of Pharmacist-led Medication Review in the Primary Health Care Centres in Chile

Thesis

Antonio Osvaldo Ahumada Canale

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Doctor of Philosophy

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

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CERTIFICATE OF ORIGINAL AUTHORSHIP

I Antonio Osvaldo Ahumada Canale 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.

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Abstract

Background: Cardiovascular diseases (CVD) pose a burden on healthcare systems. There is evidence that pharmacist-led medication review with follow-up (MRF) improves therapeutic goal achievement in CVD risk factors, such as hypertension, type 2 diabetes mellitus and dyslipidaemia.

Objectives: To evaluate the economic impact of MRF added to Chilean primary care in CVD risk factors, by assessing the cost-effectiveness in older adults.

Methodology: A systematic review was conducted to evaluate the economic evaluations of pharmacist-led MRF in outpatients with CVD risk factors. Recommendations were generated to design a cluster randomised controlled trial (cRCT).

A cRCT was conducted in public primary care centres (clusters) in Chile to study the effect of MRF added to usual care compared to usual care alone. Older adults with five or more prescriptions, moderate or high CVD risk and enrolled in a primary care CVD prevention program were included. The intervention had three components: Pharmacists' training, MRF, and a practice change facilitator. Patients were followed-up for a year. For the economic analysis, health-related quality of life (HRQoL) was measured and was used to estimate quality-adjusted life-years (QALYs). Costs were evaluated form the public third-party payer perspective and were measured as 2019 United States dollars (USD). A cost-effectiveness threshold of 16,207 USD was used.

A trial-based cost-utility analysis was performed. Costs and QALYs were estimated through a multilevel model that accounted for clustering and covariates, while missing data was addressed using multiple imputation. Uncertainty was evaluated through a non-parametric bootstraping. As a second analysis, a state-transition microsimulation model was developed to extrapolate outcomes

to a lifetime time horizon. Patient-level data was used to derive the model's probabilities. Deterministic and probabilistic sensitivity analyses were performed.

Results: Eleven studies were included in the systematic review. Eight found the intervention to be cost effective, while two found it to be dominant. Both, the trial-based and model analyses deemed the intervention as cost-effective. Incremental cost-effectiveness ratios of $434/QALY and $751/QALY respectively, were found. The trial-based analysis found increased dominant iterations when patients with more than nine medications were evaluated. In the model, a difference between groups of 5.9% in CVD mortality was observed. Sensitivity analyses showed either cost-effectiveness or dominance.

Conclusion: International evidence shows that MRF was value for money in outpatient settings. An adapted MRF method was deemed as a cost-effective addition to primary care in Chile with low uncertainty. Formal implementation should be considered by policy makers.

Dissemination of Research

Peer-reviewed publications

1. **Ahumada-Canale A**, Quirland C, Martinez-Mardones FJ, Plaza-Plaza JC, Benrimoj S, Garcia-Cardenas V. Economic evaluations of pharmacist-led medication review in outpatients with hypertension, type 2 diabetes mellitus, and dyslipidaemia: a systematic review. Eur J Heal Econ; 2019; 20(7): 1103–16.
2. **Ahumada-Canale A**, Vargas C., Martinez-Mardones FJ, Plaza-Plaza JC, Benrimoj S, Garcia-Cardenas V. Cost-utility Analysis of a Medication Review for Cardiovascular Outcomes: A Microsimulation Model. (SUBMITTED TO VALUE IN HEALTH (VIH-2020-0114))
3. **Ahumada-Canale A**, Vargas C., Balmaceda C. Martinez-Mardones FJ, Plaza-Plaza JC, Benrimoj S, Garcia-Cardenas V. Medication Review with follow-up for Cardiovascular Outcomes: A Trial based Cost-utility Analysis. (SUBMITTED TO CIRCULATION (CIRCULATIONAHA/2020/046444))
4. Martínez-Mardones F, Fernandez-Llimos F, Benrimoj SI, **Ahumada-Canale A**, Plaza-Plaza JC, S Tonin F, et al. Systematic review and meta-analysis of medication reviews conducted by pharmacists on cardiovascular diseases risk factors in ambulatory care. J Am Heart Assoc. 2019; 8(22):e013627.
5. Martínez-Mardones F, Benrimoj SI, **Ahumada-Canale A**, Plaza-Plaza JC, Garcia-Cardenas V. Clinical impact of medication reviews with follow-up in cardiovascular older patients in primary care: the Polaris trial, a cluster-randomized controlled trial. (UNDER REVIEW IN CIRC CARDIOVASC QUAL OUTCOME (CIRCCQO/2020/006575)).

6. Martínez-Mardones F, Benrimoj SI, **Ahumada-Canale A**, Plaza-Plaza JC, Venegas-Araneda P, Garcia-Cardenas V. Medication reviews with follow up on older patients with chronic kidney disease and cardiovascular risk factors: a cluster randomized controlled trial. (UNDER REVIEW IN EUR HEART J (EURHEARTJ-D-20-00680))

Authorship on national clinical guidelines

1. **Ahumada-Canale, A**., Martinez-Mardones, F.J., Plaza-Plaza, Valdés, C. Manual for conducting medication reviews with follow-up in primary care centres, 2019. Web source: https://www.sscoquimbo.cl%2Fgob-cl%2Fdocumentos%2Ffiles%2Finred%2Ffarmacia%2F28-05-2018%2FAtencion%2520Farmaceutica%2520y%2520SFT%2520en%2520APS%25202018.pdf&usg=AOvVaw1TAA8qfegTMfl0vakLIznd
2. **Ahumada-Canale, A**., Martinez-Mardones, F.J., Plaza-Plaza. Technical guidelines for the implementation of medication reviews in primary care. Chilean Ministry of Health, 2018. Web source: http://quimica.uc.cl/images/noticias/2019/2019_07_12_MANUAL-SEGUIMIENTO-FARMACO-TERAPEUTICO1_compressed.pdf

Conferences proceedings

1. 11th Health Services and Policy Research Conference by the Health Services Research Association of Australia & New Zealand. December 4-6 2019, Auckland, New Zealand. Oral presentation.

   Cost-utility analysis of pharmacist-led medication review in primary care patients with hypertension, type 2 diabetes mellitus and dyslipidaemia .

   Ahumada-Canale A, Martinez-Mardones FJ, Plaza-Plaza JC, Benrimoj S, Garcia-Cardenas V.

2. 2º *Simpodader Internacional*. June 29 – 30th, 2018. Granada, Spain. Poster.

Economic Evaluations of Pharmacist-led Medication Review in Cardiovascular Diseases Risk Factors: Systematic Review.

Ahumada-Canale A, Quirland C, Martinez-Mardones FJ, Plaza-Plaza JC, Benrimoj S, Garcia-Cardenas V.

3. 1st International Conference Pharmacy practice research: postgraduate students, postdoctoral fellows and supervisor's symposium conference organised by the International Pharmaceutical Federation special interest group on pharmacy practice research. June 25 – 27th, 2018, Lisbon, Portugal. Three-minute thesis presentation.

   Pharmacist-led Medication Review with follow-up on elderly patients in cardiovascular disease risk factors using polypharmacy: A pilot study.

   Antonio Ahumada, José Plaza-Plaza, Shalom Benrimoj, Victoria García-Cárdenas.

4. XXXIII Public Health Conference of the University of Chile. January 10-12th, 2018, Santiago, Chile. Poster.

   A pilot study of a pharmacist-led medication review with follow-up program in older adults with polypharmacy of a cardiovascular prevention program in Chilean primary care.

   Ahumada-Canale A, Martinez-Mardones FJ, Vielma C, Ebensperger R, Plaza-Plaza JC, Benrimoj S, Garcia-Cardenas V.

Invited presentations

1. A pilot study of a pharmacist-led medication review with follow-up program in older adults with polypharmacy of a cardiovascular prevention program in Chilean primary care. 1st San Bernardo Municipality Health Scientific Meeting. August 31st, 2018. Santiago Chile.
2. Pharmacist-led Medication Review with Follow-up: The Polaris Trial. Public Health Institue Annual Meeting. November 30th, 2017. Santiago, Chile.

3. Pharmacist-led Medication Review with Follow-up: The Polaris Trial 1st Valparaiso and San Antonio Health Service Administration Pharmacist Meeting. October 22nd , 2018. El Tabo, Chile

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Finally, to my wife Fabiola, thank you for your unconditional love, support and patience along this journey. To my parents that allowed me to be where I am today, teaching me the values and principles to find my way through life. To my colleagues, especially Carmen and Elyssa, for always

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Preface

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

This document was structured as a thesis by compilation. Chapter 1 presents a synopsis describing the general approach of this thesis and research. Chapter 2 provides the background for cardiovascular diseases' clinical and economic impact, particularly in Chile. Medication review with follow-up is proposed as a clinically effective strategy to address cardiovascular risk factors. Chapter 3 introduces the basic concepts of economic evaluations in healthcare and contains a published systematic review of pharmacist-led medication review conducted in outpatients with cardiovascular risk factors such as, hypertension, type 2 diabetes mellitus and dyslipidaemia. This study frames the current state of cost-effectiveness analyses in the area, and a quality assessment to provided recommendations for future research. Chapter 4 describes the methods of the Polaris trial, a cluster randomised controlled study that included older adults with cardiovascular risk factors in Chilean primary care. This trial was a collaboration between UTS, the Pontifical Catholic University of Chile, and the Chilean government. A description of the Polaris method of MRF is presented. Chapter 5 and 6 contain submitted papers of a trial-based cost-effectiveness analysis and a decision-analytic model, using the Polaris trial results. Chapter 7 discuss the research outputs, explores limitations of each study, addresses transferability to other settings and proposes future directions. Chapter 8 presents conclusions arising from this research.

Antonio Osvaldo Ahumada Canale is the primary author of the publications. Co-authors contributed to the conception or design of the work, data collection, data analysis and interpretation, and/or revision of the manuscripts.

Contents

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Abbreviations

ADR: adverse drug reactions

CAD: Canadian dollar

CI: confidence interval

CKD: chronic kidney disease

cRCT: cluster randomised control trial

CVD: cardiovascular diseases

DBP: diastolic blood pressure

DALY: disability-adjusted life-years

DLP: dyslipidaemias

EQ5D: EuroQoL-5D

EU: European Union

FONASA: *Fondo Nacional de Salud*

GP: general practitioner

HbA1c: glycated haemoglobin

HDL: high density lipoprotein

HF: heart failure

HTN: hypertension

HRQoL: health-related quality of life

ICC: intra-class correlation

ICER: incremental cost-effectiveness ratio

IHD: ischaemic heart disease

ISAPRE: *Institución de Salud Previsional*

LDL: low-density lipoprotein

LMICs: Low and middle-income countries

MRF: medication review with follow-up

MTM: medication therapy management

NCDs: non-communicable diseases

OR: odds ratio

PAHO: Pan American Health Association

PCNE: Pharmaceutical Care Network Europe

PCF: practice change facilitator

PI: prediction interval

PUC: *Pontificia Universidad Católica de Chile*

PW: Pharmacotherapy workup

QALYs: quality-adjusted life-years

RCT: randomised controlled trial

RN: registered nurse

SBP: systolic blood pressure

T2DM: type 2 diabetes mellitus

TC: total cholesterol

TG: triglycerides

TIDieR: template for intervention description and replication

UTS: University of Technology Sydney

USD: United States dollars

Chapter 1

Synopsis

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1.1 Research Overview

Chapter 1: Synopsis

Rationale for this work and the research's objectives are explored.

Chapter 2: International and Local Impact of Cardiovascular Diseases

An international background of the impact of cardiovascular disease on mortality, disability-adjusted life-years, and morbidity, as well as the resultant economic burden is reported. The Chilean cardiovascular context is presented and the healthcare system is described. Pharmacist-led medication review with follow-up is presented as an effective alternative to usual care to improve therapeutic objectives attainment in risk factors such as hypertension, type 2 diabetes mellitus and dyslipidaemia.

Chapter 3: Economic Evaluations of Pharmacist-led Medication Review

An overview of basic concepts of cost-effectiveness analysis along with a published systematic review of economic evaluations of pharmacist-led medication review in cardiovascular risk factors is provided.

Chapter 4: The Polaris Trial

Methods of the cluster randomized controlled trial are described. This trial included older adults, with more than five prescribed medications, with moderate or high cardiovascular risk, and members of a cardiovascular prevention program. This was conducted between January 2018 and May 2019 in 12 primary care centres in Chile. For this trial, an adapted method of medication review was developed and is described.

Chapters 5 and 6: Economic Evaluation of the Polaris Trial

Chapter 5 is a submitted article that describes the methods and results of the cost-utility analysis alongside the Polaris trial. This analysis uses utility values and costs measured directly from the study. Costs were evaluated from the public third-party payer perspective.

Chapter 6 is a submitted article describing the methods and results of a decision-analytic model that uses inputs from the literature and the Polaris trial. A state-transition microsimulation model was developed to extrapolate costs and utilities over a lifetime time horizon from the public third-party payer perspective.

Chapter 7 and 8: Discussion and Conclusion

Chapter 7 presents the discussion for this research, limitations, transferability issues and future directions in research.

Chapter 8 presents the conclusions obtained as outputs of this research project.

1.2 Rationale

Traditionally, the role of community pharmacists in Chile has been limited to the management and supply of medications. Public primary care was an unexplored field for pharmacy practice, even though this sector cares for 80% of Chilean population and every centre has its own pharmacy unit. By 2014, only 8% of primary care centres had pharmacists.

Cardiovascular diseases in Chile are the leading cause of mortality and the main cause of health expenditure. Currently cardiovascular risk factors are treated at the primary care level. Local research shows that patients with cardiovascular risk factors are generally not optimally managed. Patients who receive treatment, usually do not reach therapeutic objectives to effectively prevent cardiovascular events. The government, being aware of this challenge implemented over 20 years

ago the cardiovascular prevention program. Although these policies improved cardiovascular results, there is still a significant number of patients that do not achieve therapeutic goals in order prevent cardiovascular events such as stroke or myocardial infarction. In 2015, the pharmacy fund was created to support and increase access to medicines for hypertension, type 2 diabetes mellitus and dyslipidaemia in primary care. To assist in the supply and rational use of medicines, pharmacists were employed to manage pharmacy units in primary health care centres. However their clinical role was not clear and local research to guide this was lacking.

To explore professional pharmacy services in primary care, in 2015 a randomised controlled trial in one centre, tested the addition of pharmacist-led medication review with follow-up to usual care. This study was conducted as part of a Bachelor's thesis by a pharmacy intern. The project recruited 212 older adults who were enrolled in the existing cardiovascular prevention program in primary care. Positive outcomes were observed in the control of hypertension and type 2 diabetes mellitus. Although, this work showed initial positive clinical evidence, it had limited impact on local authorities because it was limited to one centre, was performed by a pharmacy intern, and did not include any economic evidence to assess if this intervention represented value for money. Therefore, this research aimed to produce this evidence by conducting a multicentre cluster randomised controlled trial to explore the clinical effects and cost-effectiveness of the addition of medication review with follow-up to primary care in patients with cardiovascular risk factors.

1.3 Objective

To analyse the cost-effectiveness of medication review with follow-up in cardiovascular patients of primary health care.

1.4 Specific Objectives

- To review and analyse the evidence of economic evaluations of medication reviews in cardiovascular prevention of ambulatory patients.
- To design a medication review with follow-up service for older patients with cardiovascular risk factors adapted to primary care in Chile.
- To study the cost-effectiveness alongside a trial of a medication review with follow-up service for older patients with cardiovascular risk factors adapted to primary care in Chile from the public third-party payer perspective.
- To extrapolate to a lifetime time horizon the economic evaluation of a medication review with follow-up service for older patients with cardiovascular risk factors adapted to primary care in Chile from the public third-party payer perspective.

Chapter 2

Introduction and Background

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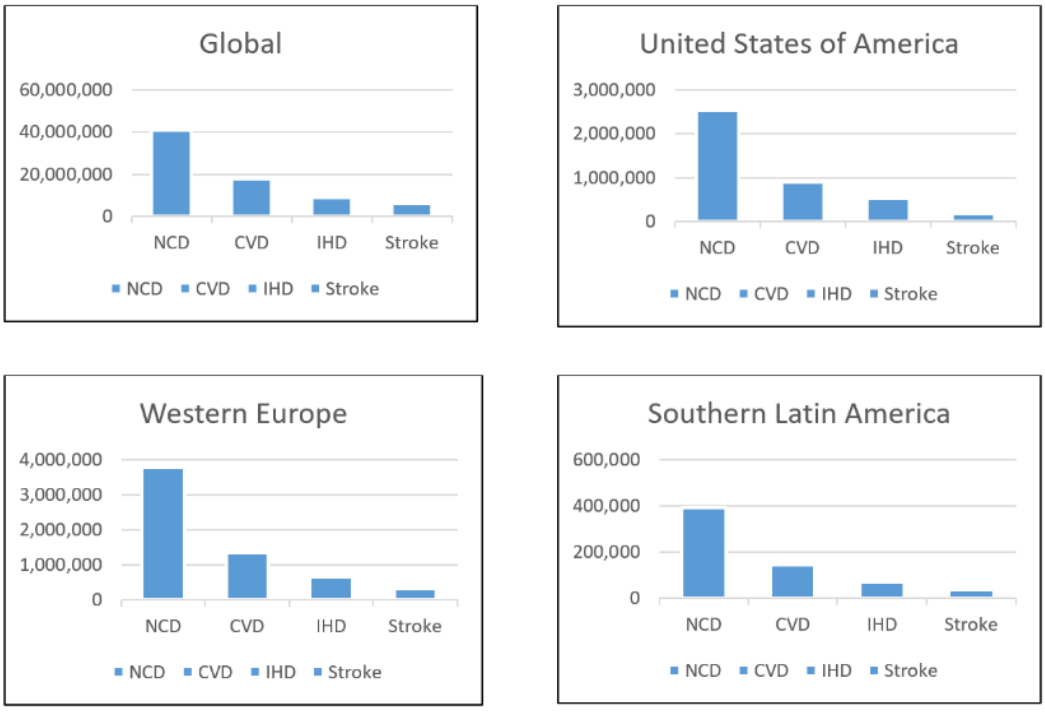
2.1 Cardiovascular diseases

2.1.1 Global Impact

The Global Burden of Disease Study in 2017 reported that non-communicable diseases (NCD) were the main driver of mortality causing 41.1 million deaths [1]. Main NCDs were cardiovascular diseases (CVD) that were defined as diseases of the heart, vascular diseases of the brain or blood vessels in general [1,2]. Worldwide, 17.8 million deaths or 43.3% of NCD related deaths were due to CVD and have increased by 21,1% from 2007 (14.7 million) to 2017 [1,3]. In 2017 Ischaemic heart disease (IHD) and stroke caused 8.9 and 6.2 million deaths respectively. These constituted 84.9% of all CVD related deaths [1,3]. An increasing trend in number of deaths is also observed from 2007 to 2017 from 7.3 to 8.9 million for IHD and from 5.3 to 6.2 million for stroke [1,3]. Similar trends are observed in different regions and countries (Figure 2.1).

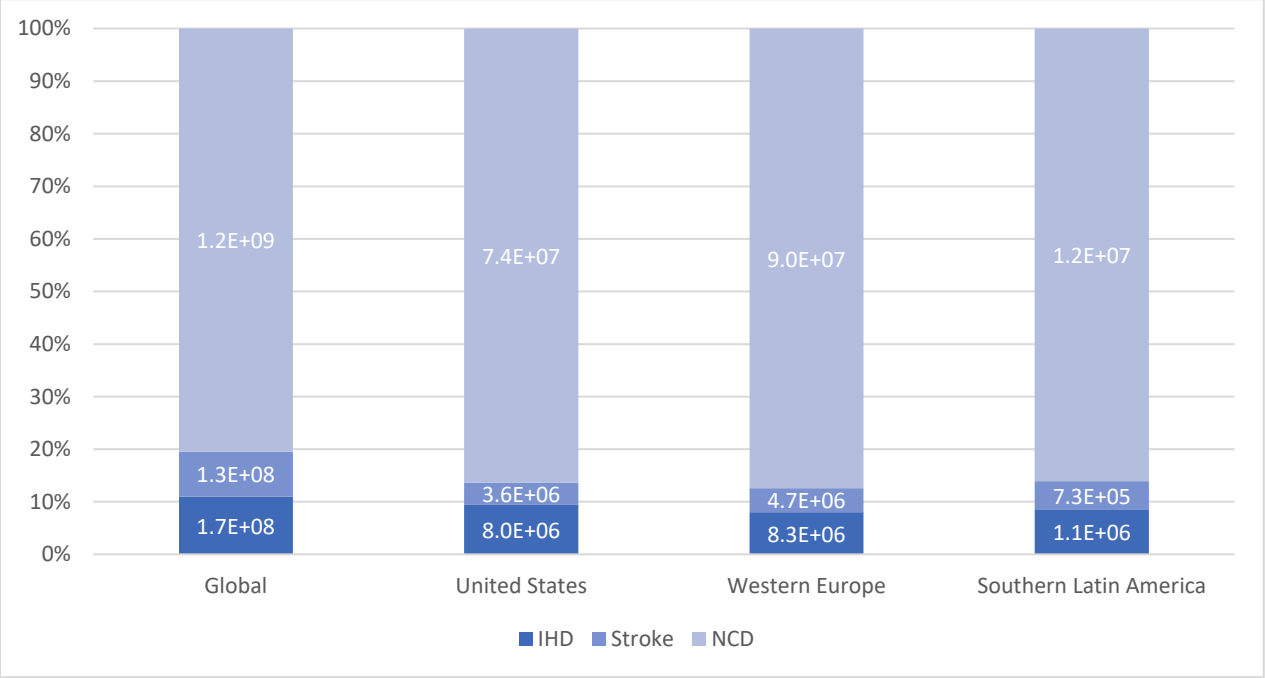
Figure 2.1. Deaths due to non-communicable or cardiovascular diseases [3].



Notes: NCD: Non-communicable diseases; CVD: Cardiovascular diseases: Cardiovascular disease; IHD: Ischaemic heart disease.

In 2017, NCDs were the leading cause of disability-adjusted life-years (DALY) causing 1.6 out of 2.5 billion, or 62.0% of all DALYs [4]. CVDs like stroke or IHD, not only cause death but also have health consequences for patients that survive an event. In this context, among NCDs the leading source of DALYs were IHD and stroke, resulting in 170 million and 132 million respectively. Both diseases were increasing in DALYs compared to 2007 generating previously 144 and 114 million respectively (Figure 2.2) [3,4].

Figure 2.2. Disability-adjusted life-years caused by non-communicable or cardiovascular diseases [3].



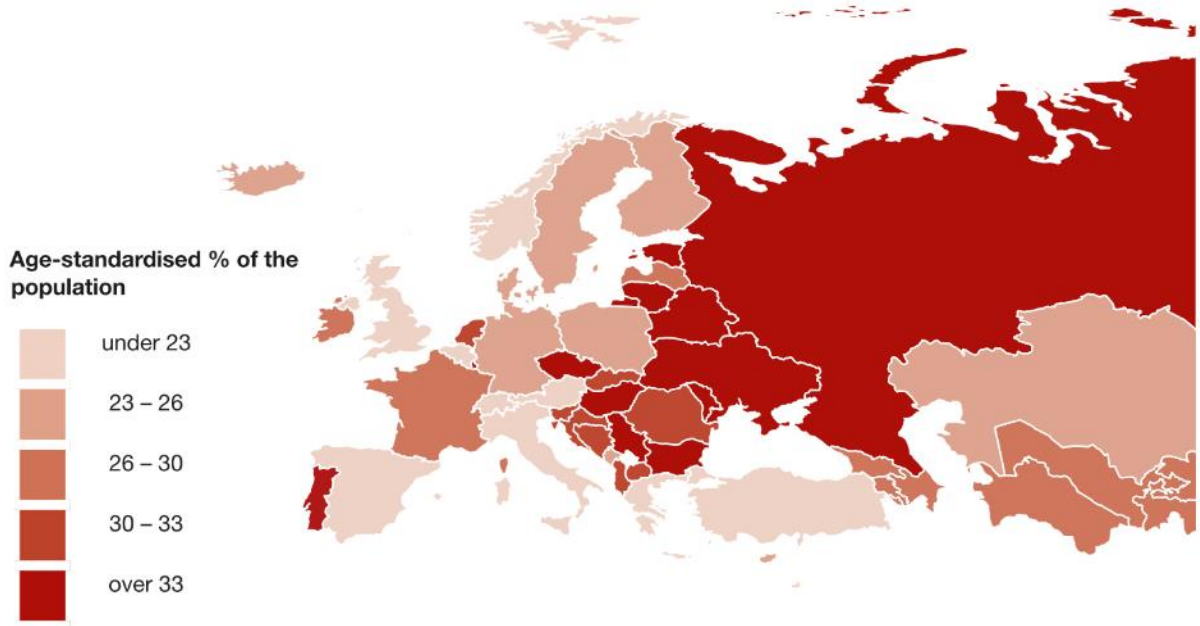
Notes: NCD: Non-communicable diseases; IHD: Ischaemic heart disease. NCD does not include IHD or stroke

2.1.2Risk Factors' Prevalence

Various risk factors make patients prone to IHD or stroke [5–7]. In the US it was estimated that 11.7% of adults have high total cholesterol, 28.5% have high LDL cholesterol, 46.0% have hypertension (HTN), 10.7% have diagnosed type 2 diabetes mellitus (T2DM), and 37.6% have pre-diabetes [8]. Similar results are reported for Europe with 23.6% [95%CI 21.5-25.7] of the population being

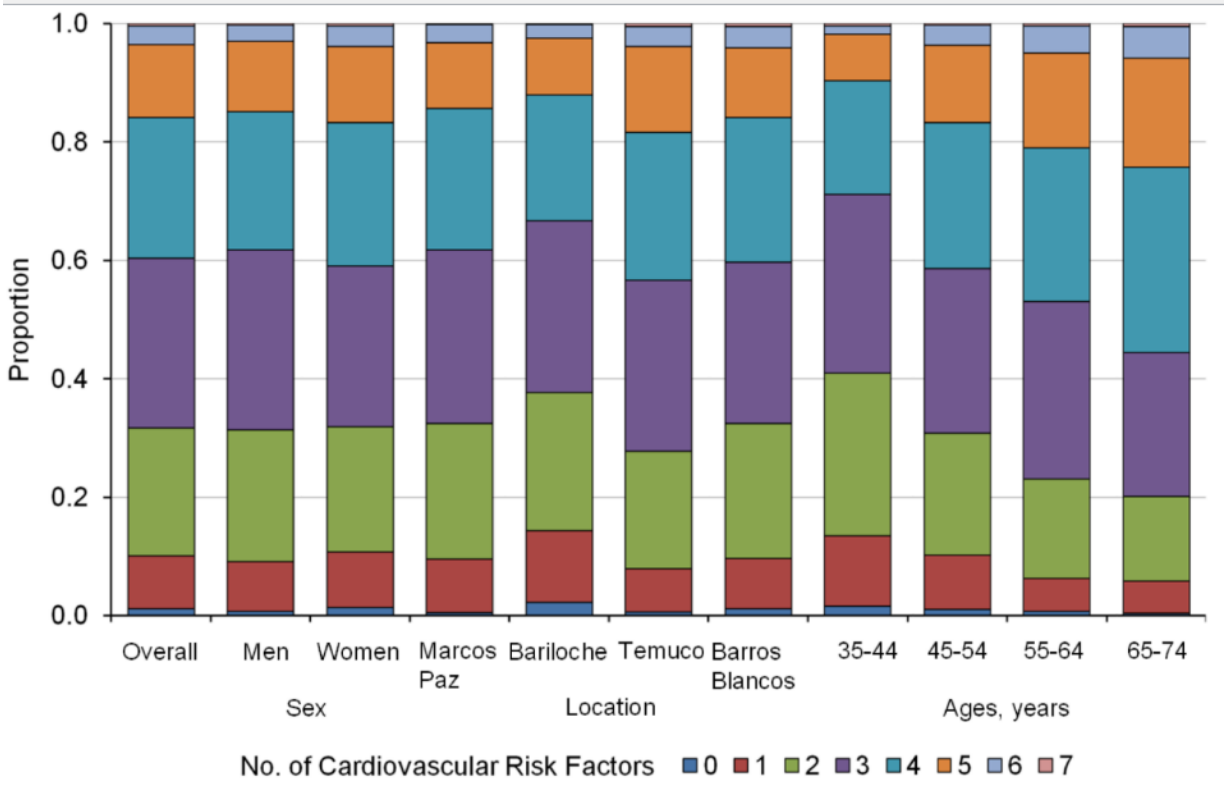
reported to be hypertensive (Figure 2.3), and 7.3% [95%CI 6.1-8.6] with T2DM [9]. In 2008, 53.7% [95%CI 48.1-58.8] of Europe had raised cholesterol levels [9] .

Figure 2.3. Prevalence of hypertension in male adults, Europe 2014 [10].



Patterns observed in The Unitised States and Europe have shown to be present in Latin America as well. The CESCAS study examined the prevalence of CVD risk factors in three southern Latin American countries, Argentina, Uruguay and Chile [11]. Risk factors included were HTN, chronic kidney disease (CKD), dyslipidaemias (DLP), T2DM, low consumption of fruit and vegetables, low physical activity, smoking and obesity. It was reported that in adults aged 35 to 74, 40.8% had HTN, 58.4% DLP, and 12.4% T2DM [11]. Most patients had multiple risk factors (Figure 2.4) thus increasing the risk of having IHD or a stroke, especially in aged population [11].

Figure 2.4. Number of concurrent cardiovascular risk factors stratified by sex, city and age [11].



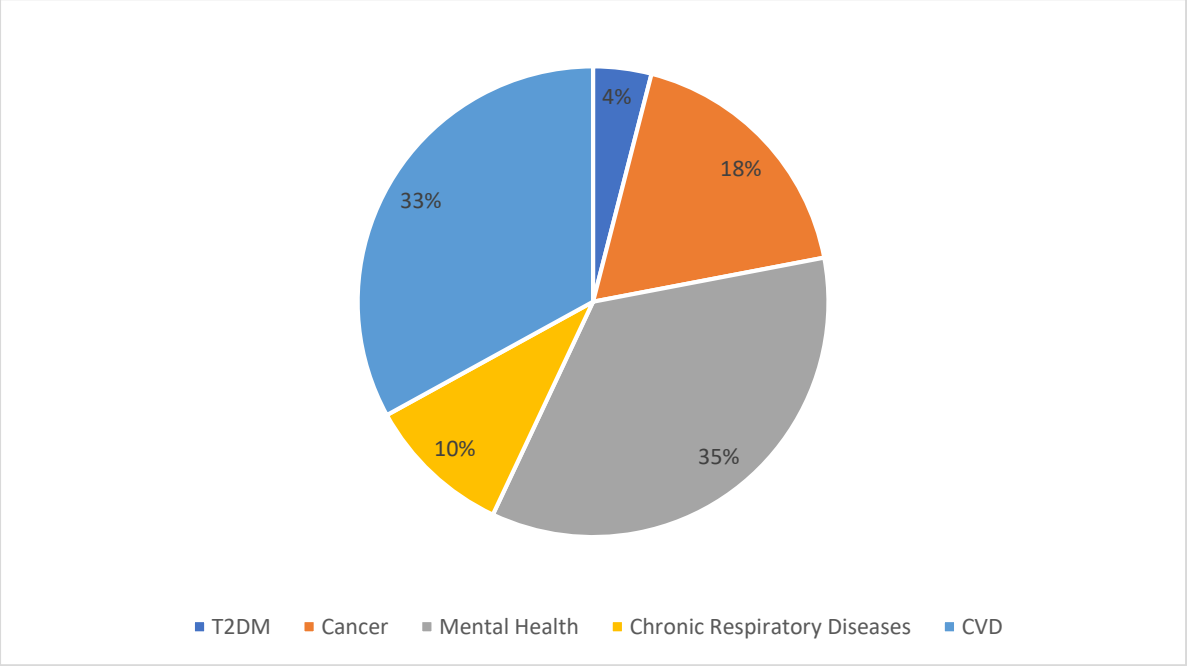
Further analysis established that population with cardiovascular risk factors had issues with disease awareness, treatment and control. Sixty-three percent of HTN patients knew that they had this risk factor, 48.7% had medicines prescribed for treatment, and 43.3% of those treated with medications achieved therapeutic objectives [12]. Twenty-one percent of patients among all HTN population reached their goals [12]. For T2DM, 79.8% of patients were aware of their condition, 73.6% of them received treatment, and 49.2% achieved target values [13]. Forty-six percent of patients achieved their goals among all diabetic population.

2.1.3 Economic Impact

The total global economic impact of NCDs from 2010 to 2030 has been calculated at 47 trillion United States dollars (USD) (Figure 2.5) [14]. Global costs for CVD were estimated to rise by 22% between 2010 and 2030, from 863 to 1044 billion USD [14]. These estimates included treatment of

IHD, stroke, heart failure and risk factors like HTN and DLP. Fifty-four percent (473.9 billion USD) were due to direct costs such as screening, prevention and hospital care, while 45.1% (389.6 billion USD) were due to indirect costs, mainly loss of productivity [14]. The data for T2DM was evaluated separately due to other complications particular to this disease. Worldwide, T2DM has costs impact of 500 billion USD that are expected to rise to 745 billion USD by 2030. This is comprised mainly of direct costs of 376 billion USD, representing 75.2% of total costs [14].

Figure 2.5. Non-communicable diseases' cost by disease type [14].

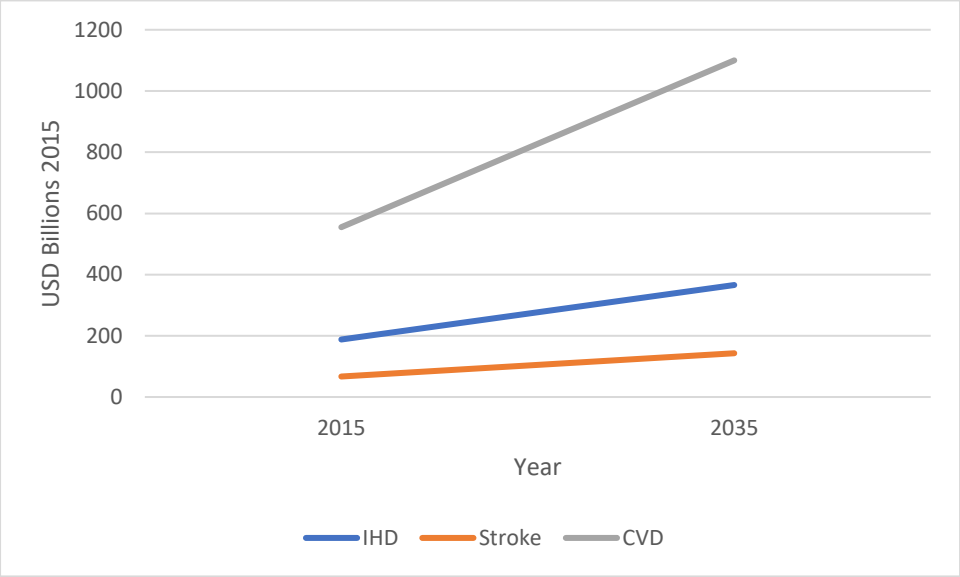


Notes: CVD: Cardiovascular diseases: NCD: Non-communicable diseases: T2DM: Type 2 diabetes mellitus

In 2014, United States' annual CVD costs were estimated at 351.2 billion USD. Direct costs were in 231.8 billion USD (physicians' and other professionals' fees, hospitalization, medicines and home health-care) and of indirect costs of 137.4 billion USD in forgone potential productivity loss attributed to premature mortality [8]. CVD accounted for 14% of the US health budget, that is the highest percentage for any disease group [8]. Direct costs have more than doubled between 1996 and

2013, from 103.5 billion USD to 213.8 billion USD [15]. Unless action is taken, it is estimated that between 2015 and 2035 this trend will increase [16]. Particularly in direct costs, increasing from 318 billion USD to 749 billion mainly driven by hospitalizations (Figure 2.6).

Figure 2.6. The United States cardiovascular diseases' cost projections [16].



Notes: IHD: Ischaemic heart disease: CVD: Cardiovascular diseases: USD: United States dollar.

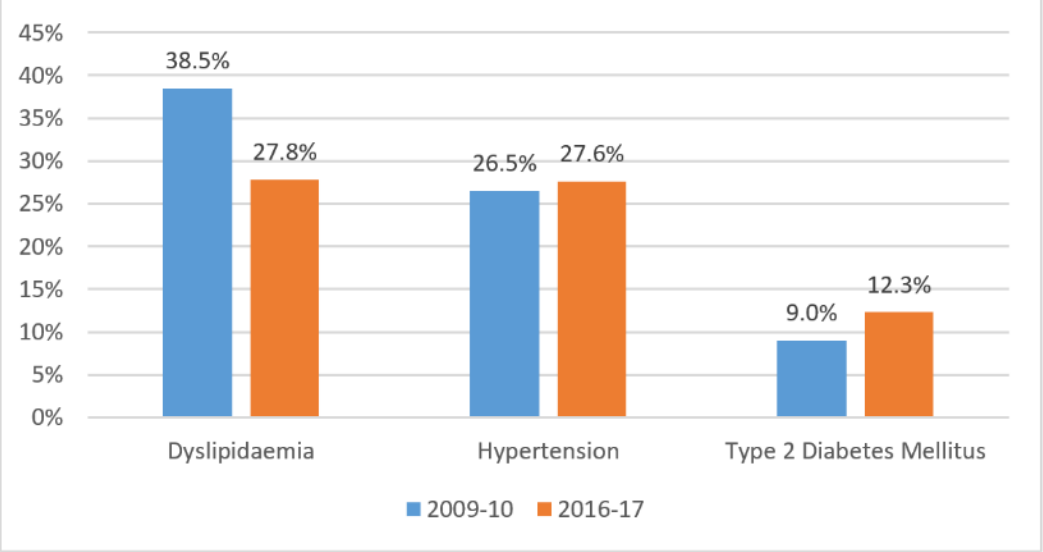
In 2015, it was reported that, in the European Union (EU), costs due to CVD accounted for €210 billion a year [10]. Fifty-three percent of these costs were due to direct medical costs, 26% due to productivity losses and 21% due to costs of dependent patients' informal care due to CVD events. Twenty eight percent of the overall cost of CVD were attributed to IHD, and 20% due to stroke [10]. Direct costs for CVD represent 8% of EU health care expenditure of which 18% were due to stroke and 17% due to IHD.

In the case of Latin America, CVD costs were of 26 billion USD with 8.8 billion attributed to direct costs and 17.2 billion to indirect costs [14]. Projections suggest that costs in low and middle-income countries (LMICs) such as those in regions like Latin America will rise at a similar level of high-income countries [14].

2.2 The Chilean Case

In 2016 the Chilean Ministry of Health reported that 26.7% of all-cause mortality was due to CVD, with 7.8% due to IHD, and 8.1% due to stroke [17]. The prevalence of CVD risk factors according to the two latest national health surveys of 2009-2010 and 2016-2017, show that although there was a decrease in prevalence of DLP over time, HTN remained stable, while T2DM increased (Figure 2.7) [18–20].

Figure 2.7. Cardiovascular risk factors prevalence in the Chilean population.



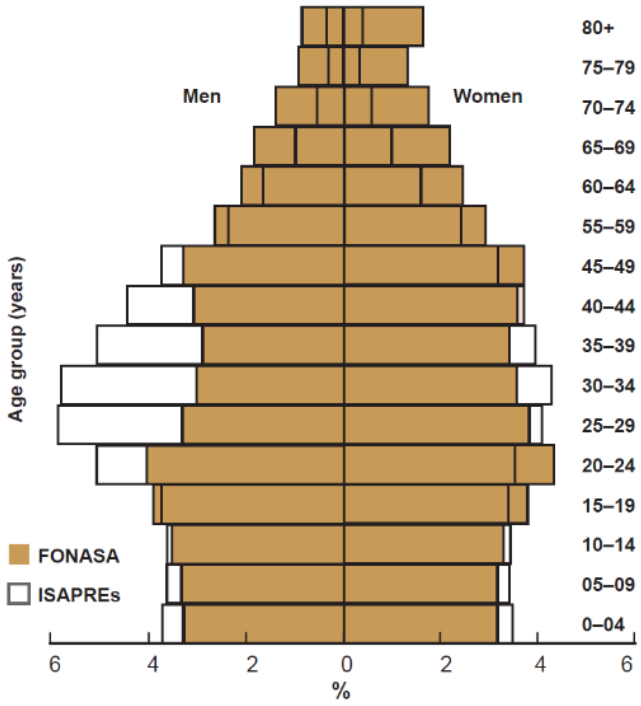
In addition, in the 2016-2017 survey, 40.1% of the population had metabolic syndrome. Also, 26.0% of the population had 5-10% 10-year coronary heart disease (CHD) risk according to Framingham tables adapted to the Chilean population, while 25.5% had risk higher than 10% risk [18,19,21].

2.2.1 Chilean Health Care System

Chileans can be covered by the public health insurance (*Fondo Nacional de Salud* or FONASA) or alternatively by various market-based private health insurance companies [22]. Those insured by FONASA have access to public facilities across all levels of care. Privately-insured patients can

choose between the various private providers. In 2017, 19.6% of the population was estimated to be cared by the private sector, while 80.4% was treated in the public health care system [23–25]. Castillo-Laborde et al. have described this healthcare system as unequal, as the insurance companies receive about 54% of health funding due to unregulated premiums that are adjusted by age and sex [26]. Reports have estimated that primary beneficiaries of the private system were younger (5.6% of older adults) working (71% vs 63% in FONASA) males (every 116 man there are 100 woman) (Figure 2.8) [22,27].

Figure 2.8. Patient age and sex distribution by insurance system [26].



Notes: FONASA: *Fondo Nacional de Salud,* National Public Health Fund. ISAPRE: *Institución de Salud Previsional*, private insurance.

For the public health care sector, patients' first contact point are primary care centres. These centres are regulated and supervised by the Chilean Ministry of Health but are administered by Municipalities [22]. Their care model is based on the family medicine model promoted by the World

Health Organization that recommends health care teams centred on patients, their family and the community. Every health care team has at least a general practitioner (GP), a registered nurse (RN), a dietitian, and administrative staff serving a geographically defined population [28]. Other health care professionals such as dentists, physiotherapists, clinical psychologists, and pharmacists can support this team but are not part of the core team [29].

In the context of increasing disease burden due to CVD and with a public system under financial pressure, in 2002, the Chilean Government created the CVD prevention program for primary care. Its main objective was: "reduce the incidence of CVD events through the control of risk factors in primary care, as well as to improve the management of CVD survivors with the aim to prevent premature morbidity and mortality and improve quality of life" [30]. Specific objectives were [30]:

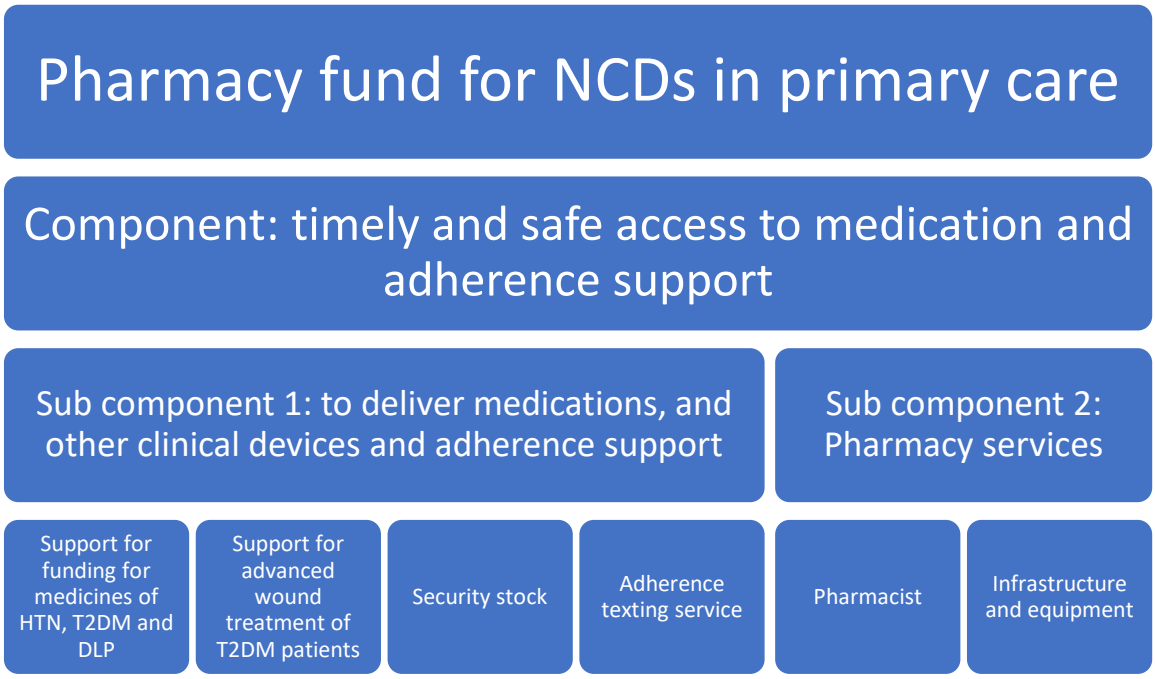
- Reduce CVD risk.
- Manage risk factors:
    - Achieve optimal blood pressure.
    - Improve metabolic control of patients with T2DM.
    - Improve cholesterol levels of DLP patients.
- Promote a healthy lifestyle.
- Prevent recurrent CVD events.
- Screening of high-risk of CKD patients.
- Approach families as the support unit that promotes behavioural changes of their members.
- Generate spaces for community dialogue to address population CVD risk factors.

From 2006 to 2017, it was reported that patients with HTN reaching blood pressure goals increased from 48% to 68% and patients with T2DM reaching their glycated haemoglobin goals increased

from 33% to 45% [31]. A study in 2018 evaluated "ideal" cardiovascular health in southern Latin American (Chile, Argentina and Uruguay) population concluding that there was a gap to be bridged in management. It was reported that twenty-three percent of the population had ideal blood pressure, 42.5% ideal total cholesterol, and 68.8% ideal fasting plasma glucose [32]. When all seven metrics were evaluated (smoking, body mass index, physical activity, diet, total cholesterol, blood pressure and fasting plasma glucose), 0.1% of that population had ideal values across all risk factors[32].

Aiming to improve CVD risk factors control, in 2015 the Chilean Government implemented the pharmacy fund for NCDs in primary care to guarantee continuity of care particularly improving access to medicines (Figure 2.9) [33]. These resources were focused mainly on medications for HTN, DLP and T2DM that are dispensed directly in the public primary care centres and without any out-of-pocket expenses to patients. Even though these centres have pharmacies, pharmacists were not included in their staff [22]. To bridge this gap, pharmacists were hired with the funding to manage the pharmacies and to promote the rational use of medicine through professional pharmacy services [33]. In 2018, it was reported that the fund added up to more than 103 million USD yearly [34].

Figure 2.9. Pharmacy fund scheme [33].



Notes NCD: Non-communicable diseases: HTN: Hypertension; DLP: dyslipidaemia; T2DM: Type 2 diabetes mellitus.

Once pharmacists were included in primary care centres, guidelines of the CVD prevention program identified them as a "complementary professional" that can aid to achieve the program objectives [30]. Three professional pharmacy services were also recommended in the guideline developed by the government: reconciliation of medications, prescription training for GPs and medication review with follow-up (MRF) [30].

2.3 Professional Pharmacy Services

According to the Pan American Health Organization (PAHO), professional pharmacy services based on primary care, should be focused on the individual, the family and the community [35]. This organization, defined these services as "*Actions in the health system seeking to guarantee integral, integrated and continuous care for individuals and communities' necessities and health problems, having medicines as one of the essential elements, contributing to equal access and rational use.*

These actions, carried out by pharmacists (or under his/her coordination) integrated to a health team and with communities involvement, have the objective to obtain concrete health results aiming to improve populations' quality of life" [35].

2.3.1 Medication Review

MRF is defined by the Pharmaceutical Care Network Europe (PCNE) as: "*a structured evaluation of a patient's medicines with the aim of optimising medicines use and improving health outcomes. This entails detecting drug-related problems and recommending interventions*" [36]. MRF has been classified into three basic types. These are described as follows [36,37]:

- Type 1 or simple: only medication history is available. It reveals drug interaction, some side effects, unusual dosage and some adherence issues.
- Type 2 or intermediate:
    - 2A: patients can be approached. It adds up on type 1 findings, and it reveals drug-food interactions, effectiveness issues and problems with over the counter medications.
    - 2B: GP information available. It adds up on type 1 findings and, it reveals drug-food interactions, effectiveness and indication issues.
- Type 3 or advanced: All information is available (medication history, GP information and patient is approachable). All drug-related problems can be potentially detected.

Research has shown that MRF is an effective strategy in CVD prevention. In 2017, Jokanovic et al. conducted an overview of systematic reviews of pharmacist-led MRF in community settings [38]. The search found 35 studies that overall reported improvements in medication management in HTN, T2DM and DLP. Meta-analyses reported improvements in glycated haemoglobin, blood pressure, cholesterol, CVD risk and number of appropriate medications. In addition, another meta-

analysis reported that MRF in CVD showed that therapeutic objectives were more likely to be achieved in HTN (odds ratio (OR) 2.73 95% prediction interval (PI) 1.05-7.08), T2DM (OR 3.11 95% PI 1.48-6.52) and total cholesterol (OR 1.91 95% PI 1.05-3.46) [39].

Although, there is evidence that MRF is effective achieving targets in CVD risk factors like HTN, T2DM, and DLP, implementation of new interventions requires changes in resource allocation. In these situations, an evaluation of the opportunity cost (the benefits and costs not only of the target intervention but also of other alternatives forgone [40]), is needed, especially in publicly funded health systems where resources are scarce. To evaluate this, economic evaluations of relevant alternatives are required.

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Chapter 3

Economic Evaluations of Medication Review in Cardiovascular Diseases Outcomes

Ahumada-Canale A, Quirland C, Martinez-Mardones FJ, Plaza-Plaza JC, Benrimoj S, Garcia-Cardenas V. Economic evaluations of pharmacist-led medication review in outpatients with hypertension, type 2 diabetes mellitus, and dyslipidaemia: a systematic review. *Eur J Heal Econ*. 2019;20(7):1103-1116. doi:10.1007/s10198-019-01080-z

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3.1 Economic Evaluations

As any health intervention in an era of scarce resources, MRF has to compete against other health technologies for funding to be included in health policies and expenditure. The data has to prove to decision-makers who usually face questions on resource allocation, that any new interventions are better value for money than relevant competing alternatives. To inform these choices, it is necessary to evaluate the opportunity cost. This type of analysis is usually referred to as an economic evaluation. It is defined as "*the comparative analysis of alternative courses of action in terms of both their costs and consequences*" [40]. Economic evaluations' main objective is to inform decisions, making a scientific and social value appraisal. To do this, it identifies, measures, values and compares costs and consequences of pertinent interventions. It utilises the best available evidence from systematic reviews, meta-analyses, and clinical trials to get an estimation of the effect. This evidence is then combined with costs from local data sources. Depending on the perspective, these costs might accrue to patients, health centres, third-party payers, the government or societal [40].

Comparison of different programs is the cornerstone of full economic evaluations (if there is no comparison, they are called partial economic evaluation). There are three types of full economic evaluations and differ mainly in the benefits measured [40]:

- Cost-benefit analysis: outcomes are transformed into monetary units. This is done through assessment of willingness to pay for a specific health outcome.
- Cost-effectiveness analysis: Uses natural unit of effect, e.g. life-years gained, blood pressure control, adverse effects avoided, among others. Their nature limits comparisons across disease areas as it can only contrast the same outcome measured.

- Cost-utility analysis: Uses quality-adjusted life-years (QALYs) as outcome. This composite measure combines health-related quality of life (HRQoL) with survival. This means that quality of life, represented through a preference weight on a scale of 0 to 1, being 0 dead and 1 the best imaginable health, is adjusted by the length of time in that state [41]. HRQoL is usually measured through generic questionaries like the EuroQoL-5D (EQ5D) [42]. This instrument measures a composite of five dimensions: mobility, self-care, daily activities, pain/discomfort, and depression/anxiety. Responses describe the respondent health state which is then valued using country specific value sets that consider society's preferences [43]. The advantage of this analysis is that it can compare interventions of different nature. For example, it can be used to compare a professional pharmacy service with a heart surgery's medical device.

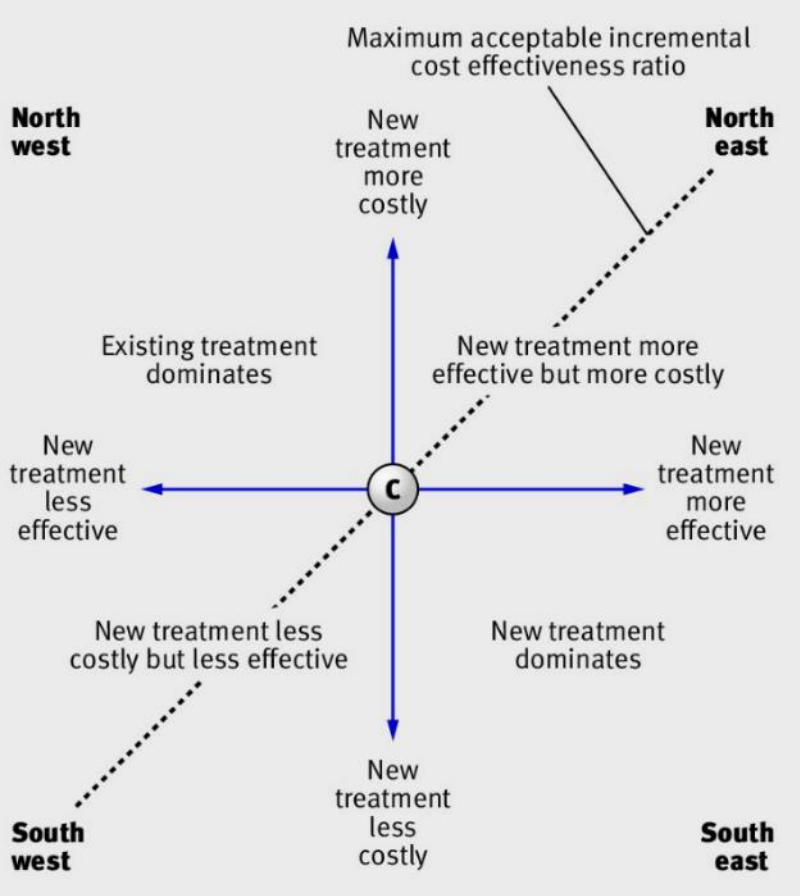
Cost-effectiveness and cost-utility analyses represent their results through incremental analysis, meaning that they compare differences between interventions in terms of costs divided by the difference of effects. The incremental cost-effectiveness ratio (ICER) represents this concept and is calculated as follows [40]:

$$\text{ICER} = \frac{Costs_A - Costs_B}{QALY_A - QALY_B}$$

The ICER yields four different scenarios that are represented in the cost-effectiveness plane (Figure 3.1) [44]. In the northwest quadrant, the intervention is less effective, and costs more than the comparator, therefore the intervention is dominated. In the southeast quadrant, the opposite is observed and the intervention is dominant. In the southwest quadrant, the intervention is less costly and less effective, and in the northeast quadrant, the intervention is more effective at higher costs. In this situation, it is necessary to establish a boundary that is defined as the cost-effectiveness threshold [45]. This value represents where and to whom opportunity costs fall. As healthcare services

aim to maximise health gains, and as generally health budgets are constrained, there are limitations to expenditure increase. Therefore, opportunity costs fall on the health sector representing the disinvestment needed to implement a new service [40]. To put it in practice, if we use a cost-effectiveness threshold of 30,000 USD per QALY, it means that 30,000 USD invested in healthcare are presumed to displace one QALY somewhere else in this sector.

Figure 3.1. Cost-effectiveness plane [46].



To conduct an economic evaluation, two sources of information or "vehicles" can be used: a single trial (also called "piggyback" economic evaluation) and decision-analytic modelling [40]. The first uses as source of all data a single clinical trial, usually a randomized controlled trial (RCT). While the latter combines available evidence from different sources to model a specific disease pathway.

This approach is used to inform a particular decision problem at a specific moment in time, in a defined setting and country [47].

Economic evaluations alongside a trial have as a strengths internal validity and that trials are widely used as a source of effectiveness data [46]. Nonetheless, this should be balanced with generalizability to represent real-life patients, and not only a limited sample of patients defined by inclusion and exclusion criteria [46]. If an economic evaluation alongside a trial had an appropriate comparator, used QALYs as a final outcome, enrolled a representative sample of the population, followed-up the sample long enough, collected sufficiently broad resource use data, was pragmatic, and collected data to assess transferability, it can be comprehensive enough to inform decision making[48].

On the other hand, if these conditions are not met, especially for limited time horizons, which is particularly important for chronic diseases, these limitations can be addressed through decision-analytic modelling [49]. Modelling combines evidence from several sources related to clinical outcomes and resource use, which can include, but are not limited to RCTs, cohort studies or surveys. This approach gives a structure to decision-making under uncertainty. According to Drummond et al. they have the particularity that: "they can compare all options, reflect all available and relevant evidence, can link intermediate to final end-points, can extrapolate over a relevant time horizon, and make it applicable to the jurisdiction" [40].

Different modelling techniques can be classified according to the type of data used (cohort vs individual-patient), and to the specific type of modelling. These are described as follows [50]:

- Cohort models: homogenous cohort data.
    - Decision tree.

    - Markov model.
    - Infectious diseases compartment model.
- Individual-patient microsimulation: calculates benefits and costs per individual patient, which then are aggregated to compute outcomes.
    - State-transition model.
    - Discrete-event simulation.
    - Agent-based model.

3.2 Cost-effectiveness of Medication Review in Cardiovascular Outcomes

In terms of economic evidence, there are published systematic reviews that address professional pharmacy services for CVD, including MRF, and these have shown positive results. A systematic review included clinical pharmacist interventions in patients with IHD, heart failure (HF) and risk factors like HTN, T2DM, DLP [51]. Inclusion criteria were studies based in RCTs and carried out either in a hospital, outpatient or community setting. Eight economic studies were found, seven in a community setting and one in an outpatient clinic. Four evaluated medicine management where cost savings were observed in T2DM control, HTN and DLP. Only two of them were full economic evaluations and were limited by lack of sensitivity analysis or because they had the economic evaluation as a secondary analysis of the clinical results. Another study focused on economic evaluations of pharmacist-led interventions on T2DM [52]. Studies were included regardless of the design (prospective and retrospective analyses and with or without a control group) and all types of professional pharmacy services with full or partial economic evaluations. Twenty-five studies were found of which 21 included MRF. Two studies considered a modelling approach and were cost-benefit analyses. Cost savings ranged from eight to 85,000 USD per person-year adjusted to 2014, while costs of avoiding diabetes-related CVD were between 62,803 and 114,576 USD. Mean

cost per one percent reduction of glycated haemoglobin was of 174 USD per person. One cost-utility analysis was found and deemed the intervention as dominant. Another systematic review analysed team-based care impact on blood pressure [53]. This multidisciplinary team was comprised of nurses, pharmacists or other health professionals collaborating with patients and GPs. Studies were included if they were carried out in high-income countries and in primary CVD prevention patients. All the interventions had medication counselling or MRF. Systolic blood pressure (SBP) values were transformed to QALYs gained over a 20-year time horizon. Median ICERs between 9,716 and 13,992 USD per QALY were observed. When this was calculated only for pharmacists, ICERs dropped to between 7,114 and 10,244 USD per QALY. It is important to note, that in two of these systematic reviews no decision-analytic models were found, while one found two modelling studies to address the decision problem. This becomes relevant, especially for CVD, as these events are usually estimated through longer periods than a trial (e.g. 10 years) and can have long-term sequelae.

There is evidence that pharmacist-led MRF is clinically effective in CVD prevention, mainly, in risk factors like HTN, T2DM and DLP. Since evidence from published literature is outdated and did not focus specifically on CVD prevention outpatients intervened with MRF, the first objective of this thesis was to conduct a systematic review in this topic.

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ORIGINAL PAPER

Economic evaluations of pharmacist-led medication review in outpatients with hypertension, type 2 diabetes mellitus, and dyslipidaemia: a systematic review

Antonio Ahumada-Canale[1] · Camila Quirland[2] · Francisco J. Martinez-Mardones[1] · José Cristian Plaza-Plaza[3] · Shalom Benrimoj[4] · Victoria Garcia-Cardenas[1]

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Abstract

Objectives To evaluate the health economics evidence based on randomized controlled trials of pharmacist-led medication review in pharmacotherapy managed cardiovascular disease risk factors, specifically, hypertension, type-2 diabetes mellitus and dyslipidaemia in ambulatory settings and to provide recommendations for future evaluations.

Methods A systematic review was carried out according to the Cochrane Handbook for Systematic Reviews. PubMed (Medline), Scopus, Web of Science, National Health System Economic Evaluation Database (NHS EED), Cochrane Library, and Econlit were searched and screened by two independent authors. Incremental cost-effectiveness ratio was the main outcome. Risk of bias was assessed with the Effective Practice and Organisation of Care tool by the Cochrane Collaboration. Economic evaluation quality was assessed with the he Consensus Health Economic Criteria list (CHEC list).

Results 5636 records were found, and 174 were retrieved for full-text review yielding 11 articles. Eight articles deemed the intervention as cost effective and two as dominant. Two cost–utility analyses were performed yielding ICERs of $612.7 and $59.8 per QALY. Four articles were considered to perform a high-quality economic evaluation and four had a low risk of bias. Future economic evaluations should consider cost–utility analysis, to describe usual care thoroughly, and use time horizons that capture the effect of cardiovascular disease prevention, a societal perspective and uncertainty analysis.

Conclusion Pharmacist-led medication review has proven to be cost effective in various studies in different settings. Policy decision makers are advised to undertake local economic evaluations reflecting the gaps observed in this systematic review and published literature. If this is not possible, a transferability assessment should be conducted.

Keywords Medication review · Pharmacist · Economic evaluation · Cardiovascular disease · Hypertension · Type 2 diabetes mellitus

JEL Classification I19

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✉ Antonio Ahumada-Canale
Antonio.o.ahumadacanale@student.uts.edu.au

[1] Graduate School of Health, University of Technology Sydney, Broadway, PO Box 123, Sydney, NSW 2007, Australia

[2] Oncology Institute, Arturo López Pérez Foundation, Santiago, Chile

[3] Facultad de Química y de Farmacia, Pontificia Universidad Católica de Chile, Santiago, Chile

[4] Emeritus Professor University of Sydney, Sydney, NSW, Australia

Introduction

Cardiovascular diseases (CVD) are a group of conditions encompassing coronary heart disease, cerebrovascular disease, and peripheral arterial disease [1]. The cost burden to healthcare systems of CVD includes direct and indirect costs [2, 3]. It is estimated that in the US alone, the cost of CVD accounts for more than $316 billion per year [2] and €210 billion per year in the European Union [3]. CVDs are caused by various factors including dyslipidaemia (DLP), hypertension (HTN), and type 2 diabetes mellitus (T2DM) which have been estimated to cost $34.8, $47.3, and $61.2 billion per year in the US [2].

Current medications used to control CVD risk factors are safe, effective, and supported by evidence-based treatment

guidelines [4–7]. In spite of worldwide efforts led by the World Health Organisation to prevent the development of CVD through integrated strategies of multi-sector policies on risk factors, control of these diseases has proven to be elusive [1]. These outcomes might arise due to patients, prescribers, and system failures.

From a pharmaceutical perspective, there are several issues that could be contributing including drug-related problems, medication errors, and non-adherence. For example, a study showed in Sweden that preventing drug-related problems (an event involving drug therapy that actually or potentially interferes with desired health outcomes [8]) could have potential cost savings of €358 million [9]. On the other hand, medication errors can be defined as "any preventable event that may cause or lead to inappropriate medication use or patient harm" [10], are a key component of drug-related problems, and can have costs that could be as high as €111,727.1 [11].

One intervention to address medication-related issues is medication reviews (MRs). These are defined as "a structured evaluation of a patient's medicines with the aim of optimising medicines use and improving health outcomes. This entails detecting drug-related problems and recommending interventions" [12]. There are three types of MRs which are classified according to the patients´ information available to the reviewer and hence the depth of the review. Simple or type 1 MR aims to identify drug interactions, some side effects, and some adherence problems and is based only on the medication history available in the pharmacy. Type 2 or intermediate MR uses patient interview or general medical practitioners (GPs) information in addition to the medication history. This review can detect some effectiveness and safety problems. Finally, Type 3 or advanced MR is the most comprehensive review that can detect most of medication-related issues and utilizes all previously cited sources of information [13]. Pharmacists have been performing MRs in various settings, showing promising results. In an overview of systematic reviews of community pharmacists, meta-analyses suggest positive impact on glycosylated haemoglobin (HbA1c), blood pressure, cholesterol, number and appropriateness of medications [14]. Positive results have also been observed in general practices, where pharmacists and GPs work together on the same health centre, showing benefits on systolic and diastolic blood pressure (SBP and DBP, respectively), HbA1c, cholesterol, and cardiovascular risk [15].

Professional pharmacy services targeting CVD risk factors management have also shown positive economic outcomes in systematic reviews [16–18]. A review targeting secondary prevention of CVD and heart failure reported clinical and economic outcomes of clinical pharmacist interventions for hospitalized patients and outpatients. All but one of the eight economic studies reported favourable results. However, not all studies were full economic evaluations (EE) [16]. Another study assessed team-based care, an intervention that includes interdisciplinary work of GPs, pharmacists, nurses, and other providers. They found a median incremental cost-effectiveness ratio (ICER) of $13,992 per quality-adjusted life years (QALY) [18]. For T2DM, a systematic review evaluated studies of pharmacist-led services (education, pharmacotherapeutic monitoring, health screening, immunization, and pharmacokinetics) and found a range of cost savings ranging from $8 to $85,000 2014 US dollars [17]. However, none of these systematic reviews addressed specifically full EE based on Randomized Controlled Trials (RCT) which are better suited to aid decision makers to adopt these services and, on the other hand, included various services provided by pharmacists [19]. Taking into account that positive clinical outcomes have been found for MR on CVD risk factor control, if this intervention proves to be cost effective, it might yield the possibility to avert costs or maximize the utility, where resources are scarce.

Therefore, the aim of this systematic review is to evaluate the health economic evidence based on RCTs of pharmacist-led MR in pharmacotherapy managed cardiovascular disease risk factors, specifically, HTN, T2DM, and DLP in ambulatory settings and to provide recommendations for future EEs.

Methods

The Cochrane Handbook for Systematic Reviews was followed [20]. For reporting purposes, the PRISMA statement was used [21]. The study protocol is published in PROSPERO (ID CRD42018085943).

Eligibility criteria

EEs were included if:

1. They were based on an RCT or cluster RCT.
2. Assessed the impact of any type of pharmacist-led MR compared to usual care [12].
3. Reported ICER (or data for calculation) from any perspective [22].
4. Included adult outpatients with HTN, T2DM, or DLP.

The exclusion criteria were:

1. Participants younger than 18 years.
2. Papers not written in English or Spanish.
3. Partial EEs, defined as evaluations that do not examine cost and consequences at the same time and/or do not compare at least two alternatives [22].
4. Studies that did not report at least pharmacists' cost.

Article retrieval and screening

The following databases were searched from inception to October 2018: PubMed (Medline), Scopus, Web of Science, National Health System Economic Evaluation Database (NHS EED), Cochrane Library, and Econlit. An example of the search strategy for PubMed is shown in Appendix 1 in Supplementary material. In addition, personal records were searched.

Screening of papers was undertaken by title and abstract review. This was done by two authors (AA and FM). The process was over inclusive, so only obviously irrelevant reports were removed. Any discrepancies were discussed to reach agreement. If this was not possible, a third researcher (VGC) was contacted. Included articles were retrieved and multiple reports of the same study were linked. Full-text papers were read and studies were selected according to the inclusion/exclusion criteria.

Data extraction, quality assessment, and analyses

A data extraction sheet was developed and piloted for data retrieval (Appendix 2 in Supplementary material). The main study outcome was ICER. If it was not stated in the original paper and data for calculation was available, it was computed when effects had a statistically significant difference [22]. For risk of bias assessment of RCTs on which the EEs were based, the Effective Practice and Organisation of Care (EPOC) tool was used [23]. Other risks of bias considered were blinding of data analysis. It was considered as high risk if researchers were also pharmacists. Studies were deemed as low risk of bias when they had at least six domains as low risk. Conversely, they were classified as high risk when five or more domains had high risk [24]. For quality assessment of EEs, the Consensus Health Economic Criteria list (CHEC list) was used [25]. If the evaluation was model-based, the Phillips checklist was applied [26]. The EEs were classified as high quality if they scored above 75%, medium quality between 51 and 74%, and low quality if scored below 50% [24]. Overall EE quality was categorized as high (+++), medium (++), or low (+) [24]. To categorize a study as high overall quality (+++), it had to be a high-quality EE and the RCT had to have a low risk of bias. Low overall EE quality (+) was stated if the EE quality was low or if the RCT had a high risk of bias. Medium quality was assigned (++) if the EE was considered as medium quality and it had medium or low risk of bias, or if it had medium risk of bias and high quality.

To compare results between countries, incremental costs and ICERs were transformed to a common year and currency (USD and 2016 prices) through the online tool developed by Cochrane Economics Methods Group and the Evidence of Policy and Practice Information and Coordinating Centre. This tool uses Purchasing Power Parities (PPP) to adjust estimates for costs and price year [27]. PPP values of the International Monetary Fund were used.

Results are presented in a summary table and in text. They were also synthesized through the permutation matrix [28]. This matrix has nine different possibilities classifying the interventions in terms of incremental costs (less costly, equal costs, or more expensive than the alternative) and incremental effectiveness (less effective, equal effectiveness, or more effective than the control intervention). Meta-analysis was not considered, because different resource uses and costs differ widely among countries or local settings [20].

Results

Study selection

5636 records were identified in the search, and after removal of duplicates, 4592 records were screened by title and abstract. Of them, 174 were retrieved for full-text review yielding 11 articles for data extraction and analysis, as described in Fig. 1. Most of the studies were excluded, because they were not based on an RCT or C-RCT.

Characteristics of included studies

Of the included studies, five were carried out in the US [29–33]. The remaining six were from Brazil [34], Canada [35], China [36], Nigeria [37], Taiwan [38], and the UK [39]. Two studies were implemented in community pharmacies [32, 39] and the rest in primary care centres [29, 30, 33–35] or hospital-based outpatient clinics [31, 36–38]. All the studies included follow-up of patients and all but one had at least one face-to-face interview [33]. Besides MR, two trials described comprehensive adherence interventions with other resources besides counselling. One of the trials gave pharmacists a standardised questionnaire to assess barriers to medication adherence with an algorithm to overcome them and provided patients a take-home toolkit that included a wallet card for recording blood pressure readings, a pillbox for 7 days, leaflets, and a pedometer [32]. The other trial by Chan et al. described an intervention that addressed adherence, knowledge and benefits, skills, perceived health, and cognitive functions [36]. Almost all the studies assessed type 3 MR, meaning that they undertook a comprehensive analysis, interviewing the patient and having access to their medication history and clinical records. There was one exception, where they did not had access to GP notes [32]. As for the methods of collaboration with GPs, in three trials, pharmacist provided a written report [32, 36, 39]. Other ways of communication were through electronic medical record [33], face-to-face meetings [30], and by telephone [31]. Seven

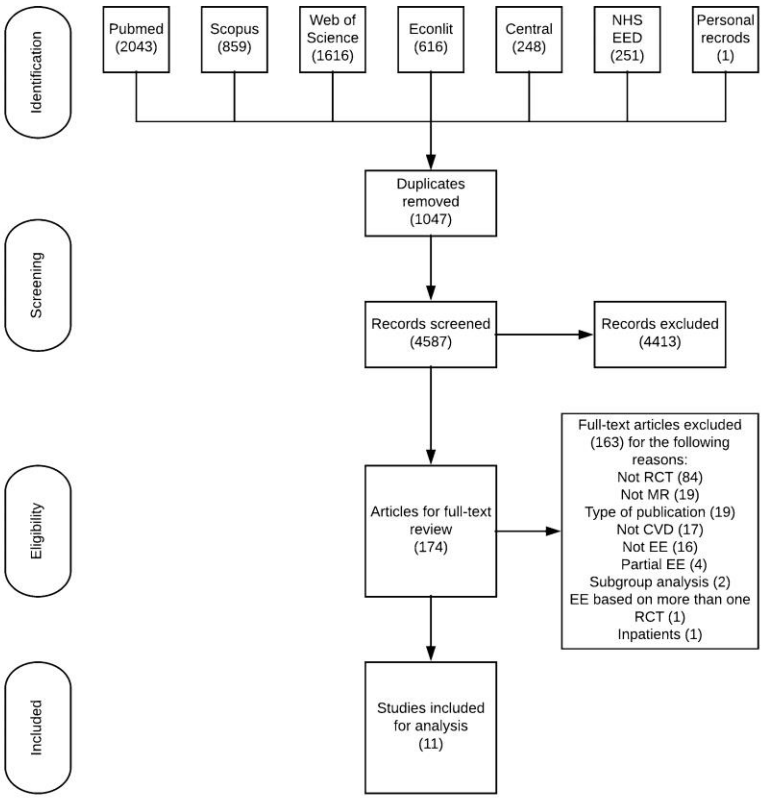

Fig. 1 Systematic review flowchart of study selection. *NHS EED* National health system economic evaluation database, *RCT* randomized controlled trial, *MR* medication review, *EE* economic evaluation, *CVD* cardiovascular diseases

trials reported the training of the pharmacists and differed widely from a certified diabetes educator to online training courses [30, 32–35, 38, 39].

In most of the trials, cost effectiveness of the interventions was described [29–33, 35, 36, 38, 39]. Two other studies developed a cost–utility analysis [34, 37]. Eight used the third payer perspective [31–35, 37–39], two adopted a societal point of view [29, 30] and one from a single provider standpoint [36]. Three studies did not state the perspective explicitly [29, 36, 39]. Eight studies quantified costs of medications [29–32, 34, 35, 37, 38], six of GPs time [30–32, 34, 37, 39], six hospitalizations [29, 32, 35, 37–39], and four emergency visits [29, 32, 34, 37]. Other costs evaluated were training of pharmacists [33, 39], materials for adherence interventions [32, 33, 37, 38], laboratory tests [37], and fixed costs [33]. Outcomes were presented in five studies as SBP [29–33], DBP [29–33], and HTN control [30–33, 39], three as quality of life [34, 37, 39], and two for CVD risk [35, 36]. Other outcomes reported were life years gained [33], refill adherence [32], and HbA1c [38]. In general, time horizons were no longer than 12 months, except for a study that lasted 36 months [34]. None of the included studies considered modelling. In addition, none declared competing interests with most receiving grants from governmental offices. One had financing from a pharmaceutical company [31] and another from a university [36]. A summary of trials characteristics can be found in Table 1.

Main findings

Findings are summarized in Table 2 and are represented graphically in Fig. 2. CVD risk was evaluated in two studies using different formulas. A study evaluated 5 year risk with an equation adapted for Chinese populations [36], whilst another used an annualized version of the United Kingdom Prospective Diabetes Study (UKPDS) [35], making them difficult to compare. The incremental effects of SBP and DBP varied from 11.0 [31] to 5.6 [32] mmHg and from 4.1 [33] to 1.0 [31] mmHg, respectively. HTN control ranged from 25 [33] to 9% [30]. Finally, when incremental QALYs were calculated, they ranged from 0.12 [37] to 1.32 [34]. On the other hand, incremental costs were less for the intervention

Table 1 Included studies characteristics

Authors	Design	Time horizon (months)	Study population	Intervention description	Effectiveness outcomes	Resources	EE type and perspective	Uncertainty treatment
Chan et al. [36]	Randomized controlled trial Intervention: 51 Control: 54	9	Patients 18 years or older, T2DM, at least 5 drugs (1 hypoglycaemic), haemoglobin A1c 8% or greater	MR with adherence intervention. Face-to-face interview with patient. Written reports were provided to the GPs	Cardiovascular risk	Pharmacist time	Cost effectiveness; single provider	NA
Bond et al. [39]	Randomized controlled trial Intervention: 941 Control: 500	12	Patients registered with general practices, aged over 17 years and with coronary heart disease (previous myocardial infraction, angina, coronary artery bypass graft and/or angioplasty)	MR with structured adherence intervention. Face-to-face interview with patient. Written reports were provided to the GPs	QoL, appropriateness of treatment, myocardial infraction, left ventricular hypertrophy, cardiac failure, blood pressure, atrial fibrillation	Medicines, GPs, hospital visits, pharmacist time and training	Cost effectiveness; third payer	NA
Chen et al. [38]	Randomized controlled trial Intervention: 50 Control: 50	6	Ambulatory patients with T2DM aged 65 years and older with haemoglobin A1c levels 9.0%	MR with adherence counselling. Face-to-face interview with patient and telephone follow-up. It was not described how the pharmacist communicated with GPs	Haemoglobin A1c	Pharmacist time, telephone, pillbox, educational handouts, medical expenses and hospitalizations	Cost effectiveness; third payer	NA
Fishman et al. [33]	Randomized controlled trial Intervention: 261 Control: 258	12	Adults aged 25 to 75 years diagnosed with HTN and taking antihypertensive medications	MR with adherence counselling. Telephone interview with patient and web-based follow-up. Patients were given a home blood pressure monitor. Interventions with GPs were web-based	SBP, DBP, HTN control, life years gained	Self-management materials, patient training, protocol and training for pharmacists, pharmacist time, home BP monitor and fixed costs	Cost effectiveness; third payer	Bootstrap
Simpson et al. [35]	Randomized controlled trial Intervention: 65 Control: 58	12	Patients with T2DM, who were regularly seen by the primary care team, and did not qualify for urgent specialist referral and assessment	MR with adherence counselling. Face-to-face interview and follow-up with patients. It was not described how the pharmacist communicated with GPs	Annualized cardiovascular risk	Pharmacist time, medications, specialists, other health-care professionals, emergency department visits, hospitalizations	Cost effectiveness; third payer	Bootstrap

Table 1 (continued)

Authors	Design	Time horizon (months)	Study population	Intervention description	Effectiveness outcomes	Resources	EE type and perspective	Uncertainty treatment
Adibe et al. [37]	Randomized controlled trial Intervention: 110 Control: 110	12	Patients with T2DM who were on oral hypoglycaemic therapy	MR with adherence counselling. Face-to-face interview and follow-up with patients. It was not described how the pharmacist communicated with GPs	QALY	Pharmacist time, self-monitoring resources, laboratory tests, drugs, emergency visits, hospitalization, dietitian, optician, podiatrist, nurse and GPs consultation	Cost–utility; third payer	Monte Carlo simulation
Okamoto et al. [29]	Randomized controlled trial Intervention: 164 Control: 166	6	Patients at least 18 years old, diagnosed with essential HTN, who are members of the managed care organization for at least 1 year, and fill prescriptions at its pharmacies. The patients had to be taking the targeted antihypertensive drugs nifedipine, verapamil, captopril, diltiazem, clonidine, terazosin, propranolol, or lisinopril, or be taking at least three prescription antihypertensive drugs	MR with adherence counselling. Face-to-face interview and follow-up with patients. It was not described how the pharmacist communicated with GPs	SBP, DBP	Drugs, clinic visits, emergency room visits, hospitalizations	Cost effectiveness; societal	NA
Obreli-Neto et al. [34]	Randomized controlled trial Intervention: 97 Control: 97	36	Patients aged 60 years or older, diagnosed with T2DM or HTN under drug treatment; regularly participated in medical, nursing, and educational activities offered at the institution; and had up-to-date results for their routine physical and laboratory tests (no more than 30 days prior to baseline measurements)	MR with adherence counselling. Face-to-face interview and follow-up with patients. It was not described how the pharmacist communicated with GPs	QALY	General practitioner, specialist, nurse, pharmacist, emergency department visits, drugs.	Cost-utility; third payer	NA

Table 1 (continued)

Authors	Design	Time horizon (months)	Study population	Intervention description	Effectiveness outcomes	Resources	EE type and perspective	Uncertainty treatment
Shireman et al. [32]	Cluster randomized controlled trial Intervention: 207 Control: 287	6	Patients 18 years or older, receipt of all blood pressure medications from the pharmacy chain, able to read, to return for six visits, self-identified as black, with uncontrolled hypertension who took at least one antihypertensive medication and completed a free blood pressure screening at their pharmacy	MR with multicomponent adherence intervention. Face-to-face interview with patient and follow-up. Written reports were provided to the GPs	SBP, DBP, HTN control, refill adherence (> 80%)	Pharmacy personnel time and TEAM tools, patient self-reported hospitalizations, emergency department visits, visits to medical specialists, visits to general GPs and the number of antihypertensive medication prescriptions	Cost effectiveness; third payer	Bootstrap
Borenstein et al. [31]	Randomized controlled trial Intervention: 98 Control: 99	12	Patients aged 18 years or older with capitated medical insurance and a diagnosis of HTN	MR with adherence counselling. Face-to-face interview with patients with follow-up. Interventions with GPs were telephone based	SBD, DBP, HTN control	GPs and pharmacist time, drugs prescribed	Cost effectiveness; third payer	NA
Polgreen et al. [30]	Cluster randomized controlled trial Intervention: 401 Control: 224	9	Patients who spoke either English or Spanish, who were aged at least 18 years, and had uncontrolled HTN	MR with adherence counselling. Face-to-face interview and follow-up with patients. Pharmacist intervened face to face with GPs	SBD, DBP, HTN control	Drugs prescribed, pharmacist and GPs time	Cost effectiveness; societal	NA

EE economic evaluation, *T2DM* type 2 diabetes mellitus, *MR* medication review, *QoL* quality of life, *SBP* systolic blood pressure, *DBP* diastolic blood pressure, *HTN* hypertension, *CVD* cardiovascular diseases, *QALY* quality-adjusted life years

Table 2 Summary of findings

Authors	Incremental effects	Incremental costs	ICER
Borenstein et al. [31]	SBP: 11 mmHg DBP: 1 mmHg BP goal: 17%	$-49.73 per patient	Intervention was dominant
Simpson et al. [35]	0.26% annualized cardiovascular risk	$-156.91 per patient	Intervention was dominant. Bootstrap determined that 66% of ICERs were dominant
Fishman et al. [33]	SBP: 8.9 mmHg DBP: 4.1 mmHg BP goal: 25% Life years gained: men: 0.22; women: 0.19	$432.1 per patient	SBP: $48.6 per mmHg DBP: $105.4 per mmHg Life years gained: men: $1964.1; women: $2274.2 per life year gained
Chan et al. [36]	1.64% of CVD risk reduction in 5 years	$71.48 per patient	$4358.27 per coronary heart disease event avoided
Chen et al. [38]	1.26% haemoglobin A1c	$85.09 per patient	$102.51 per 1% of haemoglobin A1c but incremental effects were calculated using intervention effect, not discounting control arm (incremental). Using control arm, the ICER should be $67.53 per 1% of haemoglobin A1c
Shireman et al. [32]	SBP: 5.58 (95% CI 5.68–5.47) DBP: 2.3 (95% CI 2.36–2.23) BP goal: 17.2% (95% CI 16.9–17.4%) 80% refill adherence: 23.6 (95% CI 23.3–23.9)	$119.35 per patient	SBP: $25.28 (95% CI 24.14-26.42) per mmHg DBP: $75.16 (95% CI 59.11-91.11) per mmHg BP goal: $757.55 (95% CI 738.76-776,23) per patient 80% refill adherence: $527.62 (95% CI 519.77-535.37) per patient
Polgreen et al. [30]	SBP: 6.1 mmHg DBP: 2.9 mmHg BP goal: 9%	$210.37 per patient	SBP: $34.49 per mmHg DBP: $72.55 per mmHg BP goal: $23.38 per 1%
Adibe et al. [37]	0.12 QALY	$72.96 per patient	$612.67 per QALY. Monte Carlo simulation showed that 93,8% were considered cost effective
Okamoto et al. [29]	SBP: 7.81 mmHg DBP: 3.68 mmHg	$13.02 per patient	SBP: $1.66 per mmHg DBP: $3.53 per mmHg
Obreli-Neto et al. [34]	1.302 QALY	$77.74 per patient	$59.76 per QALY
Bond et al. [39]	No significant effects	$257.79 per patient	Intervention was dominated

ICER Incremental cost-effectiveness ratio, *SBP* systolic blood pressure, *DBP* diastolic blood pressure, *BP* blood pressure, *CVD* cardiovascular diseases, *CI* confidence interval, *QALY* quality-adjusted life year

when compared to the control group in two studies [31, 35]. For trials, where costs were higher than usual care, they reported up to $432.1 per patient in 2016 US dollars [33].

As for ICERs, one had to be recalculated, because the original estimation did not consider incremental effects, failing to discount the control arm [38]. In another EE, ICERs had to be calculated, because they had not calculated directly usual care against MR [33]. For cost-effectiveness studies evaluating HTN, one trial was dominant over usual care in SBP, DBP, and HTN control [31]. For SBP, ICERs ranged from $48.6 [33] to $25.3 per mm/Hg [32]. For DBP, they ranged from $105.4 [33] to $3.5 per mm/Hg [29]. When HTN control was assessed, a study evaluated the ICER to reach patient control and valuated it at $757.6 per patient [32]. Another study assessed the cost per % of patients achieving BP and had a result of $23.4 [30] per 1% of patients reaching their BP goal. Finally, the two cost–utility studies had values of $612.67 [37] and $59.8 [34] per QALY.

Uncertainty analysis was carried out in four studies yielding positive results [32, 33, 35, 37]. Three used bootstrap [32, 33, 35] and one Monte Carlo simulation [37]. Two of them presented their results in the cost-effectiveness plane [35, 37]. One study yielded 99% of the simulated ICERs as cost effective and 66% of them as dominant [35]. The other trial considered 93.8% of the iterations as cost effective and 5.6% of them as dominant [37]. These studies built acceptability curves yielding willingness to pay for a probability of 95% of them being cost effective of $3303 per 1% reduction in annualized CVD risk [35] and $3607 per QALY gained [37].

Most of the evaluated studies deemed MR as more effective than usual care, but also more expensive [29, 30, 32–34, 36–38]. Two interventions dominated usual care, meaning that usual care caused more costs and was less effective [31, 35]. Conversely, a study did not find any difference between incremental effects and was valued as more expensive;

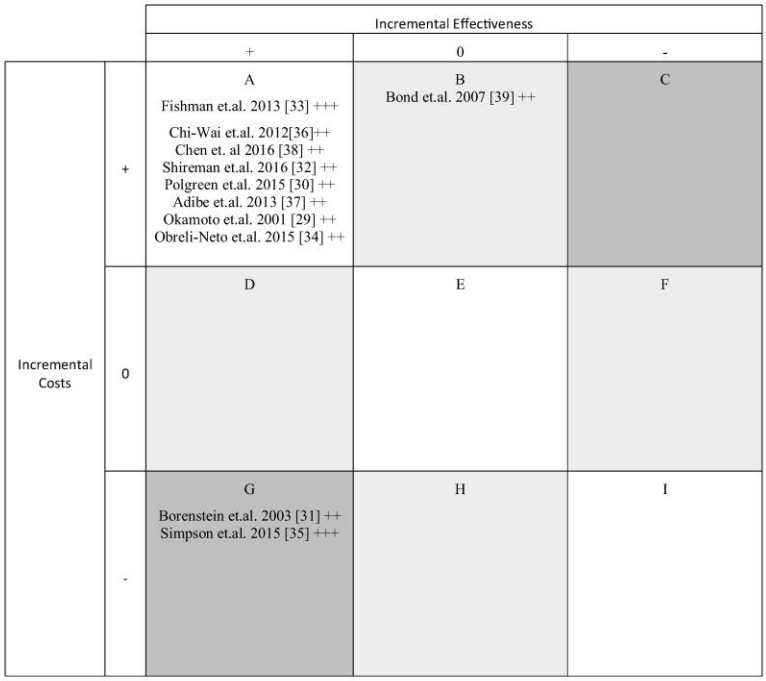

Fig. 2 Permutation matrix. Overall economic evaluation quality: (+++) high; (++) medium; (+) low. In the darkest shade, decision is strongly favoured (G: accept medication review; C: reject medication review), in the intermediate shade, decision is less favoured (D, H: accept medication review; B, F: reject medication review), and in the colourless, there is no obvious decision (A: is added effect worth added cost?; J: is reduced effect acceptable given reduced cost?; E: neutral cost and effect. Other reasons to adopt treatment?)

therefore, its adoption was not recommended in that setting (dominated) [39].

Risk of bias and quality assessment

Of the 11 EEs, four reported the clinical trial in a separate publication [40–43]. No study could blind their patients to the intervention, but given the nature of MR, it was not considered as a risk of bias. On the other hand, two studies declared blinding of outcome assessment [33, 39], and also two were free of contamination between groups, as they were randomized by centre [30, 32]. Regarding the quality of the EEs, low scores in appropriate time horizon, insufficient description of control group, lack of adequate perspective, and uncertainty treatment were observed. As for time horizon, all but one [34] of the studies lasted between 6 and 12 months. A societal perspective was used in two studies [29, 30]. In the case of the competing alternatives, three studies described with some detail usual care in addition to regular consultation with GPs [34, 37, 38]. Finally, uncertainty treatment was used in four trials [32, 33, 35, 37]. Overall quality of the studies is described in Table 3, with two of the them achieving high quality in EE assessment with a low risk of bias [33, 35]. For more details of risk of bias in each domain or EE quality, see Appendices 3 and 4 in Supplementary material.

Discussion

In this systematic review, full EEs of pharmacist-led MR on outpatients with CVD risk factors are described and assessed. Most of the EEs deemed MR as cost effective, but transferability assessment or evaluation in local setting is encouraged to assess the implementation of this professional pharmacy service in the context of current clinical guidelines, pharmacist training, and the health-care system.

In regards of other similar studies, they have shown positive economic impact, but have analysed partial economic evaluations, other groups of patients, and other services [16–18]. The systematic review from Altowaijri et al. included studies that either used MR or educational interventions for CVD risk factor in patients with coronary heart disease and heart failure in any setting [16]. Most of the economic studies included were in community pharmacy. Of these, three studies assessed smoking services, two T2DM, and one each for coronary heart disease, DLP and HTN. The only cost–utility study was carried out for a smoking aid service. The only study, where MR was dominated, was

Table 3 Economic evaluations' quality

Studies	EE quality	Risk of bias	Overall score
Simpson et al. 2015 [35]; Simpson et al. 2011 [41]	High	Low	High
Fishman et al. 2013 [33]; Green et al. 2008 [42]	High	Low	High
Shireman et al. 2016 [32]; Svarstad et al. 2010 [43]	Medium	Low	Medium
Bond et al. 2007 [39]	Medium	Low	Medium
Chen et al. 2016 [38]	High	Medium	Medium
Adibe et al. 2013 [37]	High	Medium	Medium
Polgreen et al. 2015 [30]; Carter et al. 2015 [40]	Medium	Medium	Medium
Okamoto et al. 2001 [29]	Medium	Medium	Medium
Borenstein et al. 2003 [31]	Medium	Medium	Medium
Chan et al. 2012 [36]	Medium	Medium	Medium
Obreli-Neto et al. 2015 [34]	Medium	Medium	Medium

EE economic evaluation

the MEDMAN study and will be discussed later [39]. Wang et al. included studies that intervened through an array of interventions in patients with T2DM [17]. They found 25 EE studies, where 21 carried out MR, 11 were full EE, and of them, six were cost–benefit analysis, five cost effectiveness, and one cost–utility. All had positive results with the cost–utility analysis that yielded the intervention as dominant. Most of the individual studies cited in these reviews were not included in this paper, because they were not based on RCTs (three of them met our inclusion criteria [29, 31, 39]). Finally, this is the most recent systematic review on this topic, including many recent studies not included in the previous reviews.

Cost-effectiveness analysis

Most of the studies in this review evaluated the intervention as cost effective and two classified it as dominant [31, 35]. It is important to highlight that most of the ICERs are below $100, but this should be interpreted with caution, as these are secondary outcomes, e.g., 1 mm/Hg per dollar. When outcomes such as coronary heart disease event avoided are analysed, the ICER could be as high as $4352 [36]. As for cost–utility results, the two studies reporting QALYs for MR had ICERs that did not surpass $612 [34, 37]. Furthermore, one of these studies [37] compared the ICER to standards of the Cost-effectiveness Threshold (CET) of $50,000, £30,000 or 1–3 Gross Domestic Product (GDP) per-capita, even though these values may be considered as too high, leading to the incorrect approval of interventions [44]. Adoption of services that are not cost effective is critically important in low- and middle-income countries, where budget constraints are an issue. Some authors suggest using a "supply-side" CET of about 0.6 GDP per-capita, although even using that CET, for both countries (Brazil and Nigeria), the intervention could be considered as cost effective [45].

An important issue is type of resources recorded. EE reported pharmacist training [33, 39], emergency visits [29, 32, 34, 37], and hospitalizations [29, 32, 35, 37–39]. Furthermore, no study evaluated indirect costs such as loss of productivity. Two EE declared to have a societal perspective, but the only cost borne by patients was medications due to their own country's health system [29, 30].

Transferability

Although 10 of the 11 studies reported MR as cost effective, these results should be considered carefully, as heterogeneity between trials and health-care systems may limit recommendation for their adoption in other countries or settings without carrying out a transferability analysis. For example, some of the trials differed on the components of the intervention, as some of them used various adherence aids [32, 36]. In one study, where the intervention was deemed as cost effective, pharmacists intervened face-to-face with GPs, a fact that could be considered an advantage as the relationship and inter-professional collaboration could reach a higher level than communication through written reports [30]. Nevertheless, another trial showed that through an electronic communication system with GPs and telephone interviews with patients, positive results could also be achieved [33]. On the other hand, one study in community pharmacies addressed the issue of not accessing clinical records by providing pharmacists some basic clinical information. This study failed to achieve positive outcomes [39]. Most of the studies used type 3 MR, i.e., undertaking a patient interview, having access to medication records and patients´ clinical history. This blurs the conclusion that the effects observed are due to the interaction with GPs or patients. All studies included patient follow-up which has been recently reported by a systematic review to be a determinant of MR effectiveness. Interestingly, when pharmacists had only one encounter with patients, no effect was found

on mortality, hospitalizations, falls, physical, and cognitive functioning [46]. Another important issue is the definition of usual care, as it may be different across countries, health systems, and even health-care providers. For example, one of the included studies compared pharmacist-led MR plus a home blood pressure monitor with two alternatives. One was usual care that included pamphlets, a wallet with a registry of their blood pressure and a web site that allows to schedule appointments, refill prescriptions, view medical records, lab results, and to communicate with their provider. The other alternative included usual care plus a home blood pressure monitor [33]. The type of inclusion and exclusion criteria might also affect transferability. For example, Okamoto et al. included only patients taking specific medications [29]. If a decision maker would like to use these results, they should assess if those medications are recommended on their guidelines. For example, in this case, they used nifedipine, verapamil, captopril, diltiazem, clonidine, terazosin, propranolol, or lisinopril that at the time of the study were more costly, so more economic impact was expected, but currently, they are not recommended as first line treatment for HTN [47]. Pharmacist training was described in seven studies and differed on the competencies and contents [30, 32–35, 38, 39]. Different studies estimated how many resources were used which may alter the results. A trial that estimated pharmacy technicians' time could affect the ICER if it is a main cost driver [32].

Risk of bias

Four of the EEs were classified as high quality, and of these, two had a medium risk of bias in the clinical trial potentially affecting final conclusions [37, 38]. It should be noted that we did not consider blinding of the patients that received MR a bias due to the nature of the intervention. Some of the most frequent sources were lack of blinding of outcome assessment with only two studies undertaking the blinding [33, 39]. This is a key issue, since most of the investigators were pharmacists. Two of the eleven studies considered a cluster-RCT design which minimises the risk of contamination between groups [30, 32].

Economic evaluation quality assessment

When EE alongside clinical trials of CVD are analysed it is worth noting these diseases develop over several years, so modelling should be considered to predict longer time horizons, ideally of a lifetime. CVD risk is summed as a probability of over 5–10 years, but events can happen at any time through a lifetime [36]. For example, a study developed a Markov model cohort simulation through lifetime to predict acute coronary syndrome, stroke and heart failure using the conservative assumption that the intervention would stop at 6 months and its effect would go back to baseline in 2 years. They built a cohort based on other trials and found that 48.6% of the iterations, MR would be cost effective with a CET of $50.000 [48]. On the other hand, if time horizons are longer than 1 year, discount rate should be applied for costs and effects depending on local guidelines or international standards, so time preference could be adjusted to the present values. The only study in this systematic review carried out for more than 1 year did not to take this into account [34].

Three studies described usual care as GP consultation which makes comparison complex, as every country or even health centre has different clinical protocols that may change resource utilization and baseline outcomes [34, 37, 38]. Furthermore, two other studies described a control group with other interventions such as guidelines for lowering blood pressure, pamphlets, or websites that might mean a higher baseline compared to the studies that only used GP consultation [32, 33].

Finally, as costs and effects are evaluated in a sample, population values may vary. In this context, uncertainty analysis is always recommended to assure that the results represent opportunity costs of other interventions forgone. Only four studies made this analysis [32, 33, 35, 37], but two of them took a step further building presentation devices for decision making as a cost-effectiveness planes and acceptability curves with 99% and 93.8% of the simulated ICERs as cost effective and willingness to pay $3303 per 1% reduction in annualized CVD risk and $3607 per QALY gained [35, 37].

Limitations

This systematic review is not free of publication bias, as there could be trials with negative outcomes that have not been published intentionally in peer reviewed journals, or as it is generally accepted, negative results are less likely to be published. In our review, the grey literature was not searched, but related personal records were included. However, we searched six different databases and platforms from health and economic background in an attempt to address this issue. We do acknowledge that model-based studies are recommended to project outcomes for longer periods of time; however, these were excluded from our review, as data were not based on RCTs. Decision-makers´ requirements are a key issue, as they define the decision problem and might yield some alternatives in the studies as irrelevant to their specific jurisdiction. In addition, as national guidelines differ, specific methodological quality might be required to be used in local settings. These guidelines might establish particular time horizons, perspectives, discount rates, and unit costs which may need to be taken into account [49].

Recommendations

As a product of this systematic review, an evidence-based set of recommendations are made for pharmacist-led MR on CVD risk factors EE conducted alongside clinical trials:

- *Type of economic evaluation* Cost–utility analysis is encouraged, so patients' preferences, who are the final recipients of health technologies, are represented. This approach allows comparison of MR with other interventions to represent opportunity costs for society.
- *Comparator* Usual care or any other comparator must be described thoroughly, as countries' health-care systems or even health centre procedures vary.
- *Time horizon* Because of the nature of CVD, effects (clinical outcomes or quantity and quality of life) and costs of MR on HTN, T2DM, and DLP can impact through the life span of patients. Longer time horizons should be explored. If necessary, modelling should be tried.
- *Perspective* Societal perspective should be used, as indirect costs might account as an important source of resources used. From this perspective, other narrower ones can be derived if the decision maker requires it. In addition, it should be explicitly stated on the methods.
- *Resources* All relevant resource consumption should be evaluated. This include direct costs such as pharmacists', other professionals' or technicians' time, drug costs, the intervention itself, emergency room visits, hospitalizations, training, laboratory tests, and indirect costs such as productivity loss, patient transportation, and carers among others.
- *Uncertainty analysis* To represent as accurately as possible opportunity costs for the target population, an uncertainty analysis needs to be undertaken to assure that information delivered to the decision makers' added value to the selection of health interventions.

Conclusions

Most of the EE considered the intervention to be cost effective with four being rated of high quality. This analysis provides encouragement to decision makers to perform local evaluations, so local clinical pathways, resource use, and professional expertise can be measured. We recommend the use of cost–utility analysis, thorough description of the comparator (usual care), time horizons that can capture the effect of CVD prevention, use of a societal perspective, and use of uncertainty analyses. If this is not possible, a transferability assessment should be performed, so decision makers can use this information in their jurisdiction.

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Compliance with ethical standards

Conflict of interest All the authors declare that they do not have any conflict of interest.

References

1. Mendis, S., Puska, P., Norving, B.: Global atlas on cardiovascular disease prevention and control. World Heal, Organ (2011)
2. Benjamin, E.J., Blaha, M.J., Chiuve, S.E., Cushman, M., Das, S.R., Deo, R., De Ferranti, S.D., Floyd, J., Fornage, M., Gillespie, C., Isasi, C.R., Jimnez, M.C., Jordan, L.C., Judd, S.E., Lackland, D., Lichtman, J.H., Lisabeth, L., Liu, S., Longenecker, C.T., MacKey, R.H., Matsushita, K., Mozaffarian, D., Mussolino, M.E., Nasir, K., Neumar, R.W., Palaniappan, L., Pandey, D.K., Thiagarajan, R.R., Reeves, M.J., Ritchey, M., Rodriguez, C.J., Roth, G.A., Rosamond, W.D., Sasson, C., Towfghi, A., Tsao, C.W., Turner, M.B., Virani, S.S., Voeks, J.H., Willey, J.Z., Wilkins, J.T., Wu, J.H.Y., Alger, H.M., Wong, S.S., Muntner, P.: Heart Disease and Stroke Statistics' 2017 update: a report from the American Heart Association. Circulation **135**, e146–e603 (2017). https://doi.org/10.1161/cir.0000000000000485
3. Wilkins, E., Wilson, L., Wickramasinghe, K., Bhatnagar, P., Leal, J., Luengo-Fernandez, R., Burns, R., Rayner, M., Townsend, N.: European Cardiovascular Disease Statistics 2017. Eur. Hear, Network (2017)
4. Piepoli, M.F., Hoes, A.W., Agewall, S., Albus, C., Brotons, C., Catapano, A.L., Cooney, M.T., Corrà, U., Cosyns, B., Deaton, C., Graham, I., Hall, M.S., Hobbs, F.D.R., Løchen, M.L., Löllgen, H., Marques-Vidal, P., Perk, J., Prescott, E., Redon, J., Richter, D.J., Sattar, N., Smulders, Y., Tiberi, M., Van Der Worp, H.B., Van Dis, I., Verschuren, W.M.M., Binno, S., De Backer, G., Roffi, M., Aboyans, V., Bachl, N., Carerj, S., Cho, L., Cox, J., De Sutter, J., Egidi, G., Fisher, M., Fitzsimons, D., Franco, O.H., Guenoun, M., Jennings, C., Jug, B., Kirchhof, P., Kotseva, K., Lip, G.Y.H., Mach, F., Mancia, G., Bermudo, F.M., Mezzani, A., Niessner, A., Ponikowski, P., Rauch, B., Stauder, A., Turc, G., Wiklund, O., Windecker, S., Zamorano, J.L., Achenbach, S., Badimon, L., Barón-Esquivias, G., Baumgartner, H., Bax, J.J., Dean, V., Erol, Ç., Gaemperli, O., Kolh, P., Lancellotti, P., Nihoyannopoulos, P., Torbicki, A., Carneiro, A.V., Metzler, B., Najafov, R., Stelmashok, V., De Maeyer, C., Dilić, M., Gruev, I., Miličić, D., Vaverkova, H., Gustafsson, I., Attia, I., Duishvili, D., Ferrières, J., Kostova, N., Klimiashvili, Z., Hambrecht, R., Tsioufis, K., Szabados, E., Andersen, K., Vaughan, C., Zafrir, B., Novo, S., Davletov, K., Jashari, F., Kerimkulova, A., Mintale, I., Saade, G., Petrulioniene, Z., Delagardelle, C., Magri, C.J., Rudi, V., Oukerraj, L., Çölkesen, B.E., Schirmer, H., Dos Reis, R.P., Gherasim, D., Nedogoda, S., Zavatta, M., Giga, V., Filipova, S., Padial, L.R., Kiessling, A., Mahdhaoui, A., Ural, D., Nesukay, E., Gale, C.: 2016 European Guidelines on cardiovascular disease prevention in clinical practice. Eur. Heart J. **37**, 2315–2381 (2016). https://doi.org/10.1093/eurheartj/ehw106
5. Whelton, P., Carey, R., Aronow, W., Casey, D.J., Collins, K., Dennison Himmelfarb, C., DePalma, S., Gidding, S., Jamerson, K., Jones, D., MacLaughlin, E., Muntner, P., Ovbiagele, B., Smith, S.J., Spencer, C., Stafford, R., Taler, S., Thomas, R., Williams, K.S., Williamson, J., Wright, J.J.: 2017 ACC/AHA/AAPA/ABC/ACPM/AGS/APhA/ASH/ASPC/NMA/PCNA guideline for the prevention, detection, evaluation, and management of high blood pressure in adults: a report of the American College of

Cardiology/American Heart Association Task Force on Clinical Pr. Hypertension **71**, e13–e115 (2017). https://doi.org/10.1161/HYP.0000000000000065/-/DC1.The
6. American Diabetes Association: Summary of Revisions: standards of Medical Care in Diabetes—2019. Diabetes Care **42**, S4–S6 (2019). https://doi.org/10.2337/dc19-Srev01
7. Yancy, C.W., Jessup, M., Bozkurt, B., Butler, J., Casey, D.E., Colvin, M.M., Drazner, M.H., Filippatos, G.S., Fonarow, G.C., Givertz, M.M., Hollenberg, S.M., Lindenfeld, J.A., Masoudi, F.A., McBride, P.E., Peterson, P.N., Stevenson, L.W., Westlake, C.: 2017 ACC/AHA/HFSA Focused Update of the 2013 ACCF/AHA Guideline for the Management of Heart Failure: a report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines and the Heart Failure Society of Amer. Circulation **136**, e137–e161 (2017). https://doi.org/10.1161/CIR.0000000000000509
8. Pharmaceutical Care Network Europe Foundation: The PCNE Classification V 8.02. http://www.pcne.org/upload/files/152_PCNE_classification_V7-0.pdf. Accessed 9 May 2019
9. Westerlund, T., Marklund, B.: Assessment of the clinical and economic outcomes of pharmacy interventions in drug-related problems. J. Clin. Pharm. Ther. **34**, 319–327 (2009). https://doi.org/10.1111/j.1365-2710.2008.01017.x
10. National Coordinating Council for Medication Error Reporting and Prevention. What is a medication error? New York, NY: National Coordinating Council for Medication Error Reporting and Prevention; 2015. https://www.nccmerp.org/about-medication-errors. Accessed 9 May 2019
11. Walsh, E.K., Hansen, C.R., Sahm, L.J., Kearney, P.M., Doherty, E., Bradley, C.P.: Economic impact of medication error: a systematic review. Pharmacoepidemiol. Drug Saf. **26**, 481–497 (2017). https://doi.org/10.1002/pds.4188
12. Pharmaceutical Care Network Europe: Position Paper on the PCNE definition of Medication Review 2016. https://www.pcne.org/upload/files/149_Position_Paper_on_PCNE_Medication_Review_final.pdf. Accessed 9 May 2019
13. Pharmaceutical Care Network Europe Foundation: PCNE statement on medication review 2013. https://www.pcne.org/upload/files/150_20160504_PCNE_MedRevtypes.pdf. Accessed 9 May 2019
14. Jokanovic, N., Tan, E.C., Sudhakaran, S., Kirkpatrick, C.M., Dooley, M.J., Ryan-Atwood, T.E., Bell, J.S.: Pharmacist-led medication review in community settings: an overview of systematic reviews. Res. Soc. Adm. Pharm. **13**, 661–685 (2017). https://doi.org/10.1016/j.sapharm.2016.08.005
15. Tan, E.C.K., Stewart, K., Elliott, R.A., George, J.: Pharmacist services provided in general practice clinics: a systematic review and meta-analysis. Res. Soc. Adm. Pharm. **10**, 608–622 (2014). https://doi.org/10.1016/j.sapharm.2013.08.006
16. Altowaijri, A., Phillips, C.J., Fitzsimmons, D.: A systematic review of the clinical and economic effectiveness of clinical pharmacist intervention in secondary prevention of cardiovascular disease. J Manag Care Pharm **19**, 408–416 (2013). https://doi.org/10.18553/jmcp.2013.19.5.408
17. Wang, Y., Yeo, Q.Q., Ko, Y.: Economic evaluations of pharmacist-managed services in people with diabetes mellitus: a systematic review. Diabet. Med. **33**, 421–427 (2016). https://doi.org/10.1111/dme.12976
18. Jacob, V., Chattopadhyay, S.K., Thota, A.B., Proia, K.K., Njie, G., Hopkins, D.P., Finnie, R.K.C., Pronk, N.P., Kottke, T.E.: Economics of team-based care in controlling blood pressure: a community guide systematic review. Am. J. Prev. Med. **49**, 772–783 (2015). https://doi.org/10.1016/j.amepre.2015.04.003
19. Bodrogi, J., Kaló, Z.: Principles of pharmacoeconomics and their impact on strategic imperatives of pharmaceutical research. Br. J. Pharmacol. **159**, 1367–1373 (2010). https://doi.org/10.1111/j.1476-5381.2009.00550.x
20. Higgins, J., Green, S.: Cochrane handbook for systematic reviews of interventions version 5.1. 0 [updated March 2011]. Cochrane Collab. (2011). https://www.handbook.cochrane.org. Accessed 9 May 2019
21. Moher, D., Liberati, A., Tetzlaff, J., Altman, D.G.: Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. PLoS Med. **6**, 1–6 (2009). https://doi.org/10.1371/journal.pmed.1000097
22. Drummond, M., Sculpher, M., Claxton, K., Stoddart, G.L., Torrance, G.: Methods for the economic evaluation of health care programmes. Oxford University Press, Oxford (2015)
23. Cochrane effective practice and organisation of care (EPOC): Suggested risk of bias criteria for EPOC reviews. https://epoc.cochrane.org/resources/epoc-resources-review-authors. Accessed 9 May 2019
24. Malet-Larrea, A., García-Cárdenas, V., Sáez-Benito, L., Benrimoj, S.I., Calvo, B., Goyenechea, E.: Cost-effectiveness of professional pharmacy services in community pharmacy: a systematic review. Expert Rev. Pharmacoecon. Outcomes Res. **16**, 747–758 (2016). https://doi.org/10.1080/14737167.2016.1259071
25. Evers, S., Goossens, M., de Vet, H., van Tulder, M., Ament, A.: Criteria list for assessment of methodological quality of economic evaluations: consensus on Health Economic Criteria. Int. J. Technol. Assess. Health Care **21**, 240–245 (2005). https://doi.org/10.1017/S0266462305050324
26. Philips, Z., Bojke, L., Sculpher, M., Claxton, K., Golder, S.: Good practice guidelines for decision-analytic modelling in health technology assessment. Pharmacoeconomics. **24**, 355–371 (2006). https://doi.org/10.2165/00019053-200624040-00006
27. Shemilt, I., Thomas, J., Morciano, M.: A web-based tool for adjusting costs to a specific target currency and price year. Evid. Policy. **6**, 51–59 (2010). https://doi.org/10.1332/174426410X482999
28. Nixon, J., Khan, K.S., Kleijnen, J.: Summarising economic evaluations in systematic reviews: a new approach. BMJ **322**, 1596–1598 (2001). https://doi.org/10.1136/bmj.322.7302.1596
29. Okamoto, M.P., Nakahiro, R.K.: Pharmacoeconomic evaluation of a pharmacist-managed hypertension clinic. Pharmacotherapy. **21**, 1337–1344 (2001). https://doi.org/10.1016/j.jval.2011.02.542
30. Polgreen, L.A., Han, J., Carter, B.L., Ardery, G.P., Coffey, C.S., Chrischilles, E.A., James, P.A.: Cost-effectiveness of a physician-pharmacist collaboration intervention to improve blood pressure control. Hypertension **66**, 1145–1151 (2015). https://doi.org/10.1161/HYPERTENSIONAHA.115.06023
31. Borenstein, J.E., Graber, G., Saltiel, E., Wallace, J., Ryu, S., Jackson, A., Deutsch, S., Weingarten, S.R.: Physician-pharmacist comanagement of hypertension: a randomized, comparative trial. Pharmacotherapy. **23**, 209–216 (2003). https://doi.org/10.1592/phco.23.2.209.32096
32. Shireman, T.I., Svarstad, B.L.: Cost-effectiveness of Wisconsin TEAM model for improving adherence and hypertension control in black patients. J. Am. Pharm. Assoc. **56**, 389–396 (2016). https://doi.org/10.1016/j.japh.2016.03.002
33. Fishman, P.A., Cook, A.J., Anderson, M.L., Ralston, J.D., Catz, S.L., Carrell, D., Carlson, J., Green, B.B.: Improving BP control through electronic communications: an economic evaluation. Am. J. Manag. Care. **19**, 709–716 (2013)
34. Obreli-Neto, P.R., Marusic, S., Guidoni, C.M., Baldoni, A.D., Renovato, R.D., Pilger, D., Cuman, R.K.N., Pereira, L.R.L.: Economic evaluation of a pharmaceutical care program for elderly diabetic and hypertensive patients in primary health care: a 36-month randomized controlled clinical trial. J Manag Care Spec Pharm **21**, 66–75 (2015). https://doi.org/10.18553/jmcp.2015.21.1.66

35. Simpson, S.H., Lier, D.A., Majumdar, S.R., Tsuyuki, R.T., Lewanczuk, R.Z., Spooner, R., Johnson, J.A.: Cost-effectiveness analysis of adding pharmacists to primary care teams to reduce cardiovascular risk in patients with Type 2 diabetes: results from a randomized controlled trial. Diabet. Med. **32**, 899–906 (2015). https://doi.org/10.1111/dme.12692
36. Chan, C.-W., Siu, S.-C., Wong, C.K.W., Lee, V.W.Y.: A Pharmacist Care Program: positive impact on cardiac risk in patients with type 2 diabetes. J. Cardiovasc. Pharmacol. Ther. **17**, 57–64 (2012). https://doi.org/10.1177/1074248410396216
37. Adibe, M.O., Aguwa, C.N., Ukwe, C.V.: Cost-utility analysis of pharmaceutical care intervention versus usual care in management of nigerian patients with type 2 diabetes. Value Heal. Reg. Issues. **2**, 189–198 (2013). https://doi.org/10.1016/j.vhri.2013.06.009
38. Chen, J.-H., Huang-Tz, O., Tzu-Chieh, L., Chia-Cheng Lai, E., Yang Kao, Y.-H.: Pharmaceutical care of elderly patients with poorly controlled type 2 diabetes mellitus: a randomized controlled trial. Int. J. Clin. Pharm. **38**, 88–95 (2016). https://doi.org/10.1007/s11096-015-0210-4
39. The Community Pharmacy Medicines Management Project Evaluation Team: The MEDMAN study: a randomized controlled trial of community pharmacy-led medicines management for patients with coronary heart disease. Fam. Pract. **24**, 189–200 (2007). https://doi.org/10.1093/fampra/cml075
40. Carter, B.L., Coffey, C.S., Ardery, G., Uribe, L., Ecklund, D., James, P., Egan, B., Vander Weg, M., Chrischilles, E., Vaughn, T.: Cluster-randomized trial of a physician/pharmacist collaborative model to improve blood pressure control. Circ Cardiovasc Qual Outcomes **8**, 235–243 (2015). https://doi.org/10.1161/circoutcomes.114.001283
41. Simpson, S.H., Majumdar, S.R., Tsuyuki, R.T., Lewanczuk, R.Z., Spooner, R., Johnson, J.A.: Effect of adding pharmacists to primary care teams on blood pressure control in patients with type 2 diabetes A randomized controlled trial. Diabetes Care **34**, 20–26 (2011)
42. Green, B.B., Cook, A., Ralston, J., Fishman, P., Catz, S., Carlson, J., Carrell, D., Tyll, L., Larson, E., Thompson, R.: Effectiveness of home blood pressure monitoring, web communication, and pharmacist care on hypertension control. J. Am. Med. Assoc. **299**, 2857–2867 (2008). https://doi.org/10.1001/jama.299.24.2857
43. Svarstad, B.L., Kotchen, J.M., Shireman, T.I., Crawford, S.Y., Palmer, P.A., Vivian, E.M., Brown, R.L.: The team education and adherence monitoring (TEAM) trial: pharmacy interventions to improve hypertension control in blacks. Circ. Cardiovasc. Qual. Outcomes. **2**, 264–271 (2009). https://doi.org/10.1161/CIRCOUTCOMES.109.849992
44. Neumann, P.J., Cohen, J.T., Weinstein, M.C.: Updating cost-effectiveness—the curious resilience of the $50,000-per-QALY threshold. N. Engl. J. Med. **371**, 796–797 (2014). https://doi.org/10.1056/NEJMp1405158
45. Woods, B., Revill, P., Sculpher, M., Claxton, K.: Country-level cost-effectiveness thresholds: initial estimates and the need for further research. Value Heal. **19**, 929–935 (2016). https://doi.org/10.1016/j.jval.2016.02.017
46. Huiskes, V.J.B., Burger, D.M., Van Den Ende, C.H.M., Van Den Bemt, B.J.F.: Effectiveness of medication review: a systematic review and meta-analysis of randomized controlled trials. BMC Fam. Pract. **18**, 1–15 (2017). https://doi.org/10.1186/s12875-016-0577-x
47. James, P.A., Oparil, S., Carter, B.L., Cushman, W.C., Dennison-Himmelfarb, C., Handler, J., Lackland, D.T., LeFevre, M.L., MacKenzie, T.D., Ogedegbe, O., Smith, S.C., Svetkey, L.P., Taler, S.J., Townsend, R.R., Wright, J.T., Narva, A.S., Ortiz, E.: 2014 evidence-based guideline for the management of high blood pressure in adults: report from the panel members appointed to the Eighth Joint National Committee (JNC 8). J Am Med Assoc **311**, 507–520 (2014). https://doi.org/10.1001/jama.2013.284427
48. Kulchaitanaroaj, P., Brooks, J.M., Chaiyakunapruk, N., Goedken, A.M., Chrischilles, E.A., Carter, B.L.: Cost-utility analysis of physician–pharmacist collaborative intervention for treating hypertension compared with usual care. J. Hypertens. **35**, 178–187 (2017). https://doi.org/10.1097/HJH.0000000000001126
49. Drummond, M., Barbieri, M., Cook, J., Glick, H.A., Lis, J., Malik, F., Reed, S.D., Rutten, F., Sculpher, M., Severens, J.: Transferability of economic evaluations across jurisdictions: ISPOR good research practices task force report. Value Heal. **12**, 409–418 (2009). https://doi.org/10.1111/j.1524-4733.2008.00489.x

Supplementary material

Appendix 1: Medline (Pubmed) search strategy

For MEDILNE, the search strategy was developed examining MeSH terms and keywords of articles related to the study objective. The PICO method was used (patient, intervention, comparator and outcome) [54]. It had 4 components of search terms combined by Boolean operator "OR". These are:

- Pharmacist.
- MR.
- CVD risk factor.
- Economics.

These were connected by Boolean operator "AND". The search strategy was first piloted to evaluate if retrieval of papers got relevant citations. Any relevant additional study in the authors personal records were added.

(Pharmacy OR Pharmacist* OR "Professional Role" OR "Students, Pharmacy" OR pharmacies OR "Ambulatory Care Facilities") AND ("Drug Monitoring" OR "Patient care management" OR "Practice Guidelines as Topic" OR "Preventive Health Services" OR "Pharmacology, Clinical" OR "Medication Adherence" OR "Health Education" OR "Drug therapy" OR "Delivery of Health Care" OR "Cooperative Behavior" OR "Patient Care" OR "Patient Care Management" OR "Drug Utilization Review" OR "Professional Practice" OR "Pharmaceutical Services" OR "community Health services" OR "Primary health Care" OR "Interdisciplinary Communication" OR "Patient Care Team") AND (Hyperlipidemias OR "Hypolipidemic Agents" OR lipoproteins OR "Cardiovascular Diseases" OR "Blood Pressure" OR "Hemoglobin A, Glycosylated" OR "Diabetes Mellitus" OR "Blood Glucose" OR "Hypoglycemic Agents" OR insulins OR

“cardiovascular agents” OR “Blood Pressure Determination” OR “cerebrovascular diseases”) AND (economics OR “Delivery of Health care” OR “Markov Chains” OR “Models, Economic” OR “quality of life” OR “Outcome Assessment (Health Care)” OR "Quality-Adjusted Life Years")

Appendix 2: Data extraction sheet

Data extraction sheet was formulated according Cochrane and NHS methods and it contained:

- General study characteristics:
    - Year of publication.
    - Sources of founding.
    - Design.
    - Sample size.
    - Competing interests.
    - Setting:
        - Hospital based outpatient clinic.
        - Primary care centre.
        - Community pharmacy.
    - Country.
    - Inclusion criteria.
    - Exclusion criteria.
    - Intervention with patients:
        - Face to face interview.
        - Web-based.
        - Telephone.
    - Follow-up.
    - Adherence intervention.
    - Type of adherence intervention.
        - Counselling.

        - Multifaceted.
    - Type of medication review:
        - 1: only medication information.
        - 2A: medication information and patient information.
        - 2B: medication information and clinical registry.
        - 3: all the above.
    - GPs intervention:
        - Face to face interview.
        - Electronic medical record.
        - Telephone.
    - Control group description.
    - Perspective: If it was not declared, we classified it. Since there is no standard definition we decided to categorize studies into the following:
        - Societal: including all relevant costs to all members of society (direct and indirect)
        - Third payer: costs related to a financing organism. Depending on the health care system it could be public or private.
        - Single provider: costs to the specific health centre were MR was carried out.
        - Patient: relevant costs to the patients like transportation, loss of productivity, carers, among others.
    - Type of EEs:
        - Cost-effectiveness.
        - Cost-utility.
        - Cost-benefit.

- Methods and outcomes of EE.
    - Time horizon over which costs and consequences were evaluated (months).
    - Currency.
    - Discount rate (if necessary):
        - Costs.
        - Effects.
    - Inflation rate (if necessary).
    - Reference year of analysis. If it was not reported, the average year between the beginning and the end of the study was used.
    - If model based:
        - Markov.
        - Decision tree.
        - Discrete event simulation.
    - Description of resources evaluated.
    - Data source of resource use.
    - Methods for identifying resource use.
    - Incremental costs.
    - Valuation of effects.
    - Methods used for measurement of effects.
    - Incremental effects.
    - ICER.
    - Uncertainty analysis.
    - Author´s conclusion.
- Miscellaneous.

- Pharmacist training.

Appendix 3: Risk of bias assessment

Clinical trial	A	B	C	D	E	F	G	H	I	High risk of bias	Unclear risk of bias	Low risk of bias	Overall risk of bias
Simpson et.al. 2015 [55]; Simpson et.al. 2011 [56]	+	+	+	+	-	+	-	+	-	3	0	6	Low
Fishman et.al. 2013 [57]; Green et.al. 2008 [58]	+	+	+	+	+	+	-	+	+	1	0	8	Low
Shireman et.al. 2016 [59]; Svarstad et.al. 2010 [60]	+	+	+	+	+	+	+	+	-	1	0	8	Low
Bond et.al. 2007 [61]	+	+	?	?	+	+	-	+	+	1	2	6	Low
Chen et.al. 2016 [62]	+	+	+	+	-	+	-	-	-	4	0	5	Medium
Polgreen et.al. 2015 [63]; Carter et.al. 2015 [64]	?	+	+	-	+	+	+	?	-	2	2	5	Medium
Adibe et.al. 2013 [65]	+	+	?	-	+	+	-	?	-	3	2	4	Medium
Okamoto et.al. 2001 [66]	?	?	+	+	-	+	-	?	-	3	3	3	Medium
Borenstein et.al. 2003 [67]	?	?	+	-	-	+	-	?	-	3	4	2	Medium
Chan et.al. 2012 [68]	+	?	+	+	+	+	-	-	-	3	1	5	Medium
Obreli-Neto et.al. 2015 [69]	+	?	?	+	+	+	-	-	-	3	2	4	Medium

Table 4. Risk of bias assessment of the original clinical trials. A: Random sequence generation; B: Allocation concealment; C: baseline outcome measurements similar; D: baseline characteristics similar; E: incomplete outcome data; F: Knowledge of the allocated interventions adequately prevented during the study; G: protection against contamination; H: selective outcome reporting; I: Blinding of data analysis.

Appendix 4: Economic Evaluations Quality Assessment

CHEC-list	Chan et.al. 2012 (42)	Bond et.al. 2007 (45)	Chen et.al. 2016 (44)	Fishman et.al. 2013 (39)	Shireman et.al. 2016 (38)	Borenstein et.al. 2003 (37)	Polgreen et.al. 2015 (36)	Simpson et.al. 2015 (41)	Adibe et.al. 2013 (43)	Okamoto et.al. 2001 (35)	Obreli-Neto et.al. 2015 (40)	Total
Is the study population clearly described?	1	1	1	1	1	1	1	1	1	1	1	100%
Are competing alternatives clearly described?	0	0	1	0	0	0	0	0	1	0	1	27%
Is a well-defined research question posed in answerable form?	1	1	1	1	1	1	1	1	1	1	1	100%
Is the economic study design appropriate to the stated objective?	1	1	1	1	1	1	1	1	1	1	1	100%
Is the chosen time horizon appropriate in order to include relevant costs and consequences?	0	0	0	0	0	0	0	0	0	0	0	0%
Is the actual perspective chosen appropriate?	0	0	0	0	0	0	1	0	0	0	0	9%
Are all important and relevant costs for each alternative identified?	0	1	1	1	0	1	0	1	1	1	0	64%
Are all costs measured appropriately in physical units?	1	1	1	1	0	1	0	1	1	1	1	82%
Are costs valued appropriately?	0	1	1	1	1	0	1	1	1	1	1	82%
Are all important and relevant outcomes for each alternative identified?	1	1	1	1	1	1	1	1	1	1	0	91%
Are all outcomes measured appropriately?	1	1	1	1	1	1	1	1	1	1	0	91%
Are outcomes valued appropriately?	1	1	1	1	1	1	1	1	1	1	0	91%
Is an incremental analysis of costs and outcomes of alternatives performed?	1	0	0	1	1	1	1	1	1	1	1	82%
Are all future costs and outcomes discounted appropriately?	1	1	1	1	1	1	1	1	1	1	0	91%

Table 5. Economic evaluations quality assessment.

CHEC-list	Chan et.al. 2012 (42)	Bond et.al. 2007 (45)	Chen et.al. 2016 (44)	Fishman et.al. 2013 (39)	Shireman et.al. 2016 (38)	Borenstein et.al. 2003 (37)	Polgreen et.al. 2015 (36)	Simpson et.al. 2015 (41)	Adibe et.al. 2013 (43)	Okamoto et.al. 2001 (35)	Obreli-Neto et.al. 2015 (40)	Total
Are all important variables, whose values are uncertain, appropriately subjected to sensitivity analysis?	0	0	0	1	1	0	0	1	1	0	0	36%
Do the conclusions follow from the data reported?	0	1	1	1	1	1	1	1	0	1	0	73%
Does the study discuss the generalizability of the results to other settings and patient/client groups?	1	0	1	1	1	1	1	1	0	0	1	73%
Does the article indicate that there is no potential conflict of interest of study researcher(s) and funder(s)?	1	1	1	1	1	0	1	1	1	0	1	82%
Are ethical and distributional issues discussed appropriately?	0	1	1	1	1	0	1	1	1	1	1	82%
Total	57,9%	68,4%	78,9%	84,2%	73,7%	63,2%	73,7%	84,2%	78,9%	68,4%	52,6%	71%

Table 5. Economic evaluations quality assessment. *(continued*

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Chapter 4

The Polaris Trial

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4.1 Context

In Chapter 3 the evidence for the cost-effectiveness for MRF was presented. These data were predominantly from the United States of America's health care system [57,66,67,70,71]. However, based on concerns of transferability, local evaluations are recommended when feasible [72]. The Chilean health care system, although having some similarities to other international health care systems, has its own policies, financial management, and clinical culture.

Researchers from the *Pontificia Universidad Católica de Chile* instigated a study where a pharmacy intern implemented MRF [73]. This six-month RCT compared the addition of MRF against usual care of the Chilean CVD program (described in Chapter 2). Simple 1:1 randomisation was achieved using Microsoft Excel©. The trial was carried out in an urban primary care centre which had the highest number of enrolled patients in the country (more than 100,000). In this single centre study, the pharmacy intern based at the primary care centre undertook three patient interviews (one every three months). Inclusion criteria were patients enrolled in the CVD prevention program, older than 65 years and with more than five prescriptions. One hundred and six patients were recruited. The results reported achievement of therapeutic objectives in HTN (OR 3.47 95% confidence interval (CI) 2.14-4.31] and T2DM (OR 2.52 95% CI 1.32-3.61). In addition to improvements in SBP (-10.0 mmHg 95% CI -15.0 – -5.0), glycated haemoglobin (-0.61% 95%CI -0.90 – -0.10]) and LDL cholesterol (-14.6 mg/dL 95%CI -19.2 – -1.96) were reported. These results, although not published, led to the development of a multi-centre cluster RCT (cRCT) named "Polaris" described in this chapter.

4.2 The Polaris Study

The Polaris trial was a collaborative project between University of Technology Sydney (UTS), Pontifical Catholic University of Chile (PUC) and the Chilean government. The

protocol for the cRCT was registered in clinicaltrials.gov (NCT03502109, appendix 1). The protocol attached to this chapter is primarily directed to the economic evaluation of the trial.

4.2.1 Main Objective

To evaluate the clinical, humanistic and economical outcomes of MRF in older adults from a cardiovascular risk program in primary health care.

4.2.2 Secondary Objectives

- To assess the impact of MRF in clinical outcomes and control of health problems in patients with moderate to high CVD risk in public primary care centres in Chile.
- To evaluate the impact of MRF on drug related problems and medication management in public primary care centres in Chile.
- To evaluate the cost effectiveness of MRF against usual care in older adults enrolled in a cardiovascular risk program in primary care centres, from the public third-party payer perspective.

4.2.3 Design and Setting

The study was designed as a multicentre cluster-randomized controlled 1-year trial on public primary health care centres in Santiago, Chile. There are over 600 centres national wide, 160 of which are in Santiago. Centres in Santiago were recruited and those willing to participate signed a commitment form. The intervention group performed MRF, while the control group had usual care alone. Each patient was required to attend at least four visits during a period of 12 months. Due to the nature of the study blinding was not possible for providers, but patients did not know their group.

4.2.4 Economic Evaluation Outcomes

Primary outcomes were QALYs and costs generated in the public health system as inputs to calculate the ICER.

4.2.5 Eligibility criteria

Inclusion and exclusion criteria were established (Table 4.1) for primary care centres (clusters) and patients.

Table 4.1 Eligibility criteria for the Polaris study.

Eligibility Criteria	Clusters	Patients
Inclusion Criteria	Public primary care centres with at least 1 full time pharmacist	65 years or older who signed the informed consent form
	Pharmacists were able to request laboratory exams for cardiovascular parameters such as HbA1c and lipid levels	Included in the national cardiovascular care program with diagnosis of hypertension, type 2 diabetes mellitus or dyslipidaemia
	Pharmacist were able to add their findings to medical records	Classified as Independent by the Barthel index for activities of daily living [74]
	Pharmacists could devote at least 10 hours a week (5 in the control group) to participate in the study	Moderate (5-10%) or high (>10%) 10-year CHD risk using the Chilean Framingham's adapted risk charts [21]
		Five or more daily medications
Exclusion Criteria	Primary care centres attached to a hospital.	Participants of the pilot study
	Private primary care centres.	Low (< 5%) 10-year CHD risk score using Chilean Framingham's adapted risk charts [21]

Notes: CHD: Coronary heart disease; HbA1c: glycated haemoglobin.

4.2.6 Ethics statement

This study was approved by four ethics committees (Southern, South eastern, Western and Eastern metropolitan Health Services Administrators) in Santiago, Chile and the UTS human research ethics committee in Sydney, Australia (UTS Human Research Ethics Committee REF NO. ETH17-1346). Each patient signed an informed consent form. Pharmacists reinforced that patient participation was voluntary and that they could withdraw at any time.

4.2.7 Sample size calculation

A pilot study was conducted on eight primary care centres (four in each group) on the south-eastern sector of Santiago, Chile. Pharmacist in the intervention group received 10 hours of training to provide MRF by the Polaris method and cardiovascular pharmacotherapy. The study was approved by the ethics committee of the south-eastern Health Service Administration. Patients were asked to provide informed consent.

As the study was to test the feasibility of the Polaris method and research methodology, the required number of patients to be recruited in each centre was low (N=12), with patients interviewed once per month for 3 months. Control patients were not interviewed, and their medical and pharmacy data was collected from the official records.

Simple statistical analyses (student-t test) were performed to determine the effect on clinical outcomes used to calculate sample size for the main study.

Table 4.2: Clinical outcomes of the pilot study.

Outcome	Control mean (SD) N= 35	Intervention mean (SD) N=37	Mean difference (SE)	p-value
SBP	145.7 (15.8)	134.5 (16.5)	-11.2 (3.81)	0.006
DBP	82.2 (10.1)	75.7 (10.7)	-6.50 (2.50)	0.01
HbA1c	7.58 (2.05)	7.46 (1.56)	-0.12 (0.53)	0.84
TC	227.0 (85.3)	169.5 (42.6)	-57.5 (15.8)	0.005
LDL	129.9 (49.0)	93.8 (29.3)	-36.1 (9.45)	0.002
HDL	46.9 (11.0)	46.4 (9.17)	0.41 (2.38)	0.83
TG	251.9 (227.5)	165.8 (60.1)	-86.1 (38.7)	0.03
CHD risk score	6.11 (3.60)	6.54 (4.16)	0.43 (0.91)	0.64

Notes: SE: standard error; SBP: systolic blood pressure; DBP: diastolic blood pressure; HbA1c: glycated haemoglobin; TC: total cholesterol; LDL: low-density lipoprotein cholesterol; HDL: high-density lipoprotein cholesterol; TG: triglycerides; CHD risk score: coronary heart disease score using Chilean adapted Framingham's equation.

4.2.7.1 Sample Size Estimates for Main Study

Standardized effect size was determined for the reduction in CVD risk score (0.324) in the pilot study and using a balanced control-intervention relationship of 1:1 with an 80% of statistical power and $p<0.05$. The intra-class correlation (ICC) was 0.03 and having a fixed number of clusters available (24), the resulting cluster size was 20 (design effect = 1.57). With 20% of estimated losses, calculated sample size was at least 576 patients, with 288 in each group and 11-12 clusters in each study group [75].

As some centres presented problems with patient recruitment while others retired early from the study, cluster size was increased to avoid an underpowered study. Most centres had to recruit 30 patients, although there were two centres that had to recruit 45 and one 70 to account for a larger population (median of 35).

4.2.8 Randomization

Cluster-level randomization for primary care centres was conducted to reduce the risk of cross-contamination. After receiving ethics approval and primary care centres agreed to participate, simple randomization was conducted at the cluster level with Microsoft Excel™ random function, using as unit of randomization each primary care centre. Randomization was performed with the presence of at least one representative of each municipality acting as witnesses as instructed by the ethics committees. As one cluster contributed more than 40% of the population of study, it was matched against two other clusters to prevent imbalances between groups. This initial randomization was to determine study group for these matched clusters [75]. A second, simple randomization of the remaining clusters was then conducted.

Patient-level randomisation was not performed. Patients were recruited by direct invitation in the pharmacy unit and/or by referral from GPs and RN, until the sample size number was achieved. Also, participants were not aware of their study group.

4.3 The Polaris Methodology for Medication Reviews with Follow-up

There are several methodologies and guidelines for delivering MR despite some differences in components such as follow-up, patient participation, and interaction with other health professionals. MRF methods share a common goal to optimize the pharmacological treatment in order to achieve the best possible outcomes for the patient[76].

In Latin America, most studies and local initiatives have used the Dader's method for MRF developed by University of Granada, Spain. Reports of this service showed significant results in several publications in cardiovascular patients in Spain's community pharmacy setting and it is available in Spanish language [77–79]. The national conSIGUE program popularized this strategy and reported significant impact on several outcomes such as increases of 56% on the control of health conditions, 6.6 points in HRQoL, and a 49% decrease on emergency department visits[77,79].

Nevertheless, Chilean public primary care pharmacy system differs greatly from the one in Spain. In Chile, public pharmacies are located inside the primary care centres where patients receive free medications for most chronic conditions, particularly for CVD prevention[78]. Additionally, as pharmacists share workspaces and interact with GPs and the clinical team, communication between them is common for issues concerning medications information and availability of medications at the pharmacy unit[33]. The bachelor's thesis conducted on 2015 in Chile, adapted the Dader's methodology to account for these differences, using official medical records and giving more emphasis to contact with GPs. Interestingly, in the single centre RCT study undertaken by the pharmacy intern GPs acceptance to interventions of therapy modifications was superior to those reported by the conSIGUE program (94% vs 50%)[73]. Most of the pharmacist's interventions from the adapted methodology concerned pharmacotherapy modifications,

with only 17% being educational and adherence interventions [73]. In the conSIGUE program, half of the interventions did not required involvement with GPs [77].

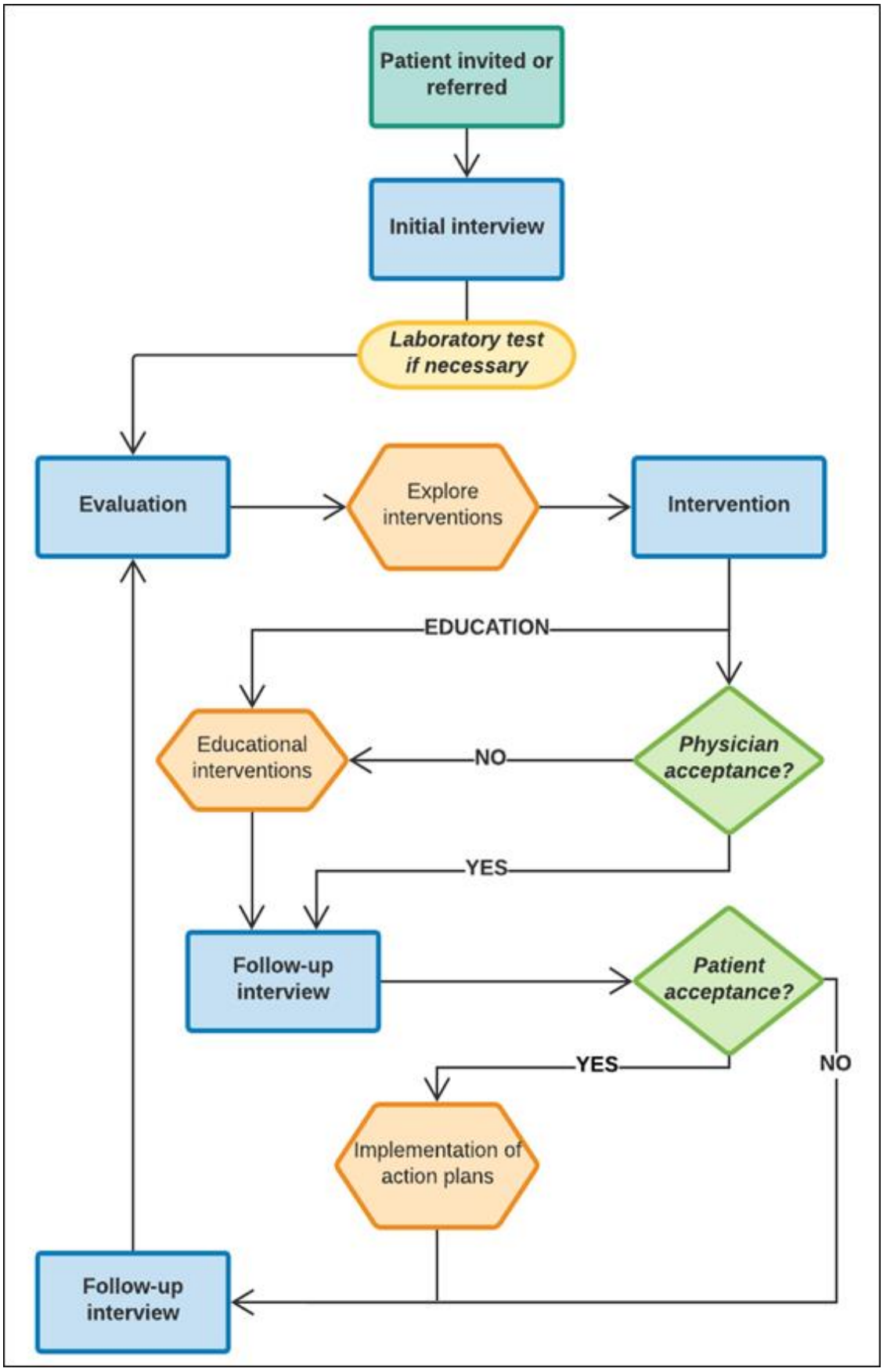
Another problem observed in the Dader's Method for MRF was the lack of sufficient guidance in the pharmacotherapy's evaluation process as it only suggests a general structure, thus depending heavily on the clinical experience and knowledge of the pharmacist and overextending the process. As an example, in the conSIGUE program, "study" and "evaluation" phases used on average 163±114min per patient, 65% of the total MRF service, compared to 35±12 minutes (or 37% of the total MRF service) in the bachelor's thesis [73,77].

Therefore, to develop a Chilean contextualised MRF method, several other methods in addition to Dader's were reviewed, including Pharmacotherapy Workup (PW), United States' medication therapy management (MTM) and United Kingdom's 7-step medication review approach [80–82]. Inputs from the bachelor's thesis were also used [73]. The result of this adaptation was named "Polaris MRF" adopting the name used in this study.

The Polaris MRF method simplified data collection as it was extracted from the patient's official medical and pharmacy records. The method also provides detailed guidance on the evaluation process using process flowcharts to take advantage of the additional available information and encouraged face-to-face contact with GPs to suggest therapy modifications.

As Dader's method use components from MTM and PW, common elements present in all methods as the general structure and patient relevance were maintained, with a circular follow-up and evaluation processes relationship (Figure 4.1).

Figure 4.1. Polaris Method for medication reviews with follow-up.



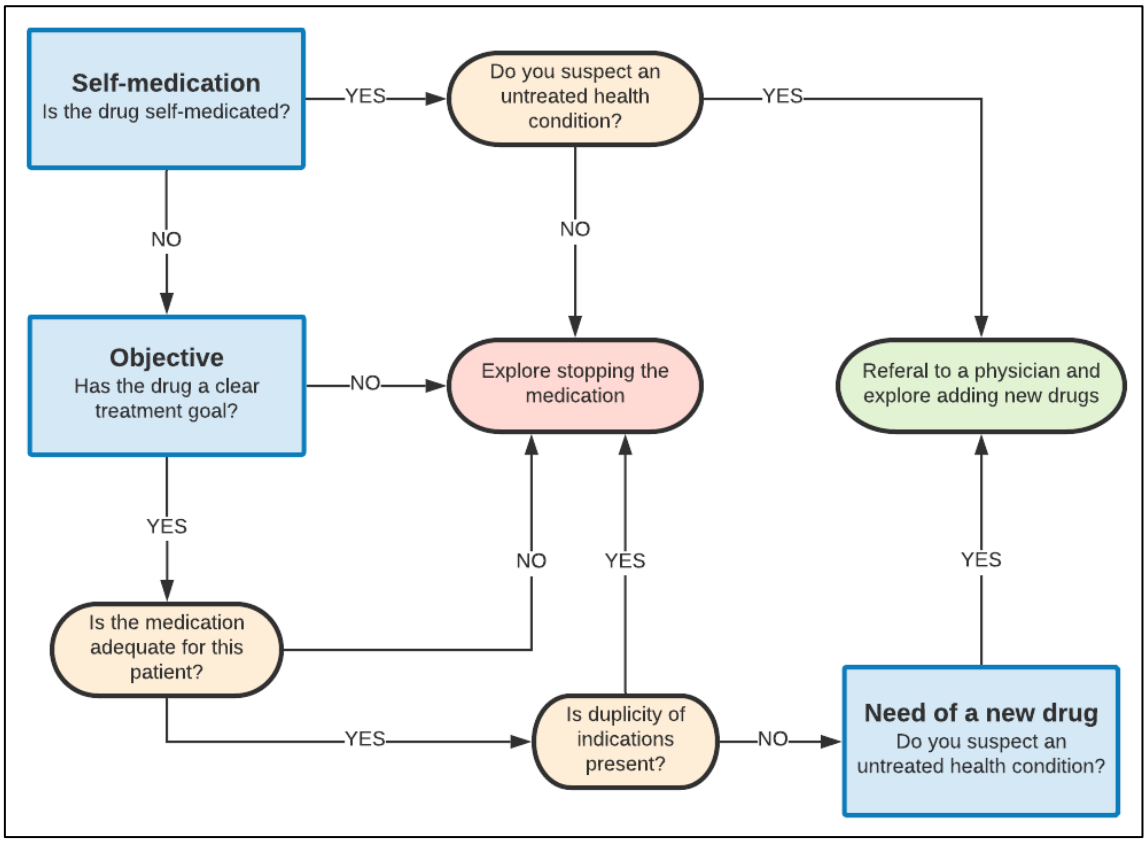
For the evaluation phase, flowcharts were developed as guidance to the process and include recommendations on how to solve these problems, as reported by the evidence and the bachelor's thesis [73,77,80–82]. Current clinical guidelines and evidence are used to establish the risk-benefit balance for each indication and suggest therapeutic modificatios when necessary.

The flowcharts followed the original approaches for the analysis on the pharmacotherapy by need or indication, effectiveness, medication adherence and safety [73,78,80–82].

Need or Indication Analysis

This phase analysed the medications and health conditions, exploring inappropraite indications and duplications (Figure 4.2).

Figure 4.2. Need or indication analysis.



Effectiveness Analysis

The objective is to analyse if medications described as “needed” by the previous analysis are effective in achieving the therapeutic targets established by the clinical team. It accounts for factors like underdosing, medication non-adherence and undertreated conditions (Figure 4.3).

As medication non-adherence is a complex phenomenon, a specific flowchart is provided to explore common causes and suggested interventions (Figure 4.4).

Figure 4.3: Effectiveness analysis.

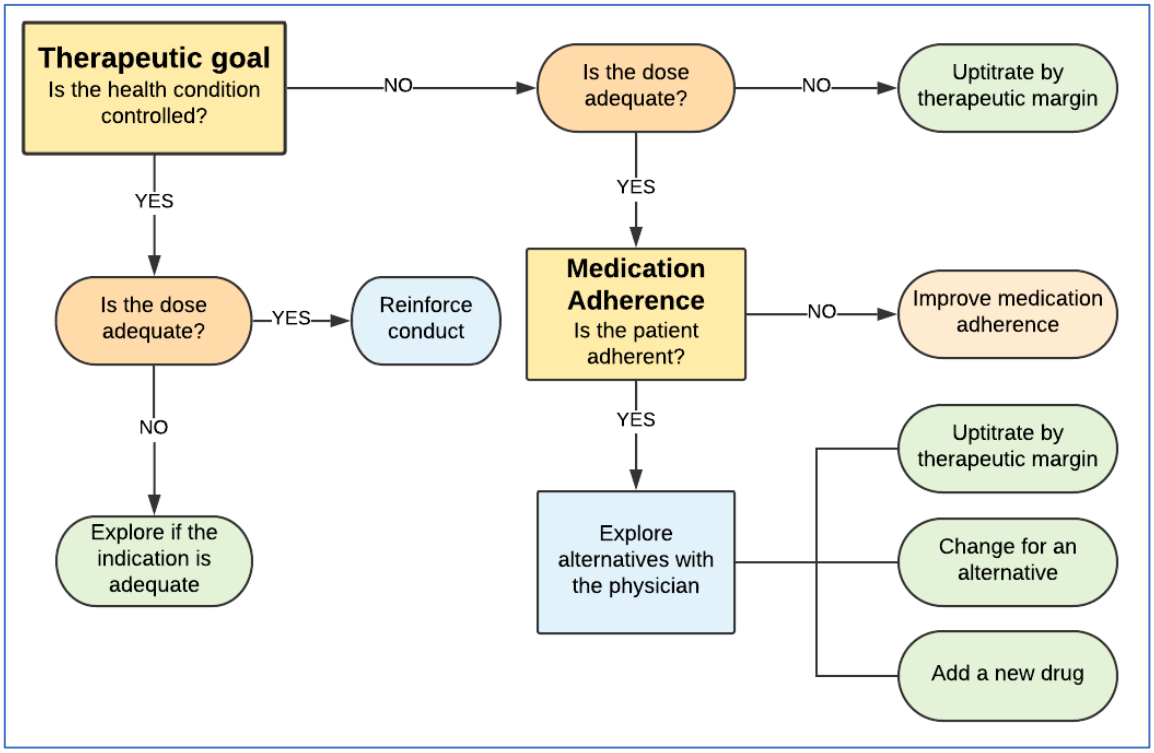
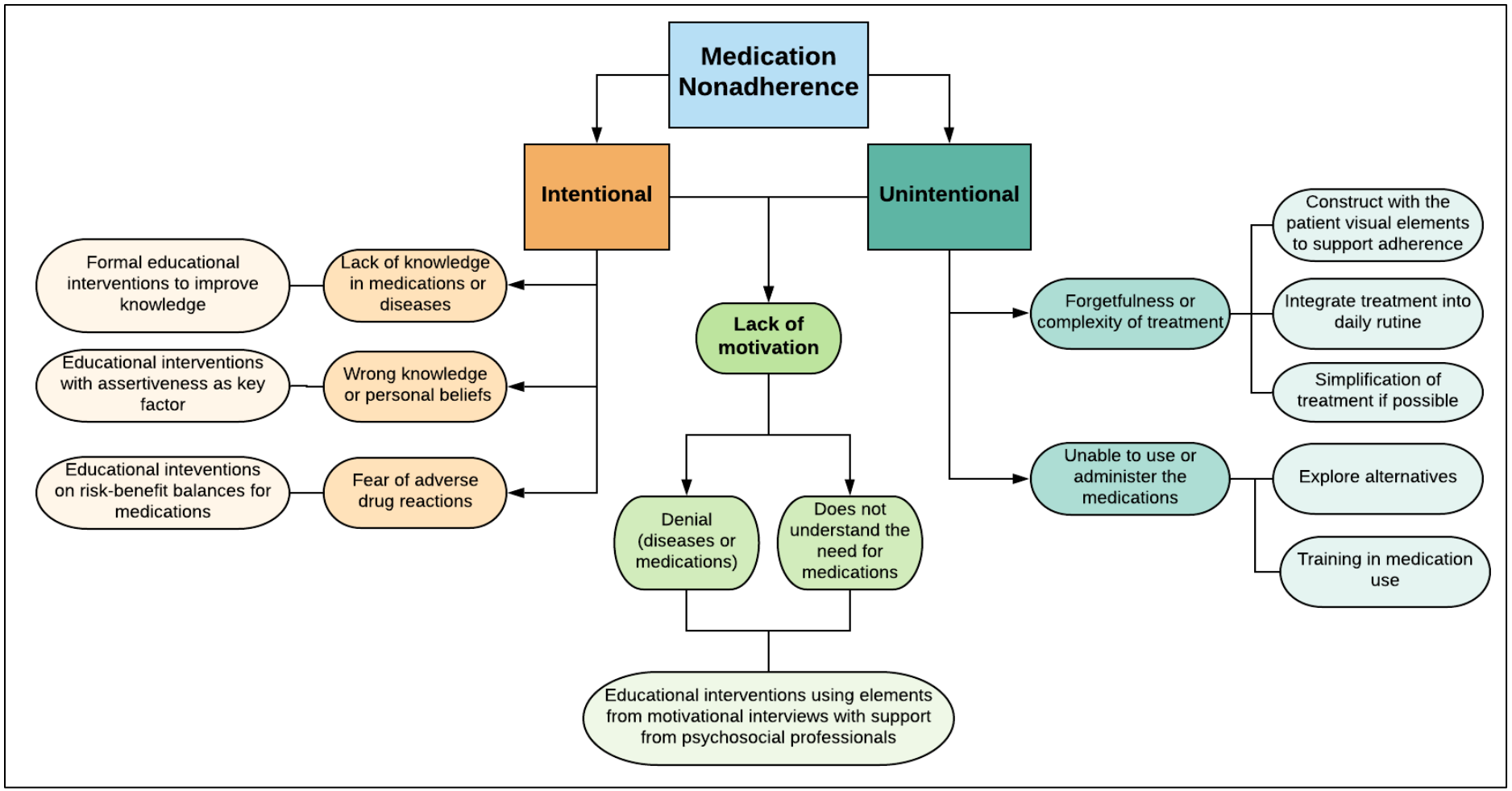


Figure 4.4: Medication non-adherence analysis.

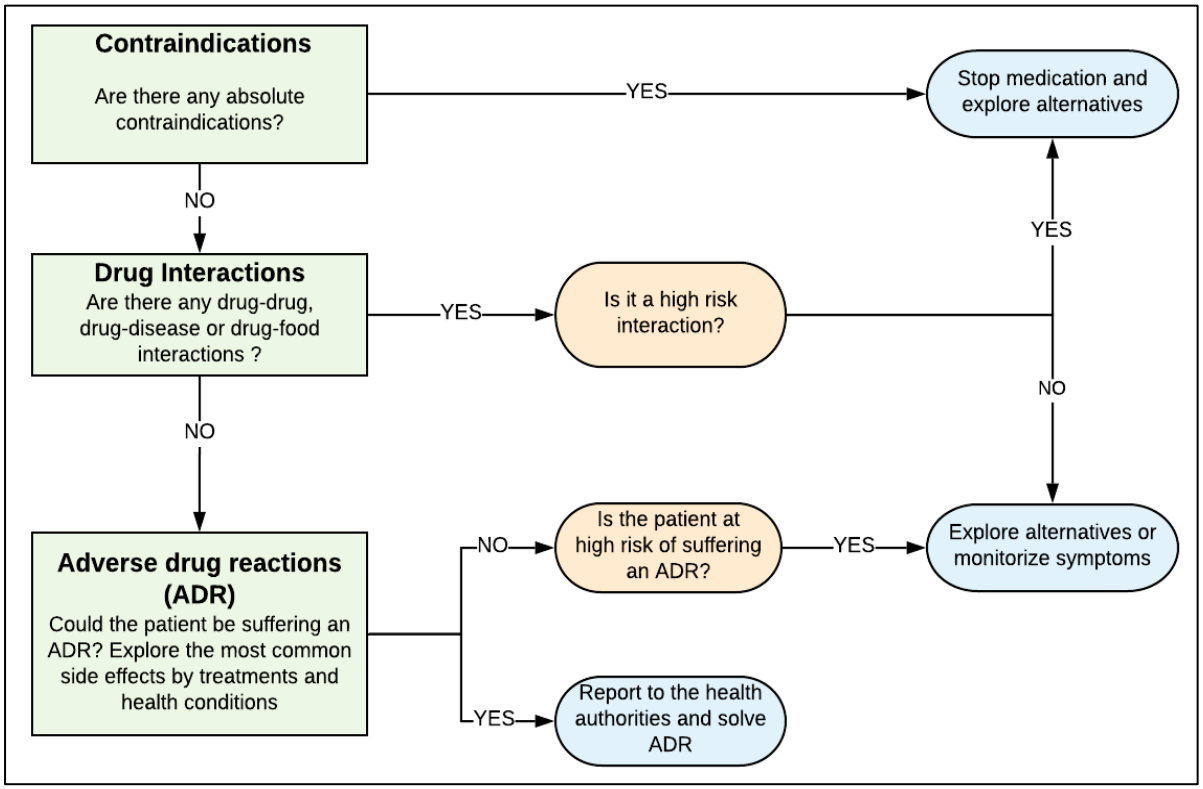


Analysis for safety of the medications

The analysis for safety of pharmacotherapy was divided on two stages: an initial analysis on the effect of characteristics or properties of each medication, and a second analysis to account for the patient personal characteristics (as kidney or liver diseases) that could influence medications safety.

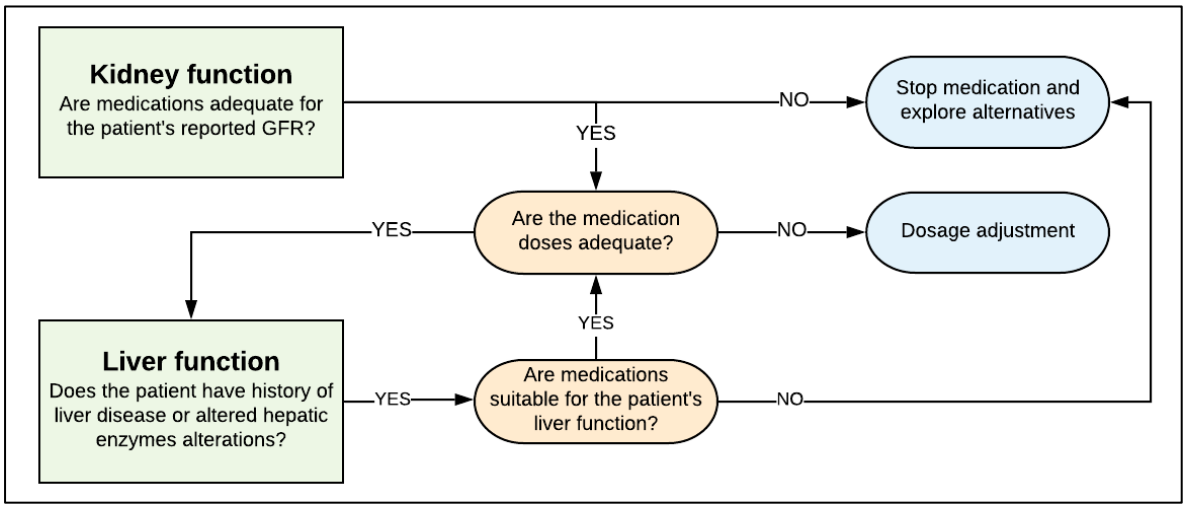
This part of evaluation and analysis focusses on potential contraindications, drug interactions and adverse drug reactions (ADR) (Figure 4.5). Individual medication profile for absolute contraindications and moderate to severe interactions and ADR should be addressed as a priority.

Figure 4.5. Safety analysis by medication characteristics



The second safety analysis accounts for individual-patient health characteristics and conditions that could increase risks while using medications, evaluating results from kidney and liver tests (Figure 4.6).

Figure 4.6. Safety analysis by patient characteristics.



Notes: GFR: Glomerular filtration rate

Description of the MRF Service and TIDieR Checklist

As a product of this process, with the objective to standardize and encourage replication of this intervention by clinicians or other researchers, the template for intervention description and replication (TIDieR) checklist was completed [83].

4.3.1 Template for Intervention Description and Replication Checklist for the Polaris trial

TIDieR
Template for Intervention Description and Replication

The TIDieR (Template for Intervention Description and Replication) Checklist:

Information to include when describing an intervention and the location of the information

Item number	Item
1.	**BRIEF NAME** Polaris method for medication review with follow-up (MRF) in primary care.
2.	**WHY** A meta-analysis conducted in 2019 evaluated the effect of MRF in cardiovascular disease (CVD) risk factors in different ambulatory settings. Although the data had high heterogeneity, prediction intervals (PI) showed that pharmacists-led MRF improved the control of hypertension (OR 2.73 [PI 1.05, 7.08]), type 2 diabetes mellitus (OR 3.11 [PI 1.17, 5.88]), and high cholesterol (OR 2.52 [PI 1.06, 5.34]). [39] MRF has shown positive results in the management of chronic conditions, particularly in cardiovascular diseases. MRF addresses some causes of treatment failure in CVD patients such as clinical inertia and medication non-adherence [73]. **WHAT** MRF was conducted four times a year on older patients, attending a primary care centre, with five or more prescribed medicines and moderate-to-high 10-year coronary heart disease (CHD) risk using Framingham's scores adapted to the Chilean population [21].

3. **Materials**: The research team funded by the project funds, used face-to-face teaching to train two practice change facilitators (PCF), in the Polaris method of MRF and implementation science. PCFs, also funded by the project funds, trained pharmacists in the intervention group in the process and delivery of MRF according to the Polaris methods. Face-to-face case studies and patient simulations with role-playing were used. A registered nurse (RN) lecturer trained pharmacists in vitals assessment using previously calibrated blood pressure measurement units (OMRON® HEM-7121), blood glucose monitors (PRODIGY® AUTOcode) with pen-like needles, finger oximeters (Choicemmed ® MD300C11) and measurement tapes. The same instruments were used during the intervention period. The RN lecturer also trained pharmacists from the intervention group in health education using face-to-face training, didactic materials and games.

   A standardized MS Excel ® registry was used for gathering all patient data using codification without personal information (Figure 4.7).

4. **Procedures**: Pharmacists of the intervention group were trained for 15 hours. This was divided in three hours for MRF methods, data recording and the development of a clinical case; one and a half hours for pharmacist-general practitioner collaboration; four and a half hours in training of vitals assessment, health education, clinical interview techniques using clinical cases; three hours in cardiovascular pharmacotherapy; three hours of MRF role-playing simulation performed in couples so each pharmacist could do it at least once.

   Pharmacists of the control group were trained by the PCF for one and a half hours in data recording, and by a registered RN lecturer for one and a half hours in vitals assessment.

   PCF were pharmacists with experience in clinical pharmacy and MRF. They were assigned to support in situ the delivery of MRF service and had periodical meetings with pharmacists and health centres' managers. The PCF resolved causes of barriers and

encouraged the implementation of MRF in each primary care centre, providing additional in-situ training or collaborating with the centre manager when necessary. PCFs were trained for three hours on implementation models' strategies to address implementation factors [84].

All patients continued to receive standard care by the national CVD program guidelines provided by a team of local general practitioners (GPs), RN and dietitians. According to these guidelines, Pharmacists are complementary professionals to this core team. [30]

Once recruited by the centres, patients were invited to the study and signed an informed consent form. MRF was conducted in a step-wise approach: it started with a brief review of medical and pharmacy records prior to the initial interview, then an initial interview (30 minutes), followed by an evaluation phase to develop an action plan, face-to-face collaboration with GPs (when needed), and a minimum of three follow-ups to implement and evaluate interventions (20 minutes each).

Patients that met the inclusion criteria were invited to the study by the pharmacist or pharmacy technicians in the pharmacy unit. Another option was a referral by a GP, RN or other professionals.

The following steps were followed to conduct MRF:

- Before the first interview, a brief review of the patients' health problems and pharmacotherapy documented in the patients' medical records was conducted. This review was done to evaluate current conditions, therapy and other relevant information, and to ensure or maintain the currency of clinical records.
- An initial interview (estimated on 30 minutes) was conducted to collect all clinical data and medicines information directly from the patient. Non-adherence to medications was measured using a medication adherence questionnaire (MAQ). Quality of life was registered through the EQ-5D-3L instrument administered by the pharmacists as most patients were illiterate. Pharmacist assessed/measured the patient's vitals, using a standardized technique defined by national guidelines of the cardiovascular health program. This data was registered in clinical records and was used for the next phase along with the

information registered by other professionals on previous consultations. Patients' knowledge of their health conditions was explored by pharmacists using four questions - What is it? What is causing it? What are its risks? Do you think you will always have the health problem? For each medications the questions were - What it is for? What are their benefits? What are their risks? How do you take it? Pharmacists did not provide any clinical or educational intervention during this initial interview unless there was a need for urgent actions to address severe or acute health issues/ problems. Pharmacists were able to order laboratory exams if the patient did not have updated results (in the last 4 months).

- After the initial interview, pharmacists conducted a desk medication review using collected data. Standardized flowcharts provided by the research team were used to assess health problems and detect/resolve all drug-related problems (DRP). Problems representing an immediate risk for the patient were prioritized (Figures 4.1-6, translated directly from the Spanish versions). Pharmacists then developed an action plan to resolve any issues or DRP. For educational interventions, no additional contact with other health professionals was required. Interventions that included modifications to pharmacotherapy were undertaken face-to-face to GPs. Pharmacists did not have any prescribing authority.
- The second interview (first follow-up) was focused on providing educational interventions. Only those accepted by the patient were implemented. No more than three interventions were allowed per interview as more could cause confusion and compromise their effectiveness. If there were no other issues, or the clinical situation required action, implementation of previously agreed (with GPs) pharmacotherapy changes could be performed.
- In the third interview (second follow-up) pharmacists evaluated the results of each intervention with the patient. Changes in pharmacotherapy agreed with the GPs were implemented with the patient's approval. The patient care plan was re-evaluated with available information.

- In the final interview (third follow-up), the pharmacist evaluated the effectiveness of all interventions with inputs and explored future steps. A final order for laboratory exams was provided to evaluate results. Pharmacists could continue following-up patients, but no more data was collected for the study.

Patients in the usual pharmacy care group received standard care as per the national CVD program guidelines provided by a team of local GPs, RN and dietitians. Usual care pharmacists collected data in 4 short interviews (15 minutes max) and from medical and pharmacy records, answering patients' questions as performed in usual care. Pharmacists informed clinical teams when urgent interventions were needed.

WHO PROVIDED

5. Primary care pharmacists trained in cardiovascular pharmacotherapy, MRF, vitals assessment, clinical interviews and pharmacist-GP collaboration. The recruited pharmacists did not have previous training in MRF before the study and did not have more than three years of experience as primary care pharmacists.

PCF trained in health services implementation factors and MRF service [84].

HOW

6. Pharmacists interviewed patients face-to-face. Also, pharmacists had face-to-face meetings with GPs to explore pharmacotherapy modifications (see process above).

WHERE

7. Interviews with patients were conducted in their respective primary care centres using private consulting zones. Pharmacists met with GPs in their clinical offices or meeting rooms.

WHEN and HOW MUCH

8. Each patient in the MRF group was interviewed at least four times for one year. The first interview was longer to gather initial patient data (average 35 minutes), with shorter follow-up visits (average 18 minutes). More interviews could be scheduled if it was clinically required.

The control group collected data at four time points during the year.

TAILORING

9. It was suggested, but not required that for patients that did not meet therapeutic goals for hypertension, type 2 diabetes mellitus or dyslipidemias; had a severe adverse drug reaction (ADR) or interaction, additional visits could be programed as clinically required. However, this only occurred with a specific pharmacist with 15 patients.

Suggested frequency of appointments was as follows:

- Hypertension: Every 7-14 days until the achievement of blood pressure goal.
- Type 2 Diabetes: every 7-14 days until the achievement of fasting glucose goal. Then 30 days later, this was measured again. Finally, goal attainment was achieved through glycated haemoglobin three months after therapy change.
- Dyslipidaemias: every 4-6 weeks until the achievement of lipid goals.

Exceptional cases: patients with a suspected moderate or severe ADR or those who have a severe pharmacological interaction had follow-ups every 7-14 days until the issue was resolved.

MODIFICATIONS

10.‡ The intervention was not modified during the study. The PCFs checked for fidelity [84].

	HOW WELL
11.	Fidelity assessment: Patient records were randomly analysed by a PCF to verify that each pharmacist was fooling the step approach and conducting the service according to the protocol. If issues arose, additional field training was provided when necessary and other interventions were agreed with pharmacists or the primary care centre managers [84].
12.‡	Fidelity assessment for adherence to the protocol: 75% of pharmacist delivered the MRF service according to the methodology.

Figure 4.7. Polaris data file.

POLARIS DATA FILE

Visit duration (min)		Civil status		Age	
PATIENT CODE		Gender		Weight (Kg)	
Educational level		Smoker		BMI	

Waist circumference	
Height (m)	

№	Health conditions	Other	Controlled (Y/N)	Worried about (Y/N)	General knowledge (Y/N)	Know Risks (Y/N)
1						
2						
3						
4						
5						
6						
7						
8						

polaris
PROGRAMA DE SEGUIMIENTO FARMACOTERAPÉUTICO

№	Medication	Other	Health condition	Other	Dosage regime				Complies (Y/N)
1						every		hours	
2						every		hours	
3						every		hours	
4						every		hours	
5						every		hours	
6						every		hours	
7						every		hours	
8						every		hours	
9						every		hours	
10						every		hours	

11						every		hours	
12						every		hours	
13						every		hours	
14						every		hours	
15						every		hours	
16						every		hours	
17						every		hours	
18						every		hours	

MEDICATION ADHERENCE AND ADVERSE DRUG REACTIONS (ADR)

№	Medication	Adherence? (Y/N)	Type of nonadherence (intentional/unintentional)		Knowledge What it is for? (Y/N)	ADR Class	ADR Details
1							
2							
3							
4							
5							
6							
7							
8							
9							
10							
11							
12							
13							
14							
15							
16							
17							
18							

VITALS AND LABORATORY TESTS

Date		
Blood pressure (mmHg)		
Heart rate (beats/min)		
Fasting glicemia (mg/dL)		
Capillary glicemia (mg/dL)		
HbA1c (%)		
ACR (mg/g)		
K+ (mEq/L)		
Na+ (mEq/L)		
GFR (ml/min) MDRD		
Serum Cr		
CrCL (Ck-Gs)		
CKD-EPI		
TC (mg/dL)		
LDL (mg/dL)		
HDL (mg/dL)		
TG (mg/dL)		
CVDR score (%)		

Standarized tests	
MAQ (Y/N)	
EQ5D	
EQ5D VAS	

OTHER

ADDITIONAL TESTS

Parameter	Range	Value
T4		
TSH		
SAT O2 (%)		

Explore DRP by provided flowcharts

Nº	Date	Medication	Other	Health condition	DRP	Obs	ADR by Naranjo	ADR Severity

Plan de acción y formulación de la intervención						Acceptance			
Evaluation time	Intervention	Background	Goal	GP intervention		GP	Motive for refuse	Patient	Motive for refuse
				Date	Time				

Patient follow-up		Obs		DRP ressolved (Y/N/P)	Date	Discharge DRP (Y/N/P)
Date	Time	First evaluation	Second evaluation			

Explore DRP by provided flowcharts

Nº	Date	Medication	Other	Health condition	DRP	Obs	ADR by Naranjo	ADR Severity

Plan de acción y formulación de la intervención						Acceptance			
Evaluation time	Intervention	Background	Goal	GP intervention		GP	Motive for refuse	Patient	Motive for refuse
				Date	Time				

Patient follow-up		Obs		DRP ressolved (Y/N/P)	Date	Discharge DRP (Y/N/P)
Date	Time	First evaluation	Second evaluation			

4.4 Economic Evaluation

The economic evaluation was designed as a cost-utility analysis. This type of evaluation was chosen because CVD have both acute and long-term consequences that may affect patients' HRQoL [85]. The evaluation was comprised of two analyses:

- Economic evaluation alongside the trial (Chapter 5). This analysis was performed with STATA© 16.1 using costs and benefits measured directly from the trial.
- Decision-analytic model (Chapter 6). The model was built using TreeAge Pro© Healthcare extrapolating costs and benefits through a lifetime time horizon using inputs from the trial and the literature.

The rest of this chapter will describe data collection for inputs of these two evaluations.

4.4.1 Health Benefits

To conduct the first analysis, the effect of MRF was measured in terms of HRQoL as input to calculate QALYs. Patients' perceived HRQoL was measured using the EQ5D, three level version questionnaire [42,86]. This tool uses both a descriptive system and a visual analogue scale. The descriptive system evaluates five dimensions: mobility, personal care, daily activities, pain and anxiety/depression, each dimension had three levels of severity codified from one (not a problem) to three (a severe problem) [42,86]. A visual analogue scale was used, where 0 was equivalent to death and 100 to the best imaginable health state possible. This assessment was performed in each interview usually by the pharmacist as most patients were illiterate. Results from each dimension were summarized in a composite measure, i.e. if a patient had low severity in each dimension it was registered as "11111". These composite measures were weighted using utility weights from a value set that used a time trade-off method on a representative sample of the study's setting [43].

4.4.2 Costs

Both analyses used cost data gathered from the trial and government published data. This required identification of resources, quantification within the trial and their valuations according to local price weights. Both evaluations used the public third-party payer perspective according to local guidelines [87]. Therefore, identified resources were direct costs to the public healthcare system. Costs are described in Table 4.3:

Table 4.3. Identified resources and unit prices used in the economic evaluation.

Resource	Resource source	Unit price (USD)	Unit price source
Pharmacist time (hour)	Trial	$22.2	Centres 2019 wages [88]
General practitioner time (hour)	Trial	$30.6	Centres 2019 wages [88]
Pathology tests	Trial	Chapter 5	Public health insurance price weights [89]
Medications	Trial	Chapter 5	National medication supply central 2019 prices [90]
Training and PCF (hour)	Trial	$33.01	Centres 2019 wages + 5% [88]
Emergency department visit	Government records	$24.82	Public health insurance price weights [89]
Hospitalization (DRG value)	Government records	$5115.21	Local diagnostic related group guidelines 2019 [91]
Specialist visit	Government records	$23.31	Public health insurance price weights [89]

Notes: DRG: diagnostic-related group; PCF: Practice change facilitator; USD: United States dollar.

Price weights and costs were reported in 2019 United States dollar (USD). Other currencies or years were updated using the online tool developed by Cochrane Economics Methods Group and the Evidence of Policy and Practice Information and Coordinating

Centre [92]. Purchasing power parity values available from the International Monetary Fund were used [93].

4.4.3 Decision-analytic Model inputs

For the model, patients' clinical data was used to calculate transition probabilities. This data was collected in the Polaris data file (Figure 4.7) and are listed in Table 4.4.

Table 4.4. Patients' clinical characteristics used for the decision-analytic model.

Baseline characteristics	Clinical parameters
Age	Body mass index
Gender	Systolic blood pressure
Smoking status	Diastolic blood pressure
Diagnosis of heart failure	Total cholesterol
Diagnosis of type 2 diabetes mellitus	LDL cholesterol
Diagnosis of atrial fibrillation	HDL cholesterol
Myocardial infarction history	Triglycerides
Stroke history	
Statin use	
Aspirin use	

With this data, the next two chapters present the analyses and results of the economic evaluation alongside the Polaris trial (Chapter 5) and the decision-analytic model to extrapolate results to a lifetime time horizon (Chapter 6).

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Chapter 5

Pharmacist-led Medication Review in Primary Care for Cardiovascular Outcomes: Cost-utility analysis alongside a cluster randomized clinical trial

Ahumada-Canale A, Vargas C., Balmaceda C. Martinez-Mardones FJ, Plaza-Plaza JC, Benrimoj S, Garcia-Cardenas V. Medication Review with follow-up for Cardiovascular Outcomes: A Trial-based Cost-utility Analysis. (SUBMITTED TO CIRCULATION (CIRCULATIONAHA/2020/046444))

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Author(s): Antonio Ahumada-Canale, University of Technology Sydney
Constanza Vargas, University of Technology Sydney
Carlos Balmaceda, Pontifical Catholic University of Chile
Francisco Martínez Mardones, University of Technology Sydney
Jose Plaza-Plaza, Pontifical Catholic University of Chile, Santiago, Chile.
Shalom Benrimoj, University of Technology Sydney, Sydney, Australia
Victoria Garcia-Cardenas, University of Technology Sydney, Sydney, Australia

Title: Medication Review with Follow-up for Cardiovascular Outcomes: A Trial Based Cost-utility Analysis

First author's surname and short title: Ahumada-Canale, BPharm

Authors:

- Antonio Ahumada-Canale, BPharm. Graduate School of Health, University of Technology Sydney. Sydney, New South Wales. Australia.
- Constanza Vargas, MSc. Centre for Health Economics Research and Evaluation. University of Technology Sydney. Sydney, New South Wales. Australia.
- Carlos Balmaceda, Msc. Unidad de Evaluación de Tecnologías en Salud, Centro de Investigación Clínica, Faculty of Medicine, Pontificia Universidad Católica de Chile. Santiago, Región Metropolitana. Chile.
- Francisco Martínez-Mardones, BPharm. Graduate School of Health, University of Technology Sydney. Sydney, New South Wales. Australia.
- Cristian Plaza-Plaza, PhD. Facultad de Química y de Farmacia, Pontificia Universidad Católica de Chile. Santiago, Región Metropolitana. Chile.
- Shalom Benrimoj, PhD. Emeritus Professor University of Sydney. Sydney, New South Wales. Australia.
- Victoria García-Cárdenas, PhD. Graduate School of Health, University of Technology Sydney. Sydney, New South Wales. Australia.

Contact information for the corresponding author:

Antonio Ahumada-Canale, BPharm, Graduate School of Health, University of Technology Sydney. PO Box 123 Broadway, New South Wales, 2007. Australia. AntonioOsvaldo.AhumadaCanale@uts.edu.au. Phone (61) 466 964 948.

Total word count: 6353

Abstract

Background: Cardiovascular diseases (CVD) pose a clinical and economic burden on health systems. Pharmacist-led medication review with follow-up (MRF) has internationally proved to be clinically effective, as well as cost-effective in the prevention of CVD. Evidence in Latin America is sparse.

Methods: A trial-based cost-utility analysis from a cluster randomized controlled trial, the Polaris trial, was conducted. Older adults with five or more prescriptions, moderate or high CVD risk and members of a primary care CVD prevention program were included. The intervention was comprised of pharmacists' training, MRF and a practice change facilitator and was compared to usual care. Patients were followed-up for a year. The economic evaluation alongside the trial was conducted from the public third-party payer perspective over the trial's time horizon. Health-related quality of life was measured directly from the trial with the EuroQoL 5D questionnaire to estimate quality-adjusted life years (QALY). Relevant resources identified were pharmacists' time, general practitioner time, practice change facilitator time, training, medications, pathology tests, emergency department visits, hospitalizations and specialists' visits. Costs were measured directly from the trial. To account for missing values, clustering effect and covariates, a multilevel model with multiple imputation was used to estimate costs and QALY. Results from the model were combined in the incremental cost-effectiveness ratio (ICER), and uncertainty was represented through non-parametric bootstrap.

Results: Six clusters per arm finished the study with 174 patients in the intervention group and 150 in the control group. Baseline differences in the number of chronic diseases and civil status were observed. Intervention costs were $76.71. The ICER for the base-case was $434.4/QALY. Bootstrap analysis deemed 98.8% of the iterations as cost-effective, and the rest as dominant. In patients with available hospitalization data and with more than nine prescriptions, the proportion of dominant iterations increased to 31.8% and 41.0% respectively.

Conclusions: Pharmacist-led MRF was deemed as a cost-effective addition to usual care with low uncertainty. Patients with more than nine prescriptions appear to benefit more from the intervention. Implementation should be evaluated.

Clinical trial registration: www.clinicaltrials.gov (NCT03502109).

Introduction

Globally, non-communicable diseases (NCD) are the leading mortality cause, being responsible for 41.1 million deaths annually with 43.3% due to cardiovascular diseases (CVD)[1]. CVD, such as stroke or ischaemic heart disease (IHD), have acute and long-term consequences that increase the economic burden on health care systems. An international study reported that stroke and IHD were the leading cause of disability-adjusted life years (DALY) accounting for 18.9% of NCD's associated DALY[2]. It is expected that by 2030 CVD will have global costs of 1 trillion USD[3]. A similar trend is expected in Latin America where costs were estimated at 26 billion USD in 2010, and are expected to rise 22% by 2030[3].

CVD are caused by known risk factors, some of which are modifiable through interventions in patients' behaviours or use of prescription medicines[4]. Evidence-based treatment guidelines have been developed for the management of the most relevant risk factors associated with CVD, mainly HTN, T2DM and DLP[5–7]. Despite the availability of these tools to control CVD, there is still evidence suggesting that therapeutic objectives are not being achieved. In the Latin American region, 76.4% of patients have high blood pressure, 31.2% high fasting glucose and 57.5% elevated cholesterol, suggesting that treatment guidelines may not be enough to manage and prevent CVD[8].

In the last 20 years, health authorities in Chile have adopted policies to address CVD, some of which follow the World Health Organization (WHO) recommendations[9]. In 2014, funding focused on HTN, T2DM and DLP was introduced to ensure access to medicines and for pharmacists to promote rational use of medications[10]. The WHO recommends the inclusion of pharmacists in patient-centred services to aid in the control of NCDs[11]. Medication review with follow-up (MRF) is one of the professional pharmacy services recommended by this organization that has been shown to be an effective strategy in controlling CVD risk factors[11]. A meta-analysis comparing MRF with usual care in ambulatory settings found that therapeutic goal attainment was improved in HTN (OR 2.73 95%PI 1.05-7.08), T2DM (OR 3.11 95%PI 1.17-5.88) and DLP (OR 1.91 95%PI 1.05-3.46)[12].

Nonetheless, when implementing a new intervention in healthcare systems with constrained budgets, economic evaluations should be conducted to assess value for money and ensure that the additional costs are worth the additional benefits gained. A systematic review reported that 10 out of 11 economic evaluations of MRF conducted alongside trials had positive outcomes in HTN, DLP and T2DM[13]. Two of these evaluations reported MRF to be dominant against usual care (more benefit at a less cost)[14,15]. Two reported cost-utility analyses (one of them conducted in Latin America) reported an incremental cost-effectiveness ratios (ICER) of US$612.7 and US$59.4/QALY. Both bellow the suggested settings' cost-effectiveness thresholds[16,17]. However transferability issues were reported, mainly because the cost-utility analyses were only performed in two studies, usual care was not always

clearly described, time horizons were usually no longer than a year, relevant resources were not reported, and an uncertainty analysis was not always performed[13].

To ascertain the transferability and produce data for the local context, a clustered randomised controlled trial (cRCT), the Polaris trial, was conducted in Chile to evaluate the clinical, economic and health-related quality of life (HRQoL) impact of pharmacist-led MRF in HTN, DLP and T2DM in the primary care setting. This paper reports on the objective to evaluate the cost-effectiveness alongside this cRCT comparing the addition of MRF to usual care compared to usual care from the public third-party payer perspective.

Methods

Measurement of effectiveness: Polaris clinical trial.

The trial is registered and described in clinicaltrials.gov (NCT03502109). In brief, the cRCT evaluated the addition of pharmacist-led MRF in primary care against usual care alone. Each primary care centre was considered a cluster and all were located in Santiago, Chile. Centres were considered eligible if they had a full-time employed pharmacist that was available to allocate 10 hours/week for trial-related activities which required, among other things, to register findings in the official patient medical record and had a private consultation room. Private funded centres and hospital-based outpatient clinics were excluded. Randomization was conducted at a cluster level. This study was approved by the ethics committee of each Health Service Administration and by the University of Technology Sydney Human Research Ethics Committee and all participants signed an informed consent form. The trial was carried out from January 2018 until July 2019, using an MRF methodology adapted to primary care based on previously published methods[18,19]. Pharmacists interviewed patients every four months over one year. This intervention (MRF) is described in detail in appendix 1, using the TIDieR checklist [20]. Overall, there were three main components of the intervention:

- Pharmacists' training: Before patient recruitment, pharmacists in the intervention group (IG) were trained in a five-day workshop that included MRF methods, general practitioner (GP)-pharmacist collaboration, CVD risk factors treatment, interview skills, patient education and vitals measurement.
- MRF: Each patient received MRF as per the described method in a step-wise approach. Before the first interview, medical and pharmacy records were reviewed. In the first visit, disease control and medications were evaluated using patients' inputs. Knowledge about medications, CVD risk factors, adverse drug reactions, and patient's preferences, were also assessed. With the collected information, a care plan was developed with recommendations and interventions tailored to each patient. Educational interventions were prioritised in the second visit. In the next phase, medication-related recommendations were made to the GP and then implemented in follow-up visits.
- Practice change facilitator (PCF): To aid in the implementation of MRF, a pharmacist with experience in this service, trained in the methods and implementation science, followed up pharmacists periodically. The objective of these visits was to assist with the fidelity of the intervention, detecting and addressing causes of barriers and facilitators[21]. As a process indicator, fidelity was evaluated as the percentage of MRF phases completed by pharmacists at each PCF visit (first interview, study and evaluation, intervention and follow-up).

Target population

Inclusion criteria were adults (65 years or older) with five or more prescriptions, enrolled in the CVD prevention program and deemed as independent according to the Barthel index for activities of daily living[22]. Patients were excluded if they had low coronary heart disease (CHD) risk according to Framingham tables adapted to the local population[23]. The IG added MRF to usual care, while the control group (CG) was usual care alone. Usual care was comprised of a family medicine model proposed by the WHO composed by a team of GPs, registered nurses (RN) and dietitians (without pharmacist involvement)[24]. This team of professionals cared for patients from a defined geographical location. They have periodical case meetings and consultations with patients every 4-6 months.

Economic Evaluation

The research was conducted and reported in accordance with the Consolidated Health Economic Evaluation Reporting Standards (CHEERS) checklist and the local guideline for economic evaluations[25,26]. The evaluation is summarised up in Table 1.

Measurements and Valuation of Patient-reported Outcomes

Patient-reported outcomes were evaluated as quality-adjusted life years (QALY). HRQoL was measured using the Chilean version of the EuroQol five-dimension three-level (EQ-5D-3L) questionnaire[27,28]. Patients determined their HRQoL perception describing their health in five dimensions (mobility, personal care, daily activities, pain and anxiety/depression); each dimension had three levels of severity. Patients were also required to rate their overall health in a visual analogue scale (VAS) that ranged from zero (worst health state imaginable) to 100 (best imaginable health). The questionnaire was administered at each visit. Ideally, it should be self-completed; nevertheless, pharmacists had to administer it to patients, as almost half of the study population was illiterate. Utility scores were calculated using the Chilean tariff that based its analysis in the time trade-off approach using a representative sample[29]. Based on these utility values, QALYs were estimated according to the area under the curve method[30].

Resource use and Costs

Resources were measured directly from the trial (Table 2). Hospitalizations, emergency department (ED) visits and specialists' visits were extracted from local data sources considering the same period as the trial for a subset of clusters with available data. Unit prices are reported in Table 2.

To determine if hospitalisations were related to medication related problems , they were evaluated by three GPs using the methodology adapted from Malet-Larrea et al[35]. The evaluators answered "yes" or "no" if it was considered that the cause of the hospitalization was related to medications. Two "yes" answers were required to establish positive causality. Cohen´s kappa index was used to determine

inter-rater agreement, and Fleiss´s kappa index was used for overall agreement. Kappa index was classified according to Landis et al. criteria[36–38].

Currency, price date and conversion

Costs are reported in 2019 United States dollars (USD) which were derived using the online tool developed by Cochrane Economics Methods Group and the Evidence of Policy and Practice Information and Coordinating Centre[39]. This method utilizes Purchasing Power Parities (PPP) to modify estimates, currency and year. PPP values of the International Monetary Fund were used[40].

Analytic methods

Baseline patient characteristics were reported for each group with means and standard deviation (SD). Continuous variables mean between groups were evaluated with the independent t-test, while for dichotomous and categorical variables the Pearson's Chi-square test was used. The base-case analysis was conducted according to the intention-to-treat (ITT) approach. Missing data appeared to be missing at random with complete baseline covariates data. To account for this, a multiple imputation model was implemented through chained equations and predictive mean matching by study group[41]. Outcome data was estimated to be missing in 15% of cases, and 20 imputed datasets were generated per missing variable. To estimate incremental costs and QALYs accounting for covariates and clustering effect, ordinary least squares regression, generalized linear models, and multilevel models using the maximum likelihood (ML) and restricted maximum likelihood (REML) approaches were used to test for model fit. The Akaike Information Criterion (AIC) in multiply imputed datasets in accordance with the methods suggested by Chaurasia et al. was used[42]. A multilevel ML model was used for costs, while for QALYs, a multilevel REML model was used[43]. As the RELM approach restricts variance and therefore uncertainty, a scenario analysis was tested using the ML approach in both regressions. The statistical parameters used to assess model fit (AIC) and ML scenario analysis are presented in appendix 3. The following baseline covariates were included: age, gender, CVD history, CHD risk higher than 10%, T2DM diagnosis, number of comorbidities, educational level by years of study (no formal education, primary, secondary and tertiary level), civil status (with or without partner), more than nine prescribed medications, baseline medication adherence and body mass index (BMI) higher than 32 kg/m^2.

The ICER was determined as the difference of costs divided by the difference of effects between groups according to the following formula[44]:

$$\text{ICER} = \frac{Costs_{IG} - Costs_{CG}}{QALY_{IG} - QALY_{CG}}$$

To calculate the 95% confidence interval (CI) around the ICER, a non-parametric bootstrap with 1000 iterations was performed[45]. To account for clustering of data, bootstrap replications were stratified by primary care centre[46]. To represent uncertainty, these results were plotted in a cost-effectiveness plane and in an acceptability curve to assess the probability of cost-effectiveness at different thresholds[47,48]. Local guidelines suggest the use of one gross domestic product (GDP) per capita as the threshold[25]. According to the World Bank, the GDP per capita in Chile in 2018 was $15,923 ($16,207 updated to 2019)[49].

A sensitivity analysis was performed for patients that completed all four visits as per protocol. Five subgroup analyses were done in the following categories: patients 75 years or older, CHD risk higher than 10%, BMI higher than 32 kg/m^2, T2DM diagnosis, and more than nine prescribed medications. A sensitivity analysis was also conducted for centres that provided cost data of hospitalizations, specialists' visits and ED visits.

Results

Twenty-four centres were initially recruited and 12 (50%) finished the trial (six in each arm). Those who dropped out did not provide any patient data. Pharmacists recruited 324 patients in total, 174 patients in the IG and 150 in the CG. Of these patients, 146 completed all four interviews in the IG and 145 in CG. Eight patients in the CG did not provide HRQoL data; therefore, were excluded from the per-protocol analysis. Baseline characteristics were similar in most categories for both groups. A significant difference in the number of chronic diseases and patients' civil status was observed (Table 3).

In terms of HRQoL, it was observed that baseline utility scores were similar (0.57 for both groups), but they differed at the fourth visit in 0.15 (0.67 in the IG and 0.52 in the CG). When comparing utility values between groups considering the first and last visits, a difference of 0.1 was observed on the IG (0.57 vs 0.67), while in usual care it decreased in 0.5 (0.57 vs 0.52). Figure 1 shows the base-case analysis utility scores per interview adjusted by clustering effect and clinical covariates.

In terms of resources used, pharmacists' time was 149.42 minutes per patient (±24.42), and GPs' time was 64.07 minutes (±20.53) in patients who finished all four interviews. Pharmacists' training in total lasted 15 hours, and the PCF spent a mean of 225.83 (±179.16) minutes with each pharmacist that finished the study. Cost savings were estimated for prescribed medications ($-28.74) and pathology tests ($-12.65) (Table 4). Taking into account all intervention's components (pharmacists, GPs, training and PCF), costs added up to $76.71 per patient in the MRF group.

In a subset of clusters (three in each arm with 228 patients) hospitalizations, specialists and ED visits were obtained (Table 5). The GPs' evaluation of medication-related hospitalizations yielded inter-rater agreement as substantial (0.64), moderate (0.43) and fair (0.30), while the overall agreement was moderate (0.45) (Table 6). Although the IG had higher costs in specialists' visits and ED visits compared with CG, hospitalizations costs in the IG were reduced by 43.53%.

In the base-case analysis, 0.063 QALYs were gained, at an additional cost of $27.37. This result in an ICER of $434.4/QALY (Table 7). Model scenario analysis did not change the conclusions (appendix 3). Bootstrapped replications were graphed in the cost-effectiveness plane where it was observed that 98.8% of the iterations were in the north-eastern quadrant and below the cost-effectiveness threshold, while 1.2% were dominant (south-eastern quadrant) (Figure 2). The acceptability curve showed that 50% of the iterations were cost-effective at a threshold of $473.13/QALY while it reached 100% at a threshold of $1,696.77/QALY (Figure 3). The per-protocol and subgroup analysis had a similar trend in ICERs point estimates, although it was found that when hospitalizations, specialists' visits and ED visits were included or when patients with more than nine prescriptions were evaluated,

dominant bootstrapped ICER iterations increased to 31.8% and 41.0% respectively. Almost every subgroup had their iterations under the cost-effectiveness threshold ($16,207/QALY). The only exception was the subgroup of patients older than 75 years, with 0.4% of their iterations lying over the cost-effectiveness threshold.

Discussion

The addition of pharmacist-led MRF was found cost-effective in the base-case analysis against usual care in primary care from the public third-party payer perspective. Using the ITT approach, accounting for missing data, covariates and clustering effect, bootstrap iterations showed that the intervention was cost-effective in 98.8% of the iterations gaining more benefits in terms of QALYs at higher costs, while the rest of the iterations were dominant. Point estimates in subgroup analysis did not change the decision noting that when hospitalizations, specialists' visits and ED visits or patients with more than nine prescriptions were evaluated, a cost-saving trend was observed with a higher proportion of dominant iterations.

This trial was conducted in the public primary care setting in Chile. The healthcare team is comprised of GPs, RN and dietitians that develop interdisciplinary work on a geographically defined population to address biomedical issues and social determinants of health[50]. A systematic review of team-based care on HTN showed that 26 out of 28 estimated ICERs were considered cost-effective at a threshold of $50,000/QALY[51]. These results suggest that usual care in this trial might be enhanced. A study that included patients with uncontrolled HTN, compared pharmacist-GP collaboration against usual care comprised of GPs only[14]. The intervention was deemed as dominant with incremental costs of $-35 and reaching blood pressure objectives in 17% more patients than usual care.

To the best of our knowledge, this is the first cost-utility analysis alongside a cRCT of pharmacist-led MRF that accounts for clustering[13]. Two studies have performed cost-utility analyses alongside RCTs of pharmacist-led medication review in cardiovascular risk factors. Adibe MO. et al. in Nigeria in 2013 studied patients with T2DM on oral hypoglycaemic drugs and were followed for a year[17]. Cost-effectiveness analysis yielded gains in 0.12 QALYs with incremental costs of $69. These values gave an ICER of $571/QALY, with an uncertainty analysis leading to 52% of the iterations below Nigeria's suggested cost-effectiveness threshold of one GDP per capita. Obreli-Neto PR. et al. in Brazil evaluated MRF compared to usual care in diabetic and hypertensive older adults over three years[16]. Similar results were observed with increased effects of 1.3 QALY at higher costs of $77.74 per patient, with an ICER of $59.76. Second-order uncertainty was not evaluated in this study. The results of our economic evaluation resulted in an ICER of $434.40 which compared to previous economic

evaluations, had less second-order uncertainty, as 98.8% of the iterations were considered cost-effective and 1.2% dominant.

In terms of resources evaluated, our study identified pharmacists, PCF and GP's time, medications, pathology tests, specialist visits, ED visits and hospitalizations. The three latter have only been included in a subset of published studies from a systematic review[13]. Hospitalizations were evaluated in six out of eleven economic evaluations, while ED visits in four. These resources, especially hospitalizations, had an impact on the evaluation, as 31.8% of the iterations were considered dominant in centres with available hospital data. A cost-effectiveness analysis in Canada evaluated MRF in primary care and had as the main outcome to reduce CVD risk in T2DM patients. A similar trend reducing CVD risk in 0.3% while saving 190 Canadian dollars (CAD) was found. Costs were mainly driven by hospitalizations with a difference of 407 CAD between groups[52]. When stochastic uncertainty was evaluated, 66% of the iterations were found dominant. In our study, patients with more than nine medications had 41.0% of iterations dominant, although this subgroup was only 22.2% of the sample. Similar results were observed in a study that included older adults with polypharmacy in the community pharmacy setting, showing that the MRF group was dominant over usual care[53]. The bootstrap analysis yielded 96.8% of the iterations as dominant with point estimates of €-250.51 and 0.0156 QALYs. A trial-based cost-effectiveness analysis that studied MRF improving blood pressure control in medical offices with pharmacists already integrated into the clinical team, found increased effects in blood pressure control with an ICER of $22.6 per 1% of patients achieving therapeutic goals [54]. Results seem to improve when pharmacists are based in primary care centres, as it encourages the development of relationships with GPs and other healthcare professionals. This generates core determinants for collaboration such as trust and/or interdependence, facilitating recommendations' implementation[55].

As an economic evaluation alongside a trial, this study has its limitations. Firstly, the time horizon is constrained due to the nature of these evaluations. This is especially relevant for CVD as they not only pose a burden with acute events but also can cause long-term disability[4]. Risk factors might show their effects over time if therapeutic objectives are not achieved[56]. Secondly, the base-case analysis used the REML approach in the multilevel model of costs restricting its variance and therefore, uncertainty with the potential to alter the results. This was evaluated calculating both, costs and QALYs using the ML which did not change the decision. Thirdly, public price weight used for pathology tests, medications, ED visits and specialists' visits could be undervalued. This was observed in a study in 2014 were only 56% of hospital expenses were covered by the actual billing[57]. Fourthly, hospitalization data was not available for all the study population. This hindered the results as an increase in dominant bootstrap iterations was observed when this data was included. Finally, cluster attrition may have

increased risk of bias; nonetheless, the number of lost clusters was similar between groups. Most of the centres withdrew because pharmacists did not have enough time to perform the intervention due to other issues, frequently related to the supply of medications. Despite efforts made by the PCF, the situation could not be reversed in some clusters.

Conclusions

Pharmacist-led MRF was deemed a cost-effective addition to primary care centres' usual care from the public third-party payer perspective. This was achieved by improving HRQoL at higher costs, which resulted in an ICER below than the cost-effectiveness threshold with low second-order uncertainty. Patients with more than nine prescribed medications seem to achieve cost savings in a higher proportion, maintaining improved benefits. These results encourage the evaluation of the implementation of MRF in the public health system by policymakers. Further evaluations to extrapolate CVD outcomes to longer time horizons should be undertaken.

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Supplementary Materials

Expanded Methods:

- TIDieR description
- Medications and laboratory tests prices
- Model fit and scenario analysis

References 51-57

References

1. Roth GA, Abate D, Abate KH, Abay SM, Abbafati C, Abbasi N, Abbastabar H, Abd-Allah F, Abdela J, Abdelalim A. Global, regional, and national age-sex-specific mortality for 282 causes of death in 195 countries and territories, 1980–2017: a systematic analysis for the Global Burden of Disease Study 2017. *Lancet*. 2018;392:1736–1788.

2. Hay SI, Abajobir AA, Abate KH. Global, regional, and national disability-adjusted life-years (DALYs) for 333 diseases and injuries and healthy life expectancy (HALE) for 195 countries and territories, 1990-2016: A systematic analysis for the Global Burden of Disease Study 2016. *Lancet*. 2017;390:1260–1344.

3. Bloom, D.E., Cafiero, E.T., Jané-Llopis, E., Abrahams-Gessel, S., Bloom, L.R., Fathima, S., Feigl, A.B., Gaziano, T., Mowafi, M., Pandya, A., Prettner, K., Rosenberg, L., Seligman B. The Global Economic Burden of Non-communicable Diseases. 2011.

4. Arnett DK, Blumenthal RS, Albert MA, Buroker AB, Goldberger ZD, Hahn EJ, Himmelfarb CD, Khera A, Lloyd-Jones D, McEvoy JW, Michos ED, Miedema MD, Muñoz D, Smith SC, Virani SS, Williams KA, Yeboah J, Ziaeian B. 2019 ACC/AHA Guideline on the Primary Prevention of Cardiovascular Disease: A Report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines. 2019.

5. American Diabetes Association. Standards of Medical Care in Diabetes-2020. *Diabetes Care*. 2020;43:S205–S206.

6. Grundy SM, Stone NJ, Bailey AL, Beam C, Birtcher KK, Blumenthal RS, Braun LT, de Ferranti S, Faiella-Tommasino J, Forman DE, Goldberg R, Heidenreich PA, Hlatky MA, Jones DW, Lloyd-Jones D, Lopez-Pajares N, Ndumele CE, Orringer CE, Peralta CA, Saseen JJ, Smith SC, Sperling L, Virani SS, Yeboah J. 2018 AHA/ACC/AACVPR/AAPA/ABC/ACPM/ADA/AGS/APhA/ASPC/NLA/PCNA Guideline on the Management of Blood Cholesterol: A Report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines. *J Am Coll Cardiol*. 2019;73:e285–e350.

7. Whelton PK, Carey RM, Aronow WS, Casey DE, Collins KJ, Dennison Himmelfarb C, DePalma SM, Gidding S, Jamerson KA, Jones DW, MacLaughlin EJ, Muntner P, Ovbiagele B, Smith SC, Spencer CC, Stafford RS, Taler SJ, Thomas RJ, Williams KA, Williamson JD, Wright JT. 2017 ACC/AHA/AAPA/ABC/ACPM/AGS/APhA/ASH/ASPC/NMA/PCNA Guideline for the Prevention, Detection, Evaluation, and Management of High Blood Pressure in Adults: A Report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines. *J Am Coll Cardiol*. 2018;71:e127–e248.

8. Seron P, Irazola V, Rubinstein A, Calandrelli M, Ponzo J, Olivera H, Gutierrez L, Elorriaga N, Poggio R, Lanas F. Ideal Cardiovascular Health in the southern cone of Latin America. *Public Health* [Internet]. 2018;156:132–139. Available from: https://doi.org/10.1016/j.puhe.2017.12.017

9. (PAHO/WHO) PAHOHO. Renewing primary health care in the Americas: A position paper of the Pan American Health Organization/World Health Organization (PAHO/WHO). 2007.

10. Chile M de S de. ORIENTACIÓN TÉCNICA PROGRAMA FONDO DE FARMACIA PARA ENFERMEDADES CRÓNICAS NO TRANSMISIBLES EN ATENCIÓN PRIMARIA. 2019.

11. OPS/OMS. Servicios farmacéuticos basados en la atención primaria de salud. Documento de posición de la OPS/OMS. 2013.

12. Martínez-Mardones F, Fernandez-Llimos F, Benrimoj SI, Ahumada-Canale A, Plaza-Plaza JC, S Tonin F, Garcia-Cardenas V. Systematic Review and Meta-Analysis of Medication Reviews Conducted by Pharmacists on Cardiovascular Diseases Risk Factors in Ambulatory Care. *J Am Heart Assoc*. 2019;8:e013627.

13. Ahumada-Canale A, Quirland C, Martinez-Mardones FJ, Plaza-Plaza JC, Benrimoj S, Garcia-Cardenas V. Economic evaluations of pharmacist-led medication review in outpatients with hypertension, type 2 diabetes mellitus, and dyslipidaemia: a systematic review. *Eur J Heal Econ* [Internet]. 2019;20:1103–1116. Available from: https://doi.org/10.1007/s10198-019-01080-z

14. Borenstein JE, Graber G, Saltiel E, Wallace J, Ryu S, Jackson A, Deutsch S, Weingarten SR. Physician-pharmacist comanagement of hypertension: A randomized, comparative trial. *Pharmacotherapy*. 2003;23:209–216.

15. Simpson SH, Lier DA, Majumdar SR, Tsuyuki RT, Lewanczuk RZ, Spooner R, Johnson JA. Cost-effectiveness analysis of adding pharmacists to primary care teams to reduce cardiovascular risk in patients with Type 2 diabetes: Results from a randomized controlled trial. *Diabet Med*. 2015;32:899–906.

16. Obreli-Neto PR, Marusic S, Guidoni CM, Baldoni A de O, Renovato RD, Pilger D, Cuman RKN, Pereira LRL. Economic evaluation of a pharmaceutical care program for elderly diabetic and hypertensive patients in primary health care: A 36-month randomized controlled clinical trial. *J Manag Care Pharm*. 2015;21:66–75.

17. Adibe MO, Aguwa CN, Ukwe C V. Cost-utility analysis of pharmaceutical care intervention versus usual care in management of nigerian patients with type 2 diabetes. *Value Heal Reg Issues*. 2013;2:189–198.

18. Scottish Government Polypharmacy Model of Care Group. Polypharmacy Guidance, Realistic Prescribing [Internet]. 3rd Editio. 2018. Available from: http://dghstatistiques.ci/assets/documents/annuaire/Annuaire-DGH-2018-v3.pdf

19. Grupo de Investigación en Atención Farmacéutica U de G. Pharmacotherapy follow-up: The Dader method (3rd revision: 2005). *Pharm Pract* [Internet]. 2006;4:44–53. Available from: http://scielo.isciii.es/scielo.php?script=sci_arttext&pid=S1885-642X2006000100008

20. Hoffmann TC, Glasziou PP, Boutron I, Milne R, Perera R, Moher D, Altman DG, Barbour V, Macdonald H, Johnston M, Kadoorie SEL, Dixon-Woods M, McCulloch P, Wyatt JC, Phelan AWC, Michie S. Better reporting of interventions: Template for intervention description and replication (TIDieR) checklist and guide. *BMJ*. 2014;348:1–12.

21. Garcia-Cardenas V, Benrimoj SI, Ocampo CC, Goyenechea E, Martinez-Martinez F, Gastelurrutia MA. Evaluation of the implementation process and outcomes of a professional pharmacy service in a community pharmacy setting. A case report. *Res Soc Adm Pharm*. 2017;13:614–627.

22. Ministerio de Salud C. Manual de Aplicación del EMPAM. 2010.

23. Icaza G, Núñez L, Marrugat J, Mujica V, Escobar MC, Jiménez AL, Pérez P, Palomo I. Estimación de riesgo de enfermedad coronaria mediante la función de Framingham adaptada para la población Chilena. *Rev Med Chil*. 2009;137:1273–1282.

24. Ministerio de Salud de Chile. Orientación Técnica Programa de Salud Cardiovascular 2017. 2017;1–85. Available from: http://www.redcronicas.cl/wrdprss_minsal/wp-content/uploads/2017/08/OT-PROGRAMA-DE-SALUD-CARDIOVASCULAR_03.pdf

25. Castillo Riquelme M, Castillo Laborde C, Loayza Saldivia S, Aravena Pastén M. Guía

Metodólogica para la evaluacion económica de intervenciones en Salud en Cile. 2013.

26. Husereau D, Drummond M, Petrou S, Carswell C, Moher D, Greenberg D, Augustovski F, Briggs AH, Mauskopf J, Loder E, ISPOR Health Economic Evaluation Publication Guidelines-CHEERS Good Reporting Practices Task Force. 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* [Internet]. 2013;16:231–50. Available from: http://www.ncbi.nlm.nih.gov/pubmed/23538175

27. Brooks R, De Charro F. EuroQol: The current state of play. *Health Policy (New York)*. 1996;37:53–72.

28. Rabin R, Gudex C, Selai C, Herdman M. From translation to version management: A history and review of methods for the cultural adaptation of the euroqol five-dimensional questionnaire. *Value Heal*. 2014;17:70–76.

29. Zarate V, Kind P, Valenzuela P, Vignau A, Olivares-Tirado P, Munoz A. Social valuation of EQ-5D health states: The chilean case. *Value Heal*. 2011;14:1135–1141.

30. Manca A, Hawkins N, Sculpher MJ. Estimating mean QALYs in trial-based cost-effectiveness analysis: The importance of controlling for baseline utility. *Health Econ*. 2005;14:487–496.

31. Chile B del congreso nacional de. ESTATUTO DE ATENCION PRIMARIA DE SALUD MUNICIPAL [Internet]. 2016 [cited 2019 Nov 14];Available from: https://www.leychile.cl/Navegar?idNorma=30745

32. FONASA. Modalidad Atención Institucional [Internet]. 2019 [cited 2020 Feb 1];Available from: https://www.fonasa.cl/sites/fonasa/mobile/prestadores/normativa/aranceles

33. Government C. CENABAST updated prices [Internet]. 2019 [cited 2019 Jul 3];Available from: https://www.cenabast.cl/precios-vigentes-en-contratos/

34. Ministerio de Salud de Chile. Norma Técnica sobre Grupos Relacionados por el Diagnóstico Internacionales Refinados IRGRD. 2014.

35. Malet-Larrea A, Goyenechea E, García-Cárdenas V, Calvo B, Arteche JM, Aranegui P, Zubeldia JJ, Gastelurrutia MA, Martínez-Martínez F, Benrimoj SI. The impact of a medication review with follow-up service on hospital admissions in aged polypharmacy patients. *Br J Clin Pharmacol*. 2016;94:831–838.

36. Cohen J. A coefficient of agreement for nominal scales. *Educ Psychol Meas*. 1960;20:37–46.

37. Fleiss J. Statistical methods for rates and proportions. New York: John Wiley & sons; 1973.

38. Landis JR, Koch GG. The Measurement of Observer Agreement for Categorical Data. *Biometrics*. 1977;33:159–174.

39. Shemilt I, Thomas J, Morciano M. A web-based tool for adjusting costs to a specific target currency and price year. *Evid Policy*. 2010;6:51–59.

40. Fund IM. World Economic Outlook Database [Internet]. 2018 [cited 2019 Apr 23];Available from: https://www.imf.org/external/pubs/ft/weo/2019/01/weodata/index.aspx

41. Faria R, Gomes M, Epstein D, White IR. A Guide to Handling Missing Data in Cost-Effectiveness Analysis Conducted Within Randomised Controlled Trials. *Pharmacoeconomics*. 2014;32:1157–1170.

42. Chaurasia A, Harel O. Using AIC in Multiple Linear Regression framework with Multiply Imputed

Data. *Heal Serv Outcomes Res Methodol*. 2012;12:219–233.

43. GOMES M, GRIEVE R, NIXON R, S.-W E, CARPENTERc J, THOMPSON SG. METHODS FOR COVARIATE ADJUSTMENT IN COST-EFFECTIVENESS ANALYSIS THAT USE CLUSTER RANDOMISED TRIALS. 2012;21:1101–18.

44. Drummond M, Sculpher M, Claxton K, Stoddart G, Torrance G. Methods for the economic evaluation of health care programmes. 4th ed. Oxford University Press; 2015.

45. Desgagné A, Castilloux A-M, Angers J-F, LeLorier J. The Use of the Bootstrap Statistical Method for the Pharmacoeconomic Cost Analysis of Skewed Data. *Pharmacoeconomics*. 1998;13:487–497.

46. De Leeuw J, Meijer E. Handbook of multilevel analysis. 2008.

47. Briggs a, Fenn P. Confidence intervals or surfaces? Uncertainty on the cost-effectiveness plane. *Health Econ*. 1998;7:723–740.

48. Fenwick E, O'Brien BJ, Briggs A. Cost-effectiveness acceptability curves - Facts, fallacies and frequently asked questions. *Health Econ*. 2004;13:405–415.

49. Bank TW. GDP per capita (current US$) [Internet]. [cited 2020 Jan 14];Available from: https://data.worldbank.org/indicator/NY.GDP.PCAP.CD?locations=CL

50. Organization PAHOH. La renovación de la Atención Primaria de Salud en las Américas. 2007.

Setting and location	Public primary care
Perspective*	Public third-party payer
Time horizon	One year
Discount rate	Not applicable
Health outcomes*	Quality adjusted-life years
Measurement of effectiveness	Cluster randomized controlled trial
Measurement and valuation of preference-based outcomes*	Health related quality of life was measured through EuroQoL 5D-3L and valued with a local value set
Resources	Pharmacists and GPs´ time, pathology tests, medications, training and practice change facilitator
Currency and price date	2019 United States dollars
Analytic methods	Multilevel model and multiple imputation
Uncertainty	Bootstrap (1000 replications)

Table 1. Base-case economic evaluation summary. *Local guideline recommendation.

Resource	Price (USD)	Source
Pharmacist time (hour)	$22.2	Centres 2019 wages [31]
General practitioner time (hour)	$30.6	Centres 2019 wages [31]
Pathology tests	Appendix 2	Public health insurance price weights [32]
Medications	Appendix 2	National medication supply central 2019 prices [33]
Emergency department visit	$33.01	Public health insurance price weights [32]
Hospitalization (DRG value)	$5115.21	Local diagnostic related group guidelines 2019 [34]
Specialist visit	$24.82	Public health insurance price weights [32]
Training and facilitator (hour)	$23.31	Centres 2019 wages + 5% [31]

Table 2. Resources' price according to the public third-party payer perspective. DRG: diagnostic-related group; USD: United States dollar.

Baseline	Intervention (6 clusters, 174 patients)	SD	Usual care (6 clusters, 150 patients)	SD	p value
Age (years)	73.07	5.82	74.08	5.99	0.13
Coronary heart disease risk (%)*	9.64	3.35	9.20	3.16	0.28
Number of medications	8.32	2.48	7.86	2.27	0.09
Number of chronic diseases	4.11	1.35	3.57	1.45	0.001
Baseline utility	0.56	0.28	0.59	0.27	0.38
Body mass index (kg/m^2)	31.14	5.84	30.82	5.20	0.60
EQ-5D VAS	63.21	21.16	67.47	19.32	0.06
	n	Percentage (%)	n	Percentage (%)	
Type 2 diabetes mellitus	107	61.49	93	62.00	0.93
Female	126	72.41	107	71.33	0.83
Smokers	25	14.37	18	12.00	0.53
With partner	103	59.20	64	42.67	0.003
Cardiovascular disease history	33	18.97	22	14.67	0.30
Educational level					
No education	79	45.40	71	47.33	0.76
Primary studies	57	32.76	57	38.00	0.32
Secondary studies	33	18.97	20	13.33	0.16
Tertiary studies	5	2.87	2	1.33	0.32

Table 3. Baseline sociodemographic and clinical characteristics. n =324. EQ-5D: EuroQoL 5 dimension questionnaire. *n = 269 patients. VAS: visual analogue scale.

Resources	Mean costs (95% CI)	
	MRF	Usual care
Medications	$154.20 (120.83 – 187.58)	$182.94 (127.24 – 238.64)
Pathology tests	$115.91 (91.34 – 140.48)	$128.56 (112.39 – 144.74)
Pharmacist time	$58.04 (38.00 – 78.08)	-
GPs time	$12.22 (8.83 – 15.62)	-
Training	$3.63	-
Practice change facilitator	$2.82	-

Table 4. Costs in the base-case analysis by study group adjusted by clustering effect and covariates.
CI: confidence interval; GP: general practitioner; MRF: medication review with follow-up.

Resource	MRF		Usual Care	
	Per patient resource use mean (SD)	Mean costs (SD)	Resource use mean (SD)	Mean costs (SD)
Medication related hospitalizations	0.06 (0.27)	$178.15 (921.59)	0.08 (0.33)	$315.45 (1,449.56)
Specialists' visits	3.09 (4.86)	$76.69 (120.61)	1.56 (2.76)	$38.63 (68.42)
Emergency department visits	0.36 (0.82)	$11.91 (27.20)	0.25 (0.66)	$8.10 (21.76)

Table 5. Costs registered outside the trial by study group. n = 228 patients. MRF: Medication review with follow-up; SD: standard deviation.

Raters	Kappa statistic	95% CI
Rater 1 vs rater 2*	0.64	0.38-0.90
Rater 1 vs rater 3*	0.43	0.15-0.71
Rater 2 vs rater 3*	0.30	-0.01-0.61
Rater 1 vs rater 2 vs rater 3†	0.45	0.35-0.54

Table 6. Inter-rater reliability between general practitioners evaluating if medication use was related to hospitalizations. *Cohen's Kappa; †Fleiss Kappa. n = 34 hospitalizations. CI: confidence intervals.

Analysis	Incremental QALY (95%CI*)	Incremental costs (95%CI*)	ICER $/QALY (95%CI*)	NE	SE	NW	SW	n
Base-case	0.063 (0.044 – 0.082)	$27.37 (0.65 – 54.09)	$434.40 (64.20 – 996.03)	98.8%	1.2%	0%	0%	324
Per protocol	0.072 (0.048 – 0.095)	$27.27 (-2.22 – 56.75)	$380.93 (-7.46 – 938.99)	97.5%	2.5%	0%	0%	283
Hospitalizations, specialists and ED costs	0.055 (0.031 – 0.079)	$9.57 (-31.43 – 50.57)	$173.86 (-536.61 – 1042.18)	68.2%	31.8%	0%	0%	228
More than 9 medications	0.11 (0.067 – 0.16)	$23.00 (-78.55 – 124.55)	$202.18 (-748.90 – 1205.65)	59.0%	41.0%	0%	0%	72
Body mass index	0.076 (0.032 – 0.12)	$33.12 (-8.85 – 75.09)	$437.59 (-26.58 – 1582.02)	96.7%	3.2%	0.1%	0%	101
Type 2 diabetes mellitus	0.093 (0.061 – 0.13)	$45.27 (-5.46 – 95.99)	$486.34 (-53.80 – 1166.76)	96.5%	3.5%	0%	0%	180
Older than 75	0.044 (0 – 0.089)	$41.66 (1.93 – 81.39)	$945.218 (-128.084 – 5091.201)	96.3%[†]	2.9%	0.8%	0%	115
CHD > 10%	0.084 (0.031 – 0.14)	$40.14 (-24.58 – 104.87)	$476.03 (-228.51 – 1986.16)	91.3%	8.6%	0.1%	0%	110

Table 7. Incremental analysis for the base-case and subgroups adjusted by clustering effect and covariates. CHD: coronary heart disease. CI: confidence interval; ED: emergency department; ICER: incremental cost-effectiveness ratio; NE: north eastern quadrant; NW: north western quadrant; QALY: quality-adjusted life years; SE: south eastern quadrant; SW: south western quadrant. *Bootstrapped CI; [†]four iterations over the cost-effectiveness threshold.

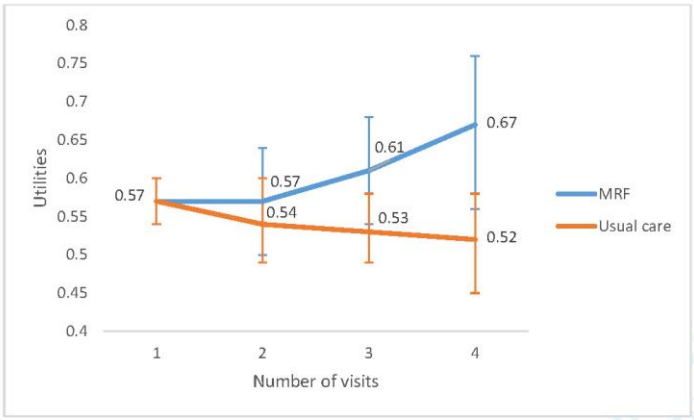


Figure 1. Base-case analysis utility scores per interview adjusted by clustering effect and covariates.
MRF: Medication review with follow-up.

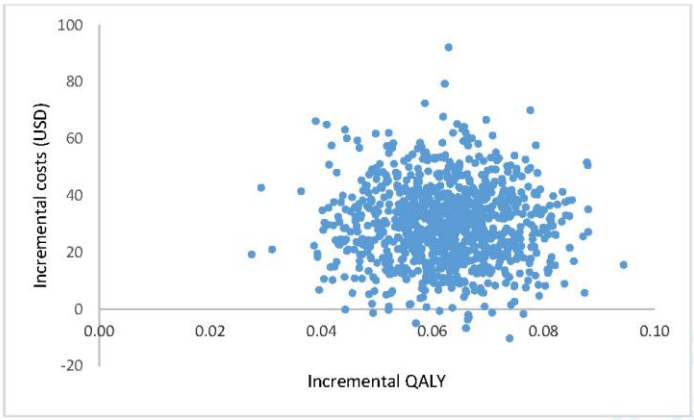


Figure 2. Cost-effectiveness plane of bootstrapped replications from base-case analysis adjusted by clustering and covariates. QALY: Quality-adjusted life years; USD: United States dollars.

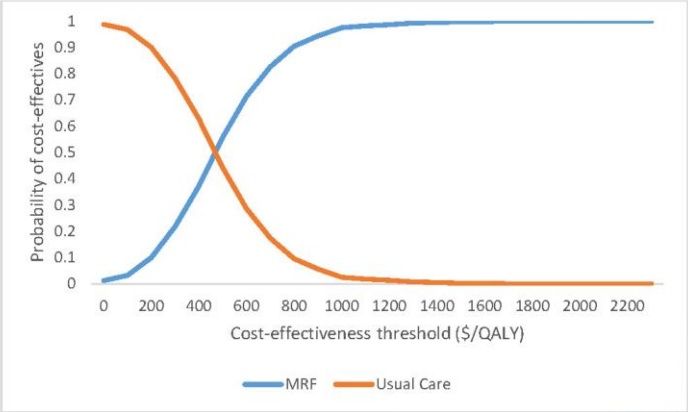


Figure 3. Acceptability curve of bootstrapped replications from base-case analysis adjusted by clustering and covariates. QALY: Quality-adjusted life years, MRF: medication review with follow-up.

Supplementary Material

Appendix 1

TIDieR checklist for the Polaris MRF method. See on chapter 4.

Appendix 2: Medications and laboratory tests prices

Laboratory test	Unit price (USD)
Glycated haemoglobin	$10.01
Fasting glucose	$2.90
Urinalysis	$6.03
Electrolytes	$2.70
Serum creatinine	$2.90
Lipid profile	$13.62

Supplemental table 2. Laboratory tests prices. USD: United States dollar.

Medication	Unit price (USD)
ASPIRIN 100MG	$0.02
ASPIRIN 500MG	$0.03
ACENOCUMAROL 4MG	$0.05
FOLIC ACID 1MG	$0.02
VALPROIC ACID 200MG	$0.06
VALPROIC ACID 10MG/ML	$4.29
VALPROIC ACID 250MG/5ML	$22.70
ALENDRONATO 70 MG	$0.40
ALOPURINOL 300MG	$0.13
ALPRAZOLAM 0,5 MG	$0.03
AMIODARONE 200 MG	$0.14
AMITRIPTILIN 25MG	$0.02
AMLODIPINE 10 MG	$0.02
AMLODIPINE 5 MG	$0.03
ARIPIPRAZOLE 10 MG	$0.15
ATENOLOL 50 MG	$0.02
ATORVASTATIN 20 MG	$0.03
BUDESONIDE INH	$2.09
BUPROPION 150 MG	$0.17
CAPTOPRIL 25MG	$0.06
CARBAMAZEPINE 200MG	$0.04
CARBAMAZEPINE 400MG LP	$2.06
LITHIUM 300 MG	$0.09
CARVEDILOL 12,5 MG	$0.05
CARVEDILOL 25 MG	$0.05
CARVEDILOL 6,25 MG	$0.05
CEFADROXIL 500 MG	$0.15
CEFADROXIL 250MG/5ML	$2.23
CELOCOXIB 200MG	$0.09
CICLOBENZAPRINE 10 MG	$0.04

Supplemental table 3. Medication prices. USD: United States dollar.

CLINDAMYCIN 300 MG	$3.59
CLONAZEPAM 0,5MG	$0.03
CLONAZEPAM 2 MG	$0.04
CLONIDINE 100 MCG	$0.76
CLOPIDOGREL 75 MG	$0.15
CHLORPHENAMINE 4MG	$0.01
CLOTRIMAZOLE 500 MG OV	$0.44
CLOTRIMAZOLE CREMA 1%	$0.43
DESLORATADIN 5 MG	$0.05
DIAZEPAM 10MG	$0.03
DICLOFENAC 50 MG	$0.02
DIGOXIN 0,25 MG	$0.06
DILTIAZEM 60 MG	$0.31
DIVAPROATE 500 MG LP	$0.25
DOXAZOCINE 2 MG	$0.36
ENALAPRIL 10 MG	$0.01
ESCITALOPRAM 10 MG	$0.06
SPIRONOLACTONE 25 MG	$0.05
FAMOTIDIN 40 MG	$0.05
FENITOINE 100 MG	$0.05
PHENOBARBITAL 100 MG COMP	$0.07
FENOTEROL + IPRATROPIUM INH	$17.19
FINASTERIDE 5MG	$0.40
FLUOXETINE 20MG	$0.02
FLUTICASONE-SALMETEROL INH	$3.91
FUROSEMIDE 40 MG CM	$0.02
GEMFIBROZIL 600 MG	$0.14
GLIBENCLAMIDE 5MG	$0.02
HIDRALAZINE 50 MG	$0.11
HYDROCHLOROTHIAZIDE 50 MG	$0.01
IBUPROFEN 400MG	$0.03
IMIPRAMINE 25MG	$0.04
INSULIN	$5.33
GLARGIN INSULIN	$29.23
LISPRO INSULIN	$31.11
NPH INSULIN	$5.19
IPRATROPIUM	$2.92
ISOSORBIDE 10 MG	$0.03
KETOPROFEN 50 MG	$0.05
LAMOTRIGINE 100 MG	$0.11
LAMOTRIGINE 50 MG	$0.04
LATANOPROST 50 MCG/ML	$2.85
LEVETIRACETAM 1000 MG	$0.26

Supplemental table 3. *Continued*

LEVETIRACETAM CM 500 MG	$0.13
LEVETIRACETAM JBE 100MG/ML	$17.73
LEVODOPA/BENSERAZIDE	$0.27
LEVODOPA/CARBIDOPA	$0.12
LEVOTHYROXINE 100 MCG	$0.03
LEVOTHYROXINE 50 MCG	$0.09
LOPERAMIDE 2 MG.	$0.05
LORATADINE 10 MG.	$0.02
LORAZEPAM 2 MG	$0.04
LOSARTAN POTASICO 50 MG	$0.02
LOVASTATIN 20MG	$0.02
MELOXICAM CM 15 MG	$0.04
METFORMIN 850 MG	$0.02
METFORMIN XR 1000 MG	$0.18
METFORMIN XR 500 MG	$0.14
METFORMIN XR 750 MG	$0.24
METILDOPA 250MG	$0.10
METHYLPHENIDATE 10 MG	$0.09
METRONIDAZOLE 500 MG	$0.15
NAPROXEN 550 MG	$0.14
NIFEDIPINE RETARD 20MG	$0.02
NITROFURANTOIN 100MG	$0.11
OLANZAPINE 10 MG	$0.10
OMEPRAZOLE 20 MG	$0.02
PARACETAMOL 500MG	$0.01
PAROXETINE 20 MG	$0.05
PRAMIPEXOLE 0.25 MG	$0.08
PRAMIPEXOLE 1 MG	$0.13
PREDNISONE 5MG	$0.02
PRIMIDONE 250 MG	$0.16
PROPRANOLOL 40 MG	$0.02
QUETIAPINE 100 MG	$0.07
QUETIAPINE 25 MG	$0.03
RANITIDINE 300 MG	$0.07
RISPERIDONE 1 MG	$0.04
RISPERIDONE 1MG/ML GTS	$2.75
RISPERIDONE 3 MG	$0.07
ROSUVASTATIN 10MG	$0.11
SALBUTAMOL INH	$1.64
SALMETEROL INH 25MG	$6.56
SERTRALINE 50 MG	$0.04
TERBINAFINE 250 MG	$0.29
TIMOLOL SOL OFT 0,5%	$1.33

Supplemental table 3. *Continued*

TRAMADOL CM 50MG	$0.08
TRAMADOL GTS 100MG/ML	$1.26
TRIHEXYPHENIDYL 2 MG	$0.18
VALSARTAN 160 MG	$0.18
VENLAFAXINA 75MG	$0.21
WARFARIN 5MG	$1.02
ZOLPIDEM 10MG	$0.16
ZOPICLONE 7,5 MG	$0.05

Supplemental table 3. *Continued*

Appendix 3: Model fit and scenario analysis

Model Fit

Quality-adjusted life years	Log-likelihood (arithmetic mean)	Akaike information criteria	Log-likelihood (geometric mean)	Geometric Akaike information criteria
Non-Mixed Models				
Ordinary least squares	318.93365	-103310.5	15.9466825	-5142.7251
Log-normal GLM	226.65067	-73410.817	11.3325335	-3647.7409
Mixed Models				
Linear REML	273.54001	-88602.963	13.6770005	-4407.3482
Linear ML	**326.10709**	**-105634.7**	**16.3053545**	**-5258.9349**
Log-normal GLM	228.4061	-73979.576	11.420305	-3676.1788

Supplemental table 4. Quality-adjusted life years' model fit. GLM: generalized linear model; ML: maximum likelihood; RELM: restricted maximum likelihood.

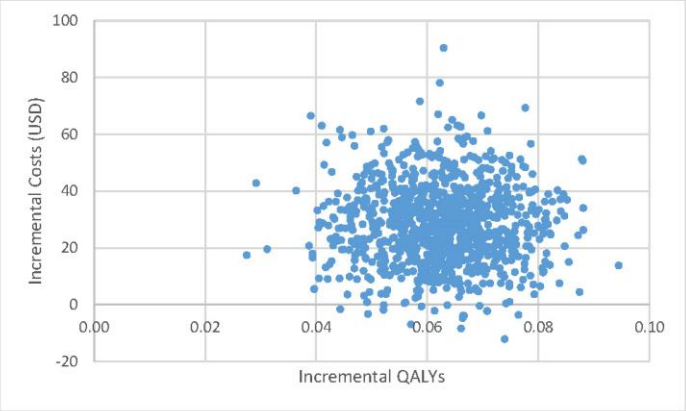
Costs	Log-likelihood (arithmetic mean)	Akaike information criteria	Log-likelihood (geometric mean)	Geometric Akaike information criteria
Non-Mixed Models				
Ordinary least squares	-3954.4641	1281270.37	-197.72321	64086.3184
Log-normal GLM	-3953.3346	1280904.41	-197.66673	64068.0205
Mixed Models				
Linear REML	**-3819.0306**	**1237389.91**	**-190.95153**	**61892.2957**
Linear ML	-3950.7	1280050.8	-197.535	64025.34
Gamma-log GLM	-3948.8043	1279436.59	-197.44022	63994.6297

Supplemental table 5. Costs' model fit. GLM: generalized linear model; ML: maximum likelihood; RELM: restricted maximum likelihood.

Scenario Analysis

	Mean	95% CI lower bound	95% CI upper bound
Incremental QALY	0.063	0.044	0.082
Incremental Costs (USD)	26.24146	-0.78947	53.27253
ICER (USD/QALY)	416.5312	46.177	984.9206

Supplemental table 6. Scenario analysis using maximum likelihood approach for costs and QALY. USD: United States dollar; QALY: Quality-adjusted life years.



Supplemental figure 8. Cost-effectiveness plane of bootstrapped replications using maximum likelihood for costs and QALYs adjusted by clustering and covariates. QALY: Quality-adjusted life years; USD: United States dollars.

Appendix 4: References 51-57

51. Jacob V, Chattopadhyay SK, Thota AB, Proia KK, Njie G, Hopkins DP, Finnie RKC, Pronk NP, Kottke TE. Economics of Team-based Care in Controlling Blood Pressure: A Community Guide Systematic Review. *Am J Prev Med*. 2015;49:772–783.

52. Simpson SH, Lier DA, Majumdar SR. Cost-effectiveness analysis of adding pharmacists to primary care teams to reduce cardiovascular risk in patients with Type 2 diabetes: Results from a randomized controlled trial. *Diabet Med*. 2015;32:899–906.

53. Jódar-Sánchez F, Malet-Larrea A, Martín JJ, García-Mochón L, López del Amo MP, Martínez-Martínez F, Gastelurrutia-Garralda MA, García-Cárdenas V, Sabater-Hernández D, Sáez-Benito L, Benrimoj SI. Cost-Utility Analysis of a Medication Review with Follow-Up Service for Older Adults with Polypharmacy in Community Pharmacies in Spain: The conSIGUE Program. *Pharmacoeconomics*. 2015;33:599–610.

54. Polgreen LA, Han J, Carter BL, Ardery GP, Coffey CS, Chrischilles EA, James PA. Cost-Effectiveness of a Physician-Pharmacist Collaboration Intervention to Improve Blood Pressure Control. *Hypertension*. 2015;66:1145–1151.

55. Bardet JD, Vo TH, Bedouch P, Allenet B. Physicians and community pharmacists collaboration in primary care: A review of specific models. *Res Soc Adm Pharm*. 2015;11:602–622.

56. D'Agostino RB, Vasan RS, Pencina MJ, Wolf PA, Cobain M, Massaro JM, Kannel W. General cardiovascular risk profile for use in primary care: The Framingham heart study. *Circulation*. 2008;117:743–753.

57. Cid Pedraza C, Bastías S. G. Evaluation of financial status of public hospitals considering the updated costs of their services. *Rev Med Chil*. 2014;142:161–167.

Chapter 6

Cost-utility Analysis of a Medication Review for Cardiovascular Outcomes: A Microsimulation Model

Ahumada-Canale A, Vargas C., Martinez-Mardones FJ, Plaza-Plaza JC, Benrimoj S, Garcia-Cardenas V. Cost-utility Analysis of a Medication Review for Cardiovascular Outcomes: A Microsimulation Model. (SUBMITTED TO VALUE IN HEALTH)

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Cost-utility Analysis of a Medication Review for Cardiovascular Outcomes: A Microsimulation Model

Journal:	*Value in Health*
Manuscript ID	VIH-2020-0114
Article Type:	Economic Evaluation
Health Areas List:	Cardiovascular Disease < Health Areas, Heart diseases < Health Areas, Stroke < Health Areas, Patient-Centered Care < Health Areas, Pharmacology / Pharmacotherapy < Health Areas
Methods of Interest List:	Economic: Simulation model < Methods of Interest, Health Policy: modeling study < Methods of Interest, Clinical Outcomes Assessment: Outcomes = Economic < Methods of Interest
Keywords Enter Your Own:	Pharmacist, Pharmacy, Health services

Title: Cost-utility Analysis of a Medication Review for Cardiovascular Outcomes: A Microsimulation Model

Running title: Cost-utility Analysis of Medication Review.

Précis: Pharmacist-led medication review has proved to be clinically effective to prevent cardiovascular events. This study shows that this intervention is cost-effective at a lifetime horizon.

Acknowledgements: This model was validated by the department of non-communicable diseases of the Chilean Ministry of Health.

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Number of Pages: 57

Number of Figures: 3

Number of Tables: 3

Supplementary material:

- Pages: 23
- Figures: 9
- Tables: 11

Abstract

Objective: To undertake a cost-utility analysis of pharmacist-led medication review with follow-up (MRF) against usual care, for patients at risk of cardiovascular diseases (CVD) from the public health sector perspective, considering a lifetime horizon.

Methods: This evaluation was based on a cluster randomized controlled trial conducted in primary care centres with full-time pharmacists. The intervention had three main components: Pharmacists' training, MRF adapted to primary care and a practice change facilitator to assist in service delivery. A state-transition microsimulation model was built to project quality-adjusted life years (QALY) and costs through a lifetime horizon. Probabilities were estimated with equations for CVD risk using patient-level data from the trial and recalculated each cycle by age and events' history. Uncertainty was evaluated through one-way and probabilistic sensitivity analysis (PSA), and was performed at different time horizons (two, five, 10, 20 and lifetime)

Results: For the base case analysis, an incremental cost-effectiveness ratio of $751/QALY was observed. According to the setting's threshold, this was considered cost-effective. The model predicted that the MRF group would have a 15.6% CVD mortality compared to 21.5% in the control group. One-way sensitivity analysis did not change the decision, while all PSA iterations fell in the northeast quadrant. Every time horizon was considered cost-effective in 100% of the iterations, except for the 2-year analysis (98.1%).

Conclusions: MRF was deemed as cost-effective in most time horizons with low uncertainty. This suggests that this intervention could be considered as a cost-effective addition to usual care.

Highlights

- Current evidence has shown that pharmacist-led medication review is an effective intervention for cardiovascular disease risk factors like hypertension, type 2 diabetes mellitus and dyslipidaemia.
- This is the first study on the field to use a state-transition model with a patient-level microsimulation technique, modelling patients with different cardiovascular risk factors accounting for their clinical history and age.
- Medication review was deemed as cost-effective at different time horizons. Even from 2 years, 98.1% of the iterations were below the cost-effectiveness threshold. Implementation at a national level should be considered, especially as cardiovascular diseases remain the leading cause of mortality.

Introduction

Cardiovascular diseases (CVD) are the leading cause of death worldwide with ischaemic heart disease and stroke, accounting for 26.8% of global deaths[1]. These events also cause deterioration of the health-related quality of life and long-term disability[2]. Healthcare costs related to these diseases are expected to have a global burden of $1000 billion by 2030[3]. Evidence-based guidelines to prevent CVD have been developed for the management of risk factors like hypertension (HTN), dyslipidaemia (DLP) and type 2 diabetes mellitus (T2DM)[4–7]..Despite the availability and implementation of these guidelines, there is evidence in countries like Argentina, Uruguay and Chile that 43.3% of hypertensive patients treated with medications still have their blood pressure above therapeutic objectives[8].

In Chile, the Ministry of Health reported in 2016 that CVD had the highest mortality of any disease accounting for 26.7% of all deaths[9]. More specifically, 7.8% due to myocardial infarction (MI) and 8.1% of stroke[9]. Eight percent of hospitalizations were due to CVD, increasing in older adults to 19.6%[10]. In 2017, 27.6% of the population had HTN, 12.3% had T2DM, and 27.8% had DLP[11,12]. These risk factors increased 10-year coronary heart disease (CHD) risk, as population estimates show that 26.0% have a 5-10% risk, and 25.5% had more than 10%[12]. This risk of events might impact the country's healthcare budget, which is among the lowest in the Organisation for Economic Co-operation and Development[13].

In 2014, the pharmacy fund for non-communicable diseases was established as one of the strategies to improve CVD prevention. It aimed to ensure timely and free access to medications for patients who receive care through the public primary care system, targeting, in particular, the treatment of HTN, DLP and T2DM[14]. The initiative included the employment of pharmacists to ensure the management of these medications. Pharmacists were also included to an existing

prevention program that originally had consultations with general practitioners (GPs), registered nurses (RN) and dietitians to address CVD risk through interdisciplinary work, aiming to reduce the associated morbidity and mortality[15]. These pharmacists were made complementary members, therefore not fully integrated into the teams but were given specific roles performing three services: reconciliation of medications, prescription training for GPs and pharmacist-led medication review with follow-up (MRF)[15].

MRF is defined as "a structured evaluation of a patient's medicines with the aim of optimising medicines use and improving health outcomes. This entails detecting drug-related problems and recommending interventions"[16]. A meta-analysis of MRF effect reported increased attainment of therapeutic goals compared with usual care in HTN (OR 2.73 95%PI 1.05-7.08), T2DM (OR 3.11 95%PI 1.17-5.88) and DLP (OR 1.91 95%PI 1.05-3.46)[17]. Achievement of these objectives should translate into lower morbidity and mortality[4–7]. From a slightly different perspective focusing on the efficiency in the use of resources, a systematic review assessing MRF in outpatient settings showed that from a total of 11 economic evaluations alongside a trial, eight were cost-effective, two were dominant against usual care, while one did not show benefits at higher costs[18].

As MRF demand increased professional resource use, it is likely to be associated with higher costs, mainly derived from additional human capital. Thus, assessing the opportunity-cost in a scenario where resources are scarce, is critical in order to ensure efficiency in the allocation of public resources and value for money. This issue can be addressed by conducting an economic evaluation of relevant competing interventions on a health problem to assess whether the additional benefits worth the additional costs, given additional resources[19]. Cost-utility analyses

are adequate to evaluate CVD as they have acute related costs and consequences due to the event, but also in the long-term, they can cause disability and therefore decrease quality of life[19].

As there is evidence that MRF has a positive clinical and economic impact, a trial named "Polaris" was implemented to study the effect of adding pharmacist-led MRF to usual care in a public primary care setting. To be aligned with governmental initiatives to prevent CVD, MRF was undertaken in patients with HTN, T2DM and DLP. The objective of this study was to undertake a cost-utility analysis of MRF compared to usual care from the public health sector perspective, considering a lifetime horizon.

Methods

The trial had a cluster randomized controlled design, and it was conducted in public primary care centres. Details of this trial are described elsewhere (NCT03502109). In brief, the trial was carried out from January 2018 to July 2019. Two hundred and eighty-three patients from 13 primary care centres completed the study (146 patients who received MRF throughout seven centres and 137 patients who received usual care throughout six centres). This study was approved by the ethics committee of each Health Service Administration and by the University of Technology Sydney Human Research Ethics Committee. All patients that participated in the trial signed the informed consent.

Target population

Centres recruited patients older than 65 years, with five or more prescription medicines, independent[20], enrolled in a CVD prevention program, with moderate (5-10%) or high (>10%) 10-year CHD risk according to adapted Framingham risk charts to the Chilean population[21].

Intervention: MRF

The complete intervention is described in detail according to the TIDieR methods (Appendix 1)[22]. However, the three main components are:

- Training of participating pharmacists in the Polaris method of pharmacist-led MRF. This method uses elements of other protocols but was adapted to the primary care system [23]. Pharmacists were trained in CVD prevention pharmacotherapy for elderly patients, interview skills, health education and inter-professional collaboration.
- The service was implemented through a step-wise approach, starting with the review of the patient's medical and pharmacy dispensing records. Then, in the first interview, a review of medications, including prescription and over the counter medications, was performed. In addition, an assessment about knowledge of each medicine, adherence, comorbidities, clinical outcomes of therapy, and signs or symptoms of adverse drug reactions was performed. If required, laboratory exams were requested from the clinical team[15]. With all the information gathered from the interview, the pharmacist evaluated any drug-related problems and developed a care plan. The plan was tailored according to patients' needs so that educational aids could be provided or changes in therapy could be agreed with the corresponding GP as needed. The recommendations were prioritised over time, starting with medication adherence, then if therapeutic objectives were not met, changes to therapy in collaboration with the GP were considered. Recommended protocol prioritization was not intended to replace clinical judgment. Each pharmacist had to interview patients at least four times over the study period.
- To aid on the implementation of MRF, a trained practice change facilitator with experience on MRF in primary care, visited the pharmacists periodically. The main objective of the visits was to conduct a fidelity assessment and systematic evaluation of

implementation factors, barriers or facilitators to MRF provision[24]. Actions recommended by the facilitator were discussed with the pharmacist or the primary care centre manager.

Comparator: Usual care

The usual care group received usual care from a pharmacist, mainly upon the patient's request. Both MRF and control patients had consultations with GPs, RN and dietitians every three to six months depending on individual CHD 10-year risk according to the CVD prevention program [15].

Outcomes

The primary outcome of this evaluation was quality-adjusted life years (QALY) and costs generated during a lifetime horizon in each group.

Decision-analytic model

Based on the trial, a cost-utility analysis was conducted following the recommendations of the local economic evaluation guideline and is reported according to the CHEERS criteria[25,26]. A summary of overall characteristics is presented in Table 1. The Ministry of Health validated the model.

Model structure and assumptions

The structure was conceptualized using inputs from a systematic review that used the Cochrane methods[27]. The results are provided in Appendix 2. Inclusion criteria were economic models of pharmacist-led interventions in CVD prevention.

The model was structured as a state-transition microsimulation with nine health states (Figure 1). This type of modelling approach was chosen due to the heterogeneity of the population and to limit the number of health states due to the potential for recurrence of events[28]. Patient-level data

from the trial was used to capture CVD risk. The sample of patients was bootstrapped to produce 100.000 resamples. Stability was assessed based on the variance, being ten times lower than the smallest difference amidst groups[28]. Each resample went in the model through a Monte Carlo simulation accumulating costs and QALYs over the patients' lifetime.

Each patient entered the model through the no CVD state, post-MI state, post-stroke state or heart failure (HF) state depending on their individual clinical history. Patients that did not have any history of MI, stroke or HF, entered the model in the no CVD state. In each cycle, a patient could either suffer a stroke, an MI, be diagnosed with HF, die due to other causes or survive without having any event. If patients suffered a stroke or an MI, they could die due to the event, die due to other cause or survive. Patients that survived a CVD event (stroke or MI) could have a recurrent event or survive until death from other causes. Some core model assumptions are:

- A patient that suffers a stroke may develop long-term sequelae impacting quality of life and costs.
- Because ischaemic stroke is more frequent than other types of stroke (e.g. haemorrhagic stroke), it was assumed that all patients would suffer this type of event[29,30].
- Patients with HF were assumed to be on state I-II according to New York Heart Association (NYHA) as stated in local guidelines for primary care patients[31,32].
- Patients with HF stayed on that state until they died from other causes.
- If patients suffered a CVD event (stroke or MI), they stayed on that state for one cycle.

TreeAge© software v2019R2.1 was used for model development and calculations.

Probabilities

Individual risk factors were used to calculate each patient's CVD risk probability. Framingham equations were used to calculate the chance of suffering an MI, stroke or HF in patients with no

CVD history[33,34]. If a patient had history of a CVD event, equations adjusted to this population were used[35]. After each cycle (one year), the probability of having an event was re-calculated, adjusting for patients' age and history of previous CVD events. Framingham equations estimated the 10-year risk of suffering a CVD, while recurrent CVD equations calculated it for 2-year risk[33–35]. In this context, these probabilities were transformed into one-year values. A summary of the characteristics of the trial sample's parameters used for the estimation of probabilities are described in Appendix 3, but patient-level data was used for the model. Other transition probabilities were obtained from the literature, and are described in Table 2[36,41]. Calculations details are explained and described in Appendix 4.

Utilities

Utility values were obtained from an international catalogue of EQ-5D scores that compiled available evidence with systematic review methods[37]. The average utility value was used for all given health states. For the no CVD health state, hypertension values were used as a proxy because all trial patients had this risk factor. Values are presented in Table 2.

Costs

Intervention costs were obtained directly from the trial and included time spent by pharmacists, GPs and practice change facilitators[38]. This data was self-reported during the trial. It was assumed that the facilitators' time remained constant over the time horizon, although it is expected that, over time, this cost would no longer be required[39]. Training costs were accounted for in the first year. Trial costs details can be found in Appendix 5.

The costs associated with each health state were obtained from local sources[40,41]. For the no CVD state, hypertension costs were assumed as a proxy. Because the cost of HF was not estimated within this data source, resources were identified and measured from current clinical

guidelines and valued using local price weights (Appendix 6)[31,40,41]. Costs per health state are presented in Table 2.

Currency, price date and conversion

All results are reported in 2019 US dollars. For conversion from original currency and update to 2019, the online tool developed by Cochrane Economics Methods Group and the Evidence of Policy and Practice Information and Coordinating Centre was used[42]. Purchasing power parity values available from the International Monetary Fund were used[43].

Sensitivity analysis

One-way sensitivity analysis was conducted for model parameters to assess the robustness of the results (Table 2). Discount rates of 0 and 6% were analysed[25]. A probabilistic sensitivity analysis (PSA) was conducted to assess the joint parameter uncertainty considering 1000 simulations assuming different time horizons (base case, 2, 5, 10 and 20 years). Beta distribution was used for utility inputs and gamma distribution for costs. A cost-effectiveness threshold of one gross domestic product per capita was used as suggested in local guidelines[25], which according to the World Bank reached $15,923 in 2018 ($16,207 updated to 2019)[44].

Results

The results of the base case analysis are presented in Table 3. MRF was associated with more benefits (measured as QALYs) compared to usual care (11.59 vs 10.47 respectively) and more costs ($3,423 vs $2,582 respectively). These values translate into a gain of 1.12 QALYs and $841 additional costs leading to an ICER of $751/QALY. This ICER is below the cost-effectiveness threshold of $16,207/QALY hence MRF is considered cost-effective compared to usual care. In terms of total QALYs, most came from patients who did not suffer a cardiovascular event, 78.9% and 74.3% in the MRF and usual care arms respectively, followed by patients who survived an MI event with 10.6% for MRF and 7.9% for usual care. In terms of

costs, the MRF group concentrated 54.6% ($1,869) of costs in the No CVD state while in the control group, it was 36.0% ($930).

Differences were found between the intervention and comparator in terms of mortality (a graphical representation is provided in Appendix 8). The model predicted that 15.6% in the intervention arm died due to cardiovascular causes increasing to 21.5% in the comparator arm. In terms of incidence of events, fewer patients suffered MI in the MRF arm versus the comparator arm, 17,282 versus 23,337 respectively. The incidence of stroke was lower but followed a similar trend as with MI. More patients receiving usual care suffered a stroke event compared to the MRF arm, 16,829 versus 11,183, respectively.

Sensitivity analysis

One-way sensitivity analysis using a tornado diagram is represented in Appendix 9. Overall, no parameter was sensitive enough to deem the intervention dominant or above the cost-effectiveness threshold. Changes in the ICER were observed in the upper and lower bound of pharmacist-GP salaries decreasing the ICER for the low-end in 47.4% ($400/QALY) and increasing for the high-end in 36.7% ($1039/QALY). When haemorrhagic stroke costs were considered, the ICER increased in 34.9%, while costs of follow-up with no sequelae increased it in 18.8%. When assessing the facilitator costs only on the first year, an ICER of $706/QALY was observed.

Probabilistic Sensitivity Analysis

PSA results are represented graphically in Figures 2 and 3. All iterations of the base case were lower than the threshold, and as the time horizon was reduced, the ICER increased. Incremental QALY decreased with the time horizon as observed comparing the lifetime horizon (1.11 QALYs) with the two-year time horizon (0.013 QALYs). The cost-effectiveness plane shows a

graphical representation of the 1000 iterations of each scenario. All the estimated ICERs lay in the northeast quadrant of the plane. This means that the intervention had higher associated cost but also increased health benefits compared to usual care. To represent the uncertainty in the function of the probability of iterations being cost-effective, Figure 3 shows the acceptability curves of all scenarios. This curve shows that the probability of MRF being cost-effective was 100% when horizons of five, 10, 20, and lifetime were considered. While it fell to 98.1% in the two-year time horizon, reaching 100% at a threshold of $40,830/QALY.

Discussion

Performing pharmacist-led MRF to prevent CVD in primary care patients from the Chilean public health care sector perspective compared to usual care was found to be cost-effective. MRF was associated with gains in terms of QALYs and higher costs, mainly driven by the intervention per se. The base case showed an ICER of $751/QALY. One-way sensitivity analysis did not change these findings. The estimated ICERs considering different time horizons were all lower than the suggested cost-effectiveness threshold. Low uncertainty was observed when assessing the two-year time horizon, where 1.9% of the PSA iterations were considered not cost-effective. The model showed face validity as in Chile, deaths due to MI and stroke in 2016 accounted for 17.6% in older adults, similar to what it is observed in the base case with 15.6% for the intervention group and 21.5% for the control group[9]. This means that allocating public resources to the implementation of MRF is a good value for money in a setting where CVD is the leading cause of mortality with an increasing burden on the public system that cares mostly of older patients[45].

This evaluation is based on data of a single clinical trial but is currently the best available evidence for the setting of interest. This issue is also relevant in terms of the comparators, as usual care is

comprised of consultations with GPs, dietitians and RN according to the model[46]. As this represents multidisciplinary care, it might reflect an enhancement compared to other studies where the comparator is GP care alone. Also, to represent a setting in terms of costs, price weights and resource use should use local sources and clinical pathways. These issues might affect the transferability to other countries and jurisdictions.

To the best of our knowledge, this is the first individual-patient microsimulation of professional pharmacy services in CVD outcomes[18,47–49]. Economic evaluations in this area have been carried using Markov models which have previously shown positive results. Some of them deemed the intervention as cost-effective[50] and other studies as dominant[51–55]. This difference might be explained by MRF methodologies which sometimes includes the ability for pharmacists to prescribe[51,53–55]. Marra et al. study explored the cost-effectiveness of "full-scope" against "partial-scope" pharmacist intervention in blood pressure control. "Full-scope" included consultation, MRF, and prescribing, while "partial-scope" excluded prescribing[53]. The difference in effect was reflected on the results (18.3 mmHg vs 7.6 mmHg), with "full-scope" intervention being dominant in 100% of the PSA iterations, while in the "Partial-scope" intervention, although it achieved cost-effectiveness in 100% of the iterations at a cost-effectiveness threshold of 40,000/QALY 2015 CAD, intervention's costs did not offset CVD events costs[53].

Patients who have had a previous CVD event or had a higher probability of having an event in the foreseeable future might benefit more from MRF. As an example, an intervention in the Netherlands that focused on lipid-lowering medications found that MRF was dominant for secondary prevention, and despite maintaining higher incremental effects for primary prevention, this was achieved at an increased cost with an ICER of €4,585/QALY, having 91.7% of the PSA iterations under a cost-effectiveness threshold of €20,000/QALY[52]. Similar results were observed

in two Markov models based on a trial that included patients with more than 20% 10-year CVD risk, yielding dominance across all scenarios, generating more QALYs (0.19 and 0.18) at lower costs (2,149 and 4,400 CAD)[54,55]. Another study examined MRF to improve blood pressure through a Markov model and evaluated different risk scenarios based on T2DM and smoking history, and patients' cholesterol/body mass index profile[50]. It was found that the group with the highest risk had the lowest ICER of $13,418/QALY, while the low-risk group was of $68,298/QALY changing the decision as a cost-effectiveness threshold of $50,000/QALY was considered. This trend might explain the results from this evaluation that were based mainly in patients of primary prevention (82.0%) and due to the inclusion criteria of moderate (5-10%) and high (more than 10%) 10-year CHD risk patients.

In addition, the choice of a microsimulation model was justified to take into account the patients' heterogeneity. T2DM is considered by itself a health problem with an increasing cost burden due to its complications. A report from the International Diabetes Federation estimated their costs on $760 billion in 2019 that could increase by 2030 to $825 billion[56]. In terms of economic models of pharmacist-led interventions, one study evaluated T2DM patients through a Markov model and found the intervention to be dominant in patients with low risk, high risk or assuming multiple CVD events in a 10-year time horizon[51]. The base case yielded an increase of 0.49 QALY and savings of $8,788. When a higher risk patients profile was modelled, the costs savings increased to $20,176 while 0.61 QALYs were gained.

As models are a simplification of reality, this study is no exempt of limitations. First, equations for CVD event probabilities were not calibrated to the Chilean population. There is a study that reported CHD risk formulas adapted to this population and showed lower risk compared to countries like the United States or Spain[21]. However, this adaptation did not capture the events of

stroke and HF, making the model less clinically plausible. Second, we assumed that patients diagnosed with HF to be in class I-II according to NYHA classification, but in reality, patients with worse functional status could as well be managed in a primary care setting. Third, in terms of data availability, complications of T2DM or renal disease could not be included due to paucity of local data and fixed available parameters like all-cause mortality hindered calculations. The latter, was available as a combined measure for people aged 85 years old and older, meaning that they had the same probability of dying due to all causes (different from CVD) compared to a 95 year old cohort. Fourth, health state utilities local data was not available, so an international catalogue was used[37]. However, preference studies have shown variations between countries which may lead to uncertainties[37]. In order to account for this limitation, these inputs were evaluated in the sensitivity analysis, which did not substantially change the results. Finally, the estimated costs of each health state might represent an underestimation of the real cost, mainly because the local source, likely reflects low price weights[40]. These prices, which have been established by the government, showed in 2014 to be undervalued, covering 56% of the actual billing[57]. Nonetheless, this assumption is conservative, as higher costs in health states would make MRF costs to have less impact on the final results.

Conclusion

This economic evaluation showed that MRF preventing CVD events is cost-effective compared to usual care in a primary care setting from the Chilean public sector perspective in the long term. The modelled patients showed increased benefits at higher costs which resulted in an ICER below the suggested cost-effectiveness threshold. This trend increased when longer time horizons were tested at low uncertainty. The implementation of MRF at a national level could be

considered by decision-makers a cost-effective addition to usual care as it might lead to avoiding CVD events.

References

1. World Health Organization (WHO). CAUSE-SPECIFIC MORTALITY, 2000–2016. Disease burden and mortality estimates. https://www.who.int/healthinfo/global_burden_disease/estimates/en/. Published 2016. Accessed November 13, 2019.
2. Matza LS, Stewart KD, Gandra SR, et al. Acute and chronic impact of cardiovascular events on health state utilities Utilization, expenditure, economics and financing systems. *BMC Health Serv Res*. 2015;15(1):1-11. doi:10.1186/s12913-015-0772-9
3. Bloom, D.E. Cafiero, E.T., Jané-Llopis, E., Abrahams-Gessel, S., Bloom, L.R., Fathima, S., Feigl, A.B., Gaziano, T., Mowafi, M., Pandya, A., Prettner, K., Rosenberg, L., Seligman, B., Stein, A.Z., & Weinstein C. *The Global Economic Burden of Non-Communicable Diseases*.; 2011.
4. NICE. Managing blood glucose in patients with type 2 diabetes. *Natl Inst Heal Care Excell*. 2019;(July):1-29. file:///C:/Users/Karen/Downloads/type-2-diabetes-in-adults-managing-blood-glucose-in-adults-with-type-2-diabetes (1).pdf.
5. NICE. Lipid modification ther therap apy y for pre prev venting cardio cardiovascular vascular disease. *Natl Inst Heal Care Excell*. 2017:1-20. doi:10.1177/1933719117732165
6. NICE. Hypertension in adults : diagnosis and management. *Natl Inst Heal Care Excell*. 2019;(August 2019).
7. Mendis S, Puska P, Norving B. Global Atlas on Cardiovascular disease prevention and control. *World Heal Organ*. 2011.
8. Benjamin EJ, Muntner P, Alonso A, et al. *Heart Disease and Stroke Statistics-2019 Update: A Report From the American Heart Association*. Vol 139.; 2019. doi:10.1161/CIR.0000000000000659
9. Chile M de S de. Serie de defunciones. http://www.deis.cl/wp-content/2017/gobCL-sitios-1.0/assets/SerieDefunciones_2000_2015.html. Accessed January 4, 2020.
10. Ministerio de Salud de Chile. Egresos Hospitalarios. http://cognos.deis.cl/ibmcognos/cgi-bin/cognos.cgi?b_action=cognosViewer&ui.action=run&ui.object=%2Fcontent%2Ffolder%5B%40name%3D%27PUB%27%5D%2Ffolder%5B%40name%3D%27REPORTES%27%5D%2Ffolder%5B%40name%3D%27Egresos%27%5D%2Freport%5B%40name%3D%27Egresos hosp. Accessed January 4, 2020.
11. Ministerio de Salud (MINSAL). Encuesta Nacional de Salud 2016-2017 Primeros resultados. *Dep Epidemiol Div Planif Sanit Subsecr Salud Pública*. 2017:61. http://web.minsal.cl/wp-content/uploads/2017/11/ENS-2016-17_PRIMEROS-RESULTADOS.pdf.
12. Ministerio de Salud del Gobiernno de Chile. Encuesta nacional de salud 2016-2017 Segunda entrega de resultados. *Dep Epidemiol Div Planif Sanit Subsecr Salud Pública*. 2018:59. https://www.minsal.cl/wp-content/uploads/2018/01/2-Resultados-

ENS_MINSAL_31_01_2018.pdf.

13. Development O for EC and. OECD Health Statistics 2019. https://www.oecd.org/health/health-data.htm. Published 2019. Accessed January 15, 2020.

14. Chile M de S de. *ORIENTACIÓN TÉCNICA PROGRAMA FONDO DE FARMACIA PARA ENFERMEDADES CRÓNICAS NO TRANSMISIBLES EN ATENCIÓN PRIMARIA*.; 2019.

15. Ministerio de Salud de Chile. Orientación Técnica Programa de Salud Cardiovascular 2017. 2017:1-85. http://www.redcronicas.cl/wrdprss_minsal/wp-content/uploads/2017/08/OT-PROGRAMA-DE-SALUD-CARDIOVASCULAR_03.pdf.

16. Griese-Mammen N, Hersberger KE, Messerli M, et al. PCNE definition of medication review: reaching agreement. *Int J Clin Pharm*. 2018;40(5):1199-1208. doi:10.1007/s11096-018-0696-7

17. Martínez-Mardones F, Fernandez-Llimos F, Benrimoj SI, et al. Systematic Review and Meta-Analysis of Medication Reviews Conducted by Pharmacists on Cardiovascular Diseases Risk Factors in Ambulatory Care. *J Am Heart Assoc*. 2019;8(22):1-16. doi:10.1161/JAHA.119.013627

18. Ahumada-Canale A, Quirland C, Martinez-Mardones FJ, Plaza-Plaza JC, Benrimoj S, Garcia-Cardenas V. Economic evaluations of pharmacist-led medication review in outpatients with hypertension, type 2 diabetes mellitus, and dyslipidaemia: a systematic review. *Eur J Heal Econ*. 2019;20(7):1103-1116. doi:10.1007/s10198-019-01080-z

19. Drummond M, Sculpher M, Claxton K, Stoddart GL, Torrance G. *Methods for the Economic Evaluation of Health Care Programmes.* 4th ed. Oxford University Press; 2015.

20. Ministerio de Salud C. *Manual de Aplicación Del EMPAM*.; 2010.

21. Icaza G, Núñez L, Marrugat J, et al. Estimación de riesgo de enfermedad coronaria mediante la función de Framingham adaptada para la población Chilena. *Rev Med Chil*. 2009;137(10):1273-1282.

22. Hoffmann TC, Glasziou PP, Boutron I, et al. Better reporting of interventions: Template for intervention description and replication (TIDieR) checklist and guide. *BMJ*. 2014;348(March):1-12. doi:10.1136/bmj.g1687

23. Grupo de Investigación en Atención Farmacéutica U de G. Pharmacotherapy follow-up: The Dader method (3rd revision: 2005). *Pharm Pract*. 2006;4(1):44-53. http://scielo.isciii.es/scielo.php?script=sci_arttext&pid=S1885-642X2006000100008.

24. Garcia-Cardenas V, Perez-Escamilla B, Fernandez-Llimos F, Benrimoj SI. The complexity of implementation factors in professional pharmacy services. *Res Soc Adm Pharm*. 2018;14(5):498-500. doi:10.1016/j.sapharm.2017.05.016

25. Castillo M, Castillo C, Loayza S, Aravena M. *Guía Metodológica Para La Evaluación Económica de Intervenciones de Salud En Chile*.; 2013.

26. Husereau D, Drummond M, Petrou S, Carswell C, Moher D, Greenberg D. Consolidated Health Economic Evaluation Reporting Standards (CHEERS)--Explanation and elaboration: A report of the ISPOR Health Economic Evaluations Publication Guidelines Task Force. *Value Heal*. 2013;16:231-250. doi:10.1016/j.jval.2013.02.002

27. Higgins J, Green S. Cochrane handbook for systematic reviews of interventions version 5.1. 0 [updated March 2011]. *Cochrane Collab*. 2011. www.cochrane-handbook.org.

28. Uwe, Siebert, Alagoz O, Bayoumi AM, et al. State-Transition Modeling: A Report of the ISPOR-SMDM Modeling Good Research Practices Task Force-3. *Value Heal*. 2012;15:812-820. doi:10.1016/j.jval.2012.06.014

29. Lavados PM, Sacks C, Prina L, et al. Pablo M Lavados, Incidence, 30-day case-fatality rate, and prognosis of stroke (PISCIS project). *Lancet*. 2005;365:2206-2215. papers://a9255c32-293f-4036-84b2-8645da0e408e/Paper/p3.

30. Emelia J. Benjamin, Paul Muntner, Alvaro Alonso, Marcio S. Bittencourt, Clifton W. Callaway, April P. Carson, Alanna M. Chamberlain, Alexander R. Chang, Susan Cheng, Sandeep R. Das FND. Heart Disease and Stroke Statistics—2019 Update: A Report From the American Heart Association. *Circulation*. 2019;139(10):e56-e528.

31. Ministerio de salud GDC. Guía Clínica Insuficiencia Cardíaca. *Soc Chil Cardiol y Cirugía Cardiovasc*. 2015:96. doi:10.1136/bmj.i1010

32. Yancy CW, Jessup M, Bozkurt B, et al. 2017 ACC/AHA/HFSA Focused Update of the 2013 ACCF/AHA Guideline for the Management of Heart Failure: A Report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines and the Heart Failure Society of Amer. *Circulation*. 2017;136(6):e137-e161. doi:10.1161/CIR.0000000000000509

33. D'Agostino RB, Vasan RS, Pencina MJ, et al. General cardiovascular risk profile for use in primary care: The Framingham heart study. *Circulation*. 2008;117(6):743-753. doi:10.1161/CIRCULATIONAHA.107.699579

34. D'Agostino, RB; Grundy, S; Sullivan LM, Wilson P. Validation of the Framingham Coronary Heart Disease Prediction Scores. *Jama*. 2001;286(2):180-187. doi:10.1001/jama.286.2.180

35. Wilson PWF, D'Agostino R, Bhatt DL, et al. An international model to predict recurrent cardiovascular disease. *Am J Med*. 2012;125(7):695-703.e1. doi:10.1016/j.amjmed.2012.01.014

36. World Health Organization (WHO). Life tables by country: Chile 2016. https://apps.who.int/gho/data/view.main.LT62010?lang=en. Published 2018. Accessed October 26, 2019.

37. Van Wilder L, Rammant E, Clays E, Devleesschauwer B, Pauwels N, De Smedt D. A comprehensive catalogue of EQ-5D scores in chronic disease: results of a systematic review. *Qual Life Res*. 2019;28(12):3153-3161. doi:10.1007/s11136-019-02300-y

38. Chile B del congreso nacional de. ESTATUTO DE ATENCION PRIMARIA DE SALUD MUNICIPAL. https://www.leychile.cl/Navegar?idNorma=30745. Published 2016. Accessed November 14, 2019.

39. Garcia-cardenas V, Ph D, Pharm M, et al. Evaluation of the implementation process and outcomes of a professional pharmacy service in a community pharmacy setting . A case report. 2017;13:614-627. doi:10.1016/j.sapharm.2016.05.048

40. Ministerio de Salud C. *INFORME FINAL DEL ESTUDIO DE VERIFICACIÓN DEL COSTO ESPERADO INDIVIDUAL PROMEDIO POR BENEFICIARIO DEL CONJUNTO PRIORIZADO DE PROBLEMAS DE SALUD CON GARANTÍAS EXPLÍCITAS 2018*.; 2019.

41. Evc- I. *ANEXO FICHAS DE DEMANDA / FICHAS VALOR PRESTACIONES / FICHAS TECNICAS - EVC-2018*.; 2018.

42. Shemilt I, Thomas J, Morciano M. A web-based tool for adjusting costs to a specific target currency and price year. *Evid Policy*. 2010;6(1):51-59. doi:https://doi.org/10.1332/174426410X482999

43. Fund IM. World Economic Outlook Database. https://www.imf.org/external/pubs/ft/weo/2019/01/weodata/index.aspx. Published 2018. Accessed April 23, 2019.

44. Bank TW. GDP per capita (current US$). https://data.worldbank.org/indicator/NY.GDP.PCAP.CD?locations=CL. Accessed January 14, 2020.

45. Castillo-Laborde C, Aguilera-Sanhueza X, Hirmas-Adauy M, et al. Health insurance scheme performance and effects on health and health inequalities in Chile. *MEDICC Rev*. 2017;19(2-3):57-64. doi:10.1590/medicc.2017.1902030011

46. (PAHO/WHO) PAHOHO. *La Renovación de La Atención Primaria de Salud En Las Américas*.; 2007.

47. A. A, C.J. P. A systematic review of the clinical and economic effectiveness of clinical pharmacist intervention in secondary prevention of cardiovascular disease. *J Manag Care Pharm*. 2013;19(5):408-416. doi:https://doi.org/10.18553/jmcp.2013.19.5.408

48. Wang Y, Yeo QQ, Ko Y. Economic evaluations of pharmacist-managed services in people with diabetes mellitus: A systematic review. *Diabet Med*. 2016;33(4):421-427. doi:10.1111/dme.12976

49. Jacob V, Chattopadhyay SK, Thota AB, et al. Economics of Team-based Care in Controlling Blood Pressure: A Community Guide Systematic Review. *Am J Prev Med*. 2015;49(5):772-783. doi:10.1016/j.amepre.2015.04.003

50. Kulchaitanaroaj P, Brooks JM, Chaiyakunapruk N, Goedken AM, Chrischilles EA, Carter BL. Cost-utility analysis of physician-pharmacist collaborative intervention for treating hypertension compared with usual care. *J Hypertens*. 2017;35(1):178-187.

doi:10.1097/HJH.0000000000001126

51. Yu J, Shah BM, Ip EJ, Chan J. A markov model of the cost-effectiveness of pharmacist care for diabetes in prevention of cardiovascular diseases: Evidence from kaiser permanente northern california. *J Manag Care Pharm*. 2013;19(2).

52. Vegter S, Oosterhof P, van Boven JFM, Stuurman-Bieze AGG, Hiddink EG, Postma MJ. Improving Adherence to Lipid-Lowering Therapy in a Community Pharmacy Intervention Program: A Cost-Effectiveness Analysis. *J Manag Care Pharm*. 2014;20(7):722-732. doi:10.18553/jmcp.2014.20.7.722

53. Marra C, Johnston K, Santschi V, Tsuyuki RT. Cost-effectiveness of pharmacist care for managing hypertension in Canada. *Can Pharm J*. 2017;150(3):184-197. doi:10.1177/1715163517701109

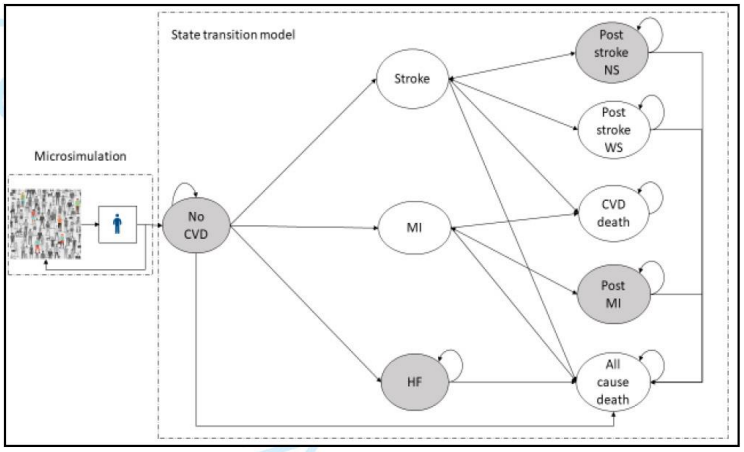
54. Al Hamarneh YN, Johnston K, Marra CA, Tsuyuki RT. Pharmacist prescribing and care improves cardiovascular risk, but is it cost-effective? A cost-effectiveness analysis of the RxEACH study. *Can Pharm J*. 2019;152(4):257-266. doi:10.1177/1715163519851822

55. Tam-Tham H, Clement F, Hemmelgarn BR, et al. A Cost Analysis and Cost-Utility Analysis of a Community Pharmacist–Led Intervention on Reducing Cardiovascular Risk: The Alberta Vascular Risk Reduction Community Pharmacy Project (RxEACH). *Value Heal*. 2019;22(10):1128-1136. doi:10.1016/j.jval.2019.05.012

56. Internation Diabetes Federation. *IDF Diabetes Atlas*.; 2019.

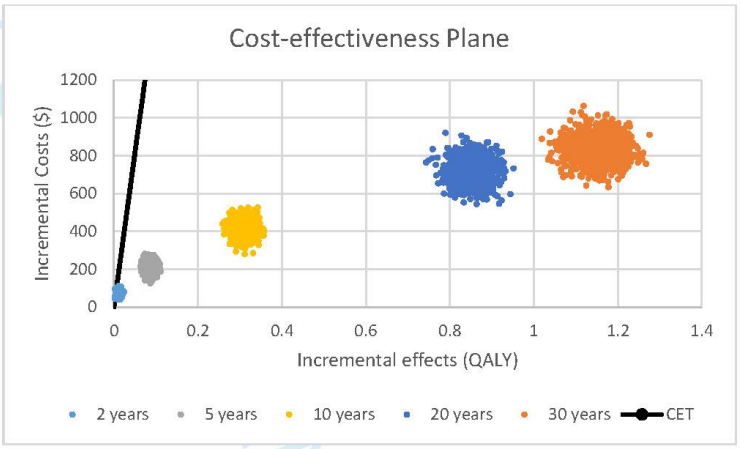
57. Cid Pedraza C, Bastías S. G. Evaluation of financial status of public hospitals considering the updated costs of their services. *Rev Med Chil*. 2014;142(2):161-167. doi:10.4067/S0034-98872014000200003

Figure 1. Decision-analytic model.



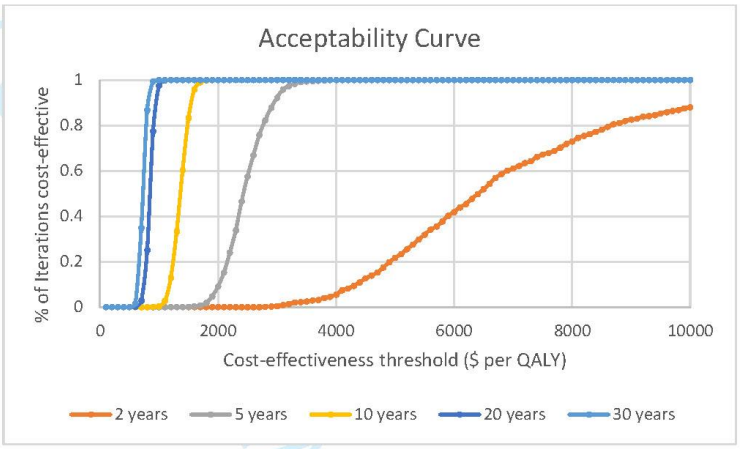
Patients were bootstrapped on the microsimulation phase. Once in the state-transition model, they started in one of the grey coloured states according to their individual clinical history (a previous stroke or myocardial infarction or history of heart failure). MI indicates myocardial infarction; No CVD, no history of cardiovascular diseases (stroke, myocardial infarction or heart failure); HF, heart failure; NS, no sequelae; WS, with sequelae.

Figure 2. Cost-effectiveness plane of pharmacist-led medication review at different time horizons against usual care.



CET indicates cost-effectiveness threshold; QALY, quality-adjusted life years.

Figure 3. Acceptability curve of pharmacist-led medication review at different time horizons against usual care.



QALY indicates quality-adjusted life year.

Table 1. Base case decision-analytic model summary.

Target population	Adults older than 65 years, independent, with five or more prescribed medicines, participating in the CVD prevention program, and with 10-year CHD higher than 5%
Setting and location	Chilean primary care health centre
Perspective	Chilean public health care sector [25]
Intervention	MRF plus usual care
Comparator	Usual care
Time horizon	Lifetime (30 years)
Discount rate	3% for costs and health benefits [25]
Health benefits	QALYs [25]
Resources	Health states: described in the literature MRF: according to trial data
Currency	2019 USD
Model structure	State transition microsimulation
Cycle length	One year
Uncertainty	One-way sensitivity analysis and PSA
Others	A half-cycle correction was used

Notes: CHD indicates coronary heart diseases; CVD, cardiovascular diseases; MRF, medication review with follow-up; PSA, probabilistic sensitivity analysis; QALY, quality-adjusted life year; USD, United States dollar.

Table 2. Model parameters. CHD indicates coronary heart diseases;

Probabilities		
Probabilities	Point estimate (source)	Observations
Patient with no CVD history suffers a stroke	Calculated with Framingham equations and calibration coefficients [33]	
Patients with no CVD history suffers an MI	Calculated with Framingham equations for hard CHD events [34] discounting coronary death	Hard CHD events are defined as MI and coronary death
Patient with no CVD history is diagnosed with HF	Calculated with Framingham equations and calibration coefficients [33]	
Patient dies from a non-CVD related cause	According to sex and age extracting CVD death [40]	Appendix 4
Dies from MI	Calculated with mortality and hospitalization data according to sex and age [10,41]	Appendix 4
Survives stroke with sequelae	M: 0.24 F: 0.38 [29]	
Dies from stroke	Calculated with mortality and hospitalization data according to sex and age [10,41]	Appendix 4
Recurrent MI or stroke	Calculated with international equations for recurrent CVD [35]	
Utilities [36]		
Health state	Utilities (standard error)	Observations
No CVD	0.86 (0.02)	Hypertension
MI	0.69 (0.036)	
Stroke	0.62 (0.068)	
HF	0.64 (0.056)	
Post MI	0.78 (0.015)	
Post stroke NS	0.68 (0.025)	
Post stroke WS	0.68 (0.025)	
Costs [38,39]		
Health state	Costs (standard error)	Observations
No CVD	$102.79 (15.73)	Hypertension

Table 2. *Continued*

MI	$1,209.11 (185.07)	
Stroke	$2,136.95 (327.08)	Haemorrhagic stroke costs were included in one-way sensitivity analyses [29].
HF diagnosis	$240.99 (36.89)	
HF follow-up	$114.40 (17.51)	
Post-MI	$268.07 (41.03)	
Post-stroke NS	$434.75 (66.54)	Haemorrhagic stroke costs were included in one-way sensitivity analyses [29].
Post-stroke WS 1st year	$1,183.76 (343.53)	Haemorrhagic stroke costs were included in one-way sensitivity analyses [29].
Post-stroke WS	$434.75 (66.54)	Haemorrhagic stroke costs were included in one-way sensitivity analyses [29].
Trial data		
Medication review[1]	$69.26 (2.65)	Local high and low-end salaries according to local regulations were included in the one-way sensitivity analysis [42]
Facilitator[1]	$3.70 (0.57)	A scenario analysis was performed using these costs only the first year [37]
Training[1]	$2.86 (0.44)	Cost accrued only in year one

Notes: F indicates female; HF, heart failure; M, male; MI, myocardial infarction; No CVD, No history of cardiovascular diseases (stroke, myocardial infarction or heart failure); NS, no sequels; WS, with sequels;. [1]Cost added only to the intervention group.

Table 3. Base case microsimulation outcomes per state.

Health state	Mean QALY		Mean Costs	
	MRF	Usual care	MRF	Usual care
No CVD	9.14	7.78	$1,869	$930
MI	0.12	0.16	$229	$283
Stroke	0.07	0.1	$248	$361
HF	0.55	0.72	$171	$140
Post MI	1.23	0.83	$533	$285
Post stroke NS	0.4	0.75	$301	$479
Post stroke WS	0.08	0.13	$72	$104
All cause death	0	0	0	0
CVD death	0	0	0	0
Total	11.59	10.47	$3,423	$2,582
Incremental	1.12		$841	
ICER	$751 per QALY			

Notes: HF indicates heart failure; ICER, incremental cost-effectiveness ratio; MI, myocardial infarction; MRF, medication review with follow-up; No CVD, No history of cardiovascular diseases (stroke, myocardial infarction or heart failure); NS, no sequelae; QALY, quality-adjusted life years; WS, with sequelae.

Supplementary Material

Appendix 1

TIDieR checklist for the Polaris MRF method. See on chapter 4.

Appendix 2: Systematic review

PubMed, Scopus and Web of Science were searched. Eligibility criteria were model-based economic evaluation of pharmacist-led MRF on CVD risk factors. Articles in languages other than English or Spanish, or conference abstracts were excluded. The search was conducted on the 13th of August 2019. Articles were screened according to eligibility criteria and then obtained for full-text review. Finally, included studies were used to retrieve information of model structure, health states, sources of information for effects and transition probabilities. Out of 1609 articles screened, the review yielded six articles that are below.

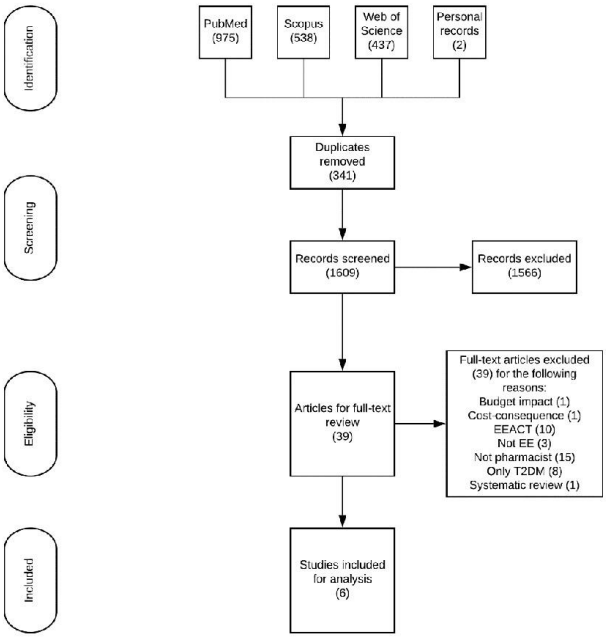


Figure 7. Systematic review flowchart. EEACT indicates economic evaluation alongside clinical trial; EE, economic evaluation; T2DM, type two diabetes mellitus.

Title	Journal	Economic analysis	Modelling approach	Patients	Cycle length	Time horizon	Health states	Utilities source	Probabilities sources	Perspective	Costs source	Discount
A Markov Model of the Cost-Effectiveness of Pharmacist Care for Diabetes in Prevention of Cardiovascular Diseases: Evidence from Kaiser Permanente Northern California	J Manag Care Pharm. 2013;19(2):102-14	Cost-utility	Markov	DM	1 year	10 year	No history of CV, history of stroke, history of CHD, Death due to CHD, death due to stroke, history of both, death due to other causes.	literature	cohort	Third party payer	literature	3% costs, 5% utilities
Cost-utility analysis of physician-pharmacist collaborative intervention for treating hypertension compared with usual care	Hypertens 35:178–187	Cost-utility	Markov	HTN	0.5 years	5-10-lifetime	ACS, stroke, heart failure, death, HTN, survival states	Sullivan catalogue	trial	Third party payer	trial + literature	3% costs
Pharmacist prescribing and care improves cardiovascular risk, but is it cost-effective? A cost-effectiveness analysis of the RxEACH study	Can Pharm J (Ott) 2019;152:257-266	Cost-utility	Markov	HTN	NA	30 years	no CVD, this year, history of CVD	Sullivan catalogue	trial	Third party payer	expert opinion and literature	1.5% for both
Improving Adherence to Lipid-Lowering Therapy in a Community Pharmacy Intervention Program: A Cost-Effectiveness Analysis	J Manag Care Pharm. 2014;20(7):722-32	Cost-utility	Markov	DLP	NA	Lifetime	MI, post MI, stroke, post stroke	UK	trial, literature	Third party payer	trial + literature	4% costs, 1.5% utilities
An Evaluation of the Cost-effectiveness of Comprehensive MTM Integrated with Point-of-Care Phenotypic and Genetic Testing for U.S. Elderly Patients After Percutaneous Coronary Intervention	J Manag Care Spec Pharm. 2018;24(2):142-52	Cost-utility	Decision tree - Markov	ACS	1 year	Lifetime	MI, post MI, stroke, post stroke	literature	literature	U.S. health care system	literature	3.5% for both
Cost-effectiveness of pharmacist care for managing hypertension in Canada	Can Pharm J (Ott) 2017;150:	Cost-utility	Markov	HTN	NA	30 years	CVD, ESRD, no CVD	Sullivan catalogue	trial	Third party payer	expert opinion and literature	5% on both

Table 1. Systematic review results.

Appendix 3: Trial characteristics

Population characteristics	Medication review with follow-up		Usual care	
	n	Mean (SD)	n	Mean (SD)
Age	146	72.95 (5.95)	137	73.93 (5.88)
	n	%	n	%
Woman	106	72.60%	106	77.37%
Smokers	22	15.07%	25	18.25%
Type 2 diabetes mellitus	91	62.33%	86	62.77%
Heart failure	8	5.48%	9	6.57%
Atrial fibrillation	3	2.05%	8	5.84%
Statin prescription	97	66.44%	82	59.85%
Acetylsalicylic acid prescription	98	67.12%	100	72.99%
Myocardial Infarction	14	9.59%	4	2.92%
Stroke	7	4.79%	11	8.03%

Table 2. Patient characteristics of the trial. SD indicates standard deviation.

Parameters	Baseline			
	Medication review with follow-up		Usual care	
	n	Mean (SD)	n	Mean (SD)
Body mass index	146	30.48 (5.57)	137	31.18 (4.51)
Systolic blood pressure	146	137.99 (19.12)	137	138.87 (14.20)
Diastolic blood pressure	146	75.61 (12.37)	137	75.03 (11.39)
Total cholesterol	146	182.68 (43.41)	137	174.61 (43.82)
LDL cholesterol	146	100.52 (38.68)	137	98.36 (35.14)
HDL cholesterol	146	45.53 (11.80)	137	45.03 (11.45)
Triglycerides	146	172.74 (91.23)	137	176.42 (69.90)
End of trial				
Body mass index	146	30.22 (5.39)	137	31.28 (4.31)
Systolic blood pressure	146	128.99 (11.64)	137	143.47 (14.43)
Diastolic blood pressure	146	71.18 (7.99)	137	77.80 (9.74)
Total cholesterol	146	162.94 (29.74)	137	189.80 (42.79)
LDL cholesterol	146	85.18 (24.04)	137	111.45 (32.95)
HDL cholesterol	146	48.31 (10.31)	137	43.60 (8.83)
Triglycerides	146	141.82 (58.53)	137	189.47 (73.23)

Table 3. Results from the trial. SD indicates standard deviation.

Appendix 4: Probabilities

- Non-CVD death

As we had available all cause death rates, we should subtract CVD death to calculate the probability of dying not related to CVD. All cause death rate was available from the World Health Organization and CVD deaths and total deaths were available from the Chilean Ministry of Health; the proportion of deaths due to CVD was estimated and used to multiply by all cause death probability to get the probability of no CVD death.

Age	CVD deaths	All cause deaths	Proportion of CVD deaths	Proportion of no CVD deaths
Men				
65-69	1030	5422	0.189967	0.810033
70-74	1251	6344	0.197194	0.802806
75-79	1321	6832	0.193355	0.806645
80 and older	3116	17406	0.179019	0.820981
Woman				
65-69	467	3551	0.131512	0.868488
70-74	751	4742	0.158372	0.841628
75-79	955	5718	0.167016	0.832984
80 and older	4281	24598	0.174039	0.825961

Table 4. Cardiovascular deaths. CVD indicates cardiovascular diseases.

Age	Probability of all-cause death	Adjusted probability
Men		
65-69	0.02034	0.016476
70-74	0.030776	0.024708
75-79	0.048019	0.038734
80-85	0.078046	0.064074
85 and older	0.152267	0.125009
Women		
65-69	0.011533	0.010016
70-74	0.018418	0.015501
75-79	0.028923	0.024093
80-85	0.053392	0.0441
85 and older	0.119143	0.098408

Table 5. All-cause death probabilities.

As mortality data was classified until 80 years old, as a conservative assumption the same probability was used for 80-85 year old death probability and 85 and older probability.

- Myocardial infraction deaths.

	Hospitalization		Deaths		Probabilities	
Age	Man	Woman	Man	Woman	Man	Woman
65-79	4715	2229	1987	977	0.421421	0.438313
80 and older	1196	1043	1414	1742	1.182274	1.670182

Table 6. Myocardial infraction deaths.

As probabilities for patients 80 and older were higher than one, it was assumed that every patient that had a MI at that age would die.

- Death due to stroke

	Hospitalization		Deaths		Probabilities	
Age	Man	Woman	Man	Woman	Man	Woman
65-79	6520	4703	1615	1196	0.247699	0.254306
80 and older	3031	3802	1702	2539	0.561531	0.667806

Table 7. Stroke deaths.

Appendix 5: Trial Costs

Item	Resource use: mean (minutes)	Price weight	Per patient cost
Pharmacist	149.43	$0.38	$56.67
GP	24.42	$0.52	$12.58
Facilitator	9.28	$0.40	$3.70
Training	7.19	$0.40	$2.86

Table 8. Trial costs. GP indicates general practitioner.

Appendix 6: Heart Failure Costs

Diagnosis	Quantity	Frequency	Price	Cost
Full blood count	1	100%	$6.25	$6.25
Plasma protein	1	100%	$2.78	$2.78
Glucose	1	100%	$2.78	$2.78
Creatinine	1	100%	$2.78	$2.78
Complete urinalysis	1	100%	$4.17	$4.17
Sodium, potassium, chloride	1	100%	$4.86	$4.86
Blood urea nitrogen	1	100%	$2.78	$2.78
Liver function tests	1	100%	$22.92	$22.92
TSH	1	100%	$9.72	$9.72
Chest x-ray	1	100%	$39.58	$39.58
Electrocardiogram	1	100%	$13.89	$13.89
Doppler echocardiogram	1	100%	$128.47	$128.47
Total				$240.97

Table 9. Diagnosis of heart failure costs.

Follow-up	Quantity	Frequency	Price (UF)	Cost
Enalapril 10mg	1460	100%	$0.01	$17.77
Losartan 50mg	365	100%	$0.03	$9.26
Carvedilol 12.5mg	1460	100%	$0.01	$11.67
General practitioner consultation	2	100%	$11.81	$23.61
Registered nurse or dietitian consultation	2	100%	$3.47	$6.94
Physiotherapy consultation	1	100%	$3.47	$3.47
Full blood count	2	100%	$6.25	$12.50
Creatinine	2	100%	$2.78	$5.56
Complete urinalysis	2	100%	$4.17	$8.33
Sodium, potassium, chloride	2	100%	$4.86	$9.72
Blood urea nitrogen	2	100%	$2.78	$5.56
Total				$114.39

Table 10. Follow-up of patients with heart failure costs. UF indicates *unidad de fomento.*

Appendix 7: Stroke costs

Haemorrhagic stroke costs were included according to the Chilean reported proportions. This population is described as follows: 65% of ischaemic stroke, 28% haemorrhagic and 7% undetermined (37). As these proportions represent higher costs, they modified the upper limit of these states (36).

Health state	USD 2019	70%	130%
Post stroke NS	569.71	398.79	740.62
Post stroke WS 1ST YEAR	1318.72	923.10	1714.33
POST STROKE WS	569.71	398.79	740.62
Stroke	5789.85	4052.89	7526.80

Table 11. Stroke costs. NS indicates no sequelae; USD, United State dollar; WS, with sequelae.

Appendix 8: Proportion of patients per cycle

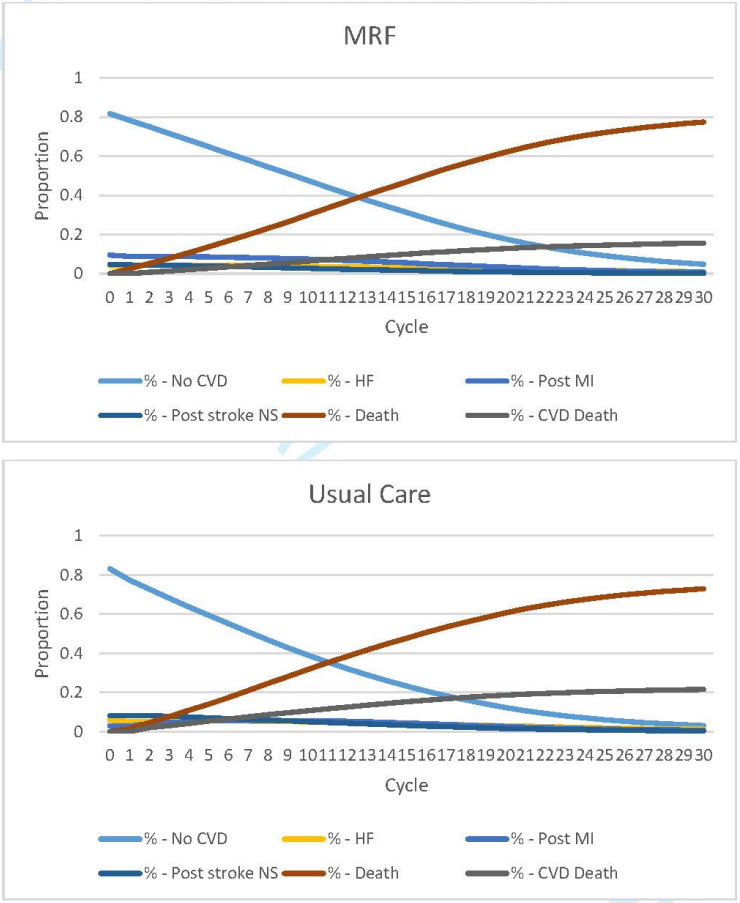


Figure 8. Proportion of patients per cycle. HF indicates heart failure; MI, myocardial infarction; MRF, medication review with follow-up; No CVD, no history of cardiovascular diseases (stroke, myocardial infarction or heart failure); NS, no sequelae.

Appendix 9: Tornado diagram

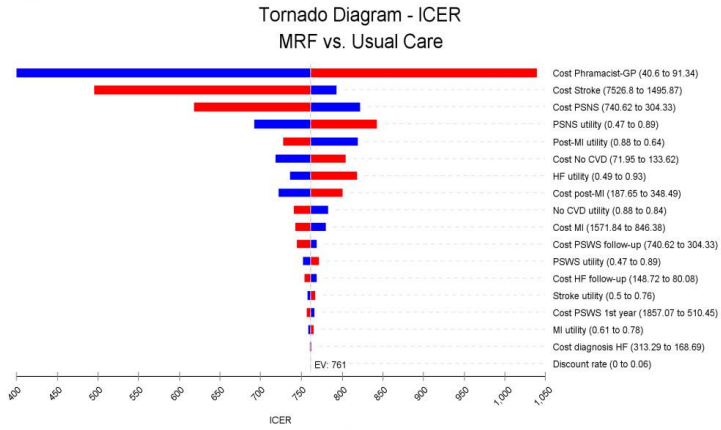


Figure 9. Tornado diagram. HF indicates heart failure; MI, myocardial infarction; MRF, medication review with follow-up; No CVD, no history of cardiovascular diseases (stroke, myocardial infarction or heart failure); PSNS, post-stroke no sequelae; PSWS, post-stroke with sequelae.

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Chapter 7

Discussion

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7.1 Contextualising Current Knowledge

The research undertaken for this thesis framed the current state of the art of economic evaluations of MRF. Using an adapted "Polaris MRF" method for primary care, we developed a cRCT undertaken within Chilean public health centres and evaluated its value for money through an economic evaluation.

A systematic review was conducted to gather evidence of medication review, a professional pharmacy service, on HTN, T2DM and DLP. As the international literature reported positive clinical and economic outcomes of MRF in CVD prevention, a cRCT was undertaken. Patients included in this study were independent older adults, with more than five prescribed medications and were enrolled in a CVD prevention program. Two cost-utility analyses were performed: (1) a trial-based evaluation using costs and utilities collected within the trial and (2) a decision-analytic model to assess the effect of MRF over a lifetime time horizon. Both analyses found the intervention to be cost-effective with ICERs of $430 and $751 per QALY. Sensitivity analysis did not change these conclusions.

Due to the absence of recent reviews addressing the impact of MRF on CVD risk factors, a systematic review was conducted. Eleven studies were considered for complete analysis. Trial's risk of bias was assessed through the Effective Practice and Organisation of Care tool from the Cochrane collaboration and economic evaluation quality was appraised with the Consensus Health Economic Criteria list [94,95]. Four trials had a low risk of bias[55,57,61,71] while four economic evaluations were rated as high quality [55,57,62,65]. Two studies had both, low risk of bias and a high-quality economic evaluation [55,57]. Cost-effectiveness was observed in eight economic evaluations [57,59,63,65,66,68,69,96] and dominance in two [55,67]. Several outcomes were used to compute ICERs, while two studies conducted cost-utility analyses [65,69].

The literature review gave rise to several recommendations that were used as inputs for the Polaris trial's economic evaluation. Firstly, a cost-utility analysis should be prioritized to represent patients' preferences and to allow for comparison across interventions. QALYs are the primary outcome in these assessments as they provide a generic measure that allows comparison between health technologies of different nature, for example, to compare MRF with a cancer drug for paediatric patients [40]. Evidence-based resource allocation decisions can be thus be made by policy makers. This is relevant for the local public health system where the Ministry of Health has to decide and prioritise where investment in health should be made [22]. Secondly, the comparator should be thoroughly described. Some studies only referred to it as "usual care" without any further description, which can hinder information for decision-makers. Usual care varies between countries and even between centres in the same system. For example, if "usual care" is provided by a GP, then it would be difficult to compare the results of the Polaris trial as in the Chilean "usual care" primary health care is comprised of a multi-professional team [29]. Thirdly, as CVDs over time can develop as acute events, can occur more frequently if risk factors are not addressed, and can generate long-term effects, a time horizon that captures their consequences should be evaluated [97]. If the researcher would like to address this time horizon, from a trial standpoint, it would mean conducting a study that lasts over patients' lifetimes. Obviously, this is not practically feasible. Decision-analytic models that use inputs from trials and literature should be used to extrapolate outcomes over time [40]. Fourthly, CVD impacts health systems in terms of resources used to prevent, treat and rehabilitate patients to restore functional status. If this is not achieved, long-term effects might hinder patients' independence and ability to be productive to the economy. Direct and indirect costs associated with health and non-health resources, borne by society and individual sectors, should be evaluated. This can be done using a societal perspective that

captures relevant direct costs to health care systems (e.g. pharmacists and other professionals' time, medications, hospitalizations, etc.) and indirect costs borne by patients (e.g. transportation, carers, out of pocket expenses, etc.) or productivity losses if patients cannot return to the work force [40]. Two studies found in the review stated that had used this perspective [66,70]. However, only out-of-pocket medication expenses were included. This is an issue, as medication costs might be borne by different sectors across jurisdictions. For example, in the Chilean setting, primary health care provides free medicines to those covered under the public system. Finally, uncertainty around the ICER should always be assessed. Point estimates give relevant information, but assessment would be incomplete if an evaluation of the precision of this estimation is not performed. Furthermore, even if confidence or credible intervals are actually described, more information should be presented. Graphical representations such as the cost-effectiveness plane and acceptability curve are recommended to present uncertainty around these values [44,98]. A positive ICER might represent a cost-effective intervention or could represent a cheaper intervention with fewer effects than the comparator. Only two of the 11 evaluations found in the literature review performed this assessment [55,65].

Chapter 2 presented evidence that MRF is clinically effective controlling HTN, DLP and T2DM, providing a justification for the study. Chapter 3, presented results from the systematic review concluding that ten out of 11 studies had positive cost-effectiveness outcomes. However, the transferability to Chile of the data was questionable. Assessing the quality of these economic evaluations resulted in recommendations that were used as inputs to develop the protocol of the Polaris trial, particularly the cost-utility analysis (Chapter 4). For this trial, the MRF methodology was adapted to the Chilean primary care setting. The methodology, although based on other published methods, included additional components [78,80–82]. The Polaris MRF method requires face-to-face inter-

professional collaboration, along with a structured evaluation to develop care plans tailored to patients' needs. This was possible as there was access to the patients' official clinical record. Clinical evaluation was standardised by specific flowcharts to assess patients' pharmacotherapy. In the initial phases, the plan prioritised education and adherence interventions. After this phase, if therapeutic goals were still not achieved, suggestions were made to GPs regarding pharmacotherapy. To ensure fidelity and implementation the intervention also included training sessions for pharmacists and the participation of a PCF. There is evidence that a PCF can positively aid in MRF implementation [99].

A trial-based cost-utility analysis was developed using the findings of the systematic review. Results from this analysis classified the intervention as cost-effective in the base-case analysis. A higher proportion of dominant iterations in subgroups that evaluated drug-related hospitalisations and patients that had nine or more prescribed medications was found in the second-order sensitivity analysis. Two other trial-based cost-utility analyses were found in the systematic review, which allowed comparisons to our trial. Adibe et al. in a RCT design conducted in Nigeria followed-up patients for 12 months [65]. Patients with T2DM and prescribed hypoglycaemics were included. Resources evaluated were the intervention, laboratory test, medications, hospital care, and primary care. HRQoL was measured with the Health Utility Index questionnaire. Incremental QALYs of 0.12 were found, while increasing costs by $68.5. An ICER of $571 per QALY was estimated and was cost-effective in 52% of iterations of the sensitivity analysis. Another trial was carried out in Brazil with a time horizon of three years. Older adults with HTN and T2DM were included. Resources evaluated were medications and visits to the GP, specialists, RN, pharmacists and emergency department. As a result, costs increased by $69.6 while 1.3 QALYs were gained with an ICER of $53.5 per QALY. The trial-based

evaluation of the Polaris trial found increased benefits gaining 0.063 QALYs at a higher cost of $27.37. This yielded an ICER of $434.4 per QALY. This was achieved with 98.8% of the iterations in the north eastern quadrant of the cost-effectiveness plane and all iterations were under the local cost-effectiveness threshold. The rest of the iterations were considered dominant. A similar trend was observed in previous studies in terms of the point estimates but our results showed less uncertainty. It is important to note that none of the previous trials had a cluster design, which might bias the results as GPs can implement recommendations suggested by pharmacists in other patients [65,69]. This is avoided in an cRCT as the usual care group centres did not have pharmacists involved in clinical practice.

This trial-based economic evaluation was performed to take advantage of the internal validity due to the random allocation of clusters in an RCT design [48]. It is expected that using this design, that the observed and unobserved characteristics are comparable between groups. In terms of generalisability, usual care alone was used as a comparator to make the evaluation applicable and feasible to the local context. Although the research design had an established protocol and a methodology for MRF, pharmacists could determine the prioritisation of interventions according to patients' clinical situation. Ultimately, to fully inform a decision from the cost-effectiveness perspective in CVD, time horizons longer than a year should be tried, ideally through a lifetime. This is required to capture all outcomes and costs derived from events such as strokes or myocardial infarctions, but also their clinical sequels may negatively affect HRQoL.

To overcome the study period limitation and to estimate effects over a lifetime time horizon, a state-transition microsimulation model was developed to extrapolate trial results [49]. This modelling technique was chosen to account for the heterogeneity of the study's population which included patients with and without previous stroke or

myocardial infarction history, a situation that changes CVD risk [100]. Heterogeneity was also an issue as our sample patients had multiple risk factors as HTN, DLP and T2DM. The latter has complications on its own with an increased risk of sight problems, neuropathy and infection, that might lead to foot ulcers, debridement and in severe cases, amputation of lower extremities [6]. The model used patient-level data to calculate CVD risk accounting for events history and age to produce precise estimates [101,102]. Inputs from the literature to inform utility values and local sources for costs were used [103,104]. Importantly, the developed model and methods were externally validated by the Chilean Ministry of Health, which in the future might have professional and practical applicability for pharmacists in the primary health care policy in Chile.

Results from the model confirmed the conclusions from the trial-based evaluation with an ICER of $751 per QALY. Conclusions did not change when different time horizons were evaluated or one-way and probabilistic sensitivity analyses were performed. Results were mainly driven by decrease in CVD events and mortality. In the base-case analysis where a lifetime time horizon was considered, 15.6% of patients in the MRF group would have died due to a myocardial infarction or a stroke, compared to 21.5% in the control group. Local published Chilean health statistics reported in 2016 that mortality in older adults due to these diseases was 17.6%, providing face validity in the model [17]. Other decision models have been published that report on a cost-effectiveness analysis of MRF against usual care. An evaluation in the Netherlands included a patient population similar to the Polaris trial but focused their intervention in lipid-lowering therapy [105]. Costs of the intervention, medication, medical and management were included. Through a Markov model, it was found that the intervention was dominant against usual care in the overall population and secondary prevention population. For primary prevention, it was considered cost-effective with an ICER of €4,585 per QALY. Another study developed a

Markov model with Canadian data from patients with uncontrolled HTN. This model used international estimates for the effect of MRF and included end-stage renal disease as one of the health states [106]. The impact of MRF was estimated for HTN control with data from a meta-analysis of pharmacist services in HTN with 34 out of 39 studies using MRF. MRF was found to be cost-effective in 100% of the iterations using a 40,000 Canadian dollar (CAD) cost-effectiveness threshold. Compared to the Polaris trial evaluation, an ICER of $751 per QALY was found driven by gains in 1.12 QALYs at an additional cost of $841. The present study included patients of primary and secondary prevention and did not assess risk factors control before recruitment. Patients with a history of CVD have higher risk of recurrence, as when clinical objectives of risk factors are not reached [102]. Another study also used a Markov model with inputs from two trials conducted in the United States [107]. Primary and secondary prevention patients were included and the focus of MRF intervention was HTN control. Subgroups with different CVD risk that varied in terms of percentage of T2DM patients, smokers, cholesterol profile, and body mass index were evaluated. Base-case analysis yielded an ICER of $26,807 per QALY. Probabilistic sensitivity analysis deemed the intervention cost-effective in 48.6% of the times. The group with the highest risk got the best value for money with an ICER of $11,493. In the Polaris trial's model, low uncertainty was observed compared to this results, showing all iterations of the probabilistic sensitivity analysis to be in the north eastern quadrant and below the cost-effectiveness threshold. In our model, it was assumed that the intervention would continue over patients' lifetime time horizon, causing augmented costs and effects. This was assumed to emulate the Chilean CVD prevention program that has periodical consultations over patients' lifetime. Kulchaitanaroaj et al. study assumed that the intervention was stopped at six

months and the effects continued for two years [107]. This might directly influence the cost-effectiveness explaining the difference with our results.

It is interesting to note that both economic analysis reached similar conclusions. The cost-utility analysis alongside the trial showed that the intervention was cost-effective against usual care and 1.2% of the iterations as dominant, while in the model's base-case analysis all the iterations were cost-effective. Over a lifetime time horizon, one would expect that these conclusions might change, however they did not. Logically, if positive outcomes were observed over a year, it would be anticipated that this effect would accumulate over time, for example in decreasing resource use such as hospitalisations or emergency department visits. These savings would make MRF to dominate usual care alone in longer time horizons. The lack of this finding might be explained by taking into account that the trial evaluation captures effects of the intervention that go beyond reaching therapeutic objectives of HTN, T2DM and DLP to reduce CVD risk. For example, the model did not include other health problems such as adverse drug events or comorbidities. These two issues are relevant, taking into account that the sample population of our trial was comprised by older adults with five or more medications, and that the most common recommendation (32.7%) was to stop a medication that was unnecessary or harmful. Both characteristics, ageing and polypharmacy, have shown to increase susceptibility to adverse drug events [108,109]. A study that addressed this issue in economic terms described the impact of adverse drug events in older adults as a "substantial" major driver of hospital costs [110]. In terms of impact in comorbidities, professional pharmacy services in older adults have achieved cost-effectiveness or dominance in other diseases such as depression or respiratory conditions [111]. Therefore, it is clear that there is a need to capture adverse drug events and comorbidities not related to CVD in the modelling, although, that would make the model cumbersome. Model complexity and data requirement would increase

exponentially particularly for microsimulations where probabilities are estimated according patient-level data [112].

7.2 Limitations

The systematic review only included cost-effectiveness analysis based exclusively on RCTs. Modelling studies that used effectiveness data from other sources were excluded. These studies might have provided valuable information even if internal validity could be an issue due to mechanisms of selection [49].

In our clinical trial, randomisation was performed at the cluster level but not at patient-level. The differences observed at baseline in the number of comorbidities and relationship status might affect outcomes. Patients with multimorbidity are associated with a higher risk of death, disability, deteriorated functional status, HRQoL and adverse drug events [113]. Partners can aid adherence, as shown by a study that deemed marital status as one of the factors associated with non-adherence in hypertensive patients [114]. Nonetheless, these differences between intervention and control patients were controlled in the regression model and did not have any impact on the results. Cluster attrition was an issue, as half of the recruited centres withdrew from the study, mostly before patient recruitment. It appears that pharmacists have to be supported by strategic decisions and processes to make time for clinical activities. Currently, non-clinical activities dominate their time and role. If they are to undertake clinical duties they should be supported with policies that deal with quality assurance, research, human resources development, medicine information, and medication selection policies [35]. In addition, they should have support in processes such as supply, financial aids, and management. If these issues are not dealt with, services related to direct patient care will be affected [35]. Another limitation was that we could only get partial access to emergency department visits, specialists' visits and hospitalisations data due to internal issues outside the research team control.

Finally, other than the pharmacists, other professionals did not receive training. Collaboration with other health team members such as GPs is required for a successful implementation of MRF. However, 92.1% of medication-related recommendations were accepted by GPs, providing evidence that pharmacists had developed interprofessional collaborations.

When decision-analytic models are developed, several assumptions need to be made. International data and estimates from the literature were used when local data and estimates were not available [101,102]. For example, Framingham equations to estimate CHD 10-year probability adapted to the Chilean population were reported [21]. This adaptation was compared to other countries where it was found that the Chilean population had lower CHD risk [21]. This was not an issue in our model as CVD mortality rates were similar to reported local values. Another caveat of using the Framingham equation adapted to Chilean population was that they only estimate CHD, excluding diseases like stroke or HF. Not evaluating these diseases might lead to a model that under represent the clinical context of CVD patients. Additionally, as the model is a simplification of reality, it was not possible to include every disease and the impact of MRF on them. As an example, CKD can be a consequence of uncontrolled HTN or T2DM and in advanced stages impacts costs and HRQoL [106]. This was not incorporated in the model due to under reporting of CKD recognized by the Ministry of Health. Some costs and QALYs had to be extracted from literature. Utility values from an international catalogue were used to populate the model as no local data was available [103]. The uncertainty around international utility scores was tested in a sensitivity analysis and did not change the conclusion. For unit prices, local government estimates were used [115]. These prices are known to undervalue resources that in turn underfinance the public health system. This was shown in a study where only 56% of real costs were covered by reimbursement in hospitals using

these estimations[116]. Using these unit prices was considered a conservative assumption as increasing the value of health states would minimise the impact of costs caused by MRF.

A limitation that was common for both our economic analyses was the perspective used. Although the public health sector perspective is recommended by local guidelines, societal view might be preferred. This perspective considers all costs and benefits that can accrue a society. However, narrower perspectives can be used such as third-party payer, health centre and patient [40]. Resources that are usually not included in the health sector perspective, but are in the societal are out-of-pocket expenses, carers and loss of productivity. Nevertheless, if the societal perspective were to be used in Chile for evaluating patients cared under the public system, no health-related out-of-pocket expenses would accrue, as primary care centres provide free health services such as consultations and medicines. In terms of informal care, as our evaluation is based in a trial that required patients to be independent, evaluation of this resource was not be necessary. Finally, including productivity loss in economic evaluations has been under debate as the estimations have proven to be troublesome [117]. Usually, productivity loss is estimated through different methods using paid work as the main input. In the case of older adults, as they are usually are retired, their activities do not necessarily have an economic output. Therefore, inclusion in economic analysis is controversial as it overlooks contribution to society performed in non-paid work (e.g. of informal care, volunteer work or household work) [118].

7.3 Transferability

For economic evaluations to be used as inputs of decision making across different settings or countries, there are different aspects of transferability that need to be assessed [119]. There are a number of key factors that may affect the transferability of our results.

Usual care was comprised of a multi-professional team composed of GPs, RNs, dietitians, and a coordinator that provide care over a geographically defined population enrolled in a CVD prevention program and pharmacist or pharmacy technicians outside this team, essentially supplying medications [29]. Usual care in other studies and countries varies considerably and sometimes is not fully or not described in the literature [72].

The Polaris trial was focused on HTN, T2DM and DLP in primary care. Usually, patients that are affected by these risk factors are older adults and our sample reflected this demographic. Nonetheless, middle-aged adults are also subject to CVD and risk factors. If results from the Polaris trial were to be used in this middle-aged adult population, they should account for lower CVD risk and higher potential increased benefits as their life span is longer than older adults. This would be also potentially prolong their productive life.

Pharmacists in the intervention group were trained in various topics that included CVD prevention pharmacotherapy, inter-professional collaboration and Polaris MRF methods. In Chile, pharmacists are qualified to practice if they study a Bachelor in pharmacy. This degree is usually centred around pharmaceutical sciences, leaving professional pharmacy services as a secondary role. Curricula have shifted in many countries toward patient-centred curriculum and therefore, training might not be necessary for every setting [120].

Usual pharmacy practice in Chile does not include clinical work, so aspects such as pathology tests orders or changes in pharmacotherapy have to be overseen by other

professionals, usually GPs. This adds costs that could be avoided. Independent pathology tests orders for example, is a practice used internationally although it is not standardised [121]. Two municipalities participating in the Polaris trial gave pharmacists the responsibility of ordering pathology tests when the patient record did not provide current time sensitive results. This was done using protocols of current clinical guidelines [30].

In our study, we found a high acceptance rate of pharmacist recommendations by doctors. A 92.9% of the recommendations made by pharmacists were accepted. As face-to-face meetings require time from both professionals, costs could be prevented if collaborative agreements or independent prescribing was implemented. A study in Canada evaluated the effect of independent prescribing on HTN in primary care. The economic evaluation found that the intervention was dominant, gaining QALYs while saving 4770 CAD per patient [122].

We used PCFs as part of the intervention adding costs but we ensured a high fidelity and implementation rate [99]. We believe these added costs would be offset by better outcomes.

7.4 Future directions

This thesis outlines the economic aspects of an impact study of the Polaris MRF method in the primary care Chilean setting. As positive results were seen, improving benefits at higher costs but below the cost-effectiveness threshold, this service should be considered for national implementation. This analysis suggests that patients would benefit if a pharmacist was added to perform MRF into the existing usual care in primary health care centres. Furthermore, taking into account that the pharmacy fund scheme includes pharmacists as a critical component, and has been implemented for the last six years, these results introduce an argument to expand this scheme to implement pharmacist-led MRF.

To ensure that this research can be translated to usual practice, an implementation program at a national level should be considered to evaluate the real-life impact of this intervention in a heterogeneous primary care system that cares for urban and rural settings, indigenous populations, and those with various social determinants of health [29]. Implementation frameworks adapted to the community pharmacy services have been described which could be applied to Chile [123]. The Polaris trial fits in the development or discovery phase described by the Framework for the Implementation of Services in Pharmacy [123]. It would be expected that each regional Health Service Administration explore if this intervention is aligned with their policy objectives. If they deem the service as suitable, a preparation phase should follow training pharmacists for service provision. Once the testing phase is over, the full implementation should follow deploying monitoring, adaptation and improvement strategies. An economic evaluation should be performed along a pragmatic study to capture real-life outcomes [40]. The final goal would be the routinisation of the service in practice to achieve cardiovascular event prevention in the long-term [124]. Two MRF guidelines based on the Polaris methods have been published with the Ministry of Health [125,126]. These are intended to lay the clinical foundations of the service moving forward as value for money has been proved in two different analyses presented in this thesis.

It is important to note that this research was performed in a heterogeneous sample that included patients of primary and secondary prevention with different risk factors. Studies in patients with higher risk have shown dominance in decision-analytic models. A study compared subgroups of secondary vs primary prevention finding dominance in the first, and cost-effectiveness in the second [105]. On the other hand, in the evaluation alongside the trial it was observed that patients with more than nine prescriptions have more

iterations that are dominant. Further research should be performed in higher risk patients or those with more than nine medications.

As discussed in the transferability section, there are elements of this intervention that limits their potential. To seek approval by pharmacist for every clinical recommendation or pathology test from GPs adds extra costs. Resource use of pharmacists, GPs and patients' time might be optimised if such action can be avoided. Studies that evaluated independent prescribing or collaborative care models that give pharmacists this added responsibility under defined and agreed protocols have been shown to be cost-effective [107,122,127,128]. This was done through modelling and showed that MRF plus prescribing faculties or under collaborative agreements were dominant compared to usual care.

This work is the first cluster randomized controlled trial conducted in Latin America of a professional pharmacy service. Since 2010, the PAHO has recommended that pharmacists should move away from a "medication-centred" view to perform clinical services [49]. Several services across different health problems have been studied in other jurisdictions that might be transferred to the Chilean setting. These services should be studied evaluating clinical and economic outcomes. For example, a systematic review found three cost-utility analysis in smoking cessation, one in osteoarthritis, and one in sleep apnoea screening, and considered them all cost-effective. This might potentially be assessed and applied in the Chilean setting [66].

Patients included in this research are members of the public health care system. It is the patients' choice to decide if they want to attend to the private or public setting. It is recognised that there are socioeconomic and demographic factors such as, sex, age, level of education, socioeconomic status, that influence this decision (older adults, woman, and patients lower socioeconomic status)[67]. The public sector carries a bigger health burden for patients that cannot afford private insurance generating inequality. However economic

evaluations traditionally have the aim of maximising the whole population overall health, thus, not providing information to policymakers on their effects on equity. “Distributional cost-effectiveness analysis” aims to assess changes in equity along with cost-effectiveness, modelling, and evaluating the social distribution of health [68]. This type of analysis seems suitable for future projects.

Chapter 8

Conclusions

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This thesis evaluated the international state of the art of economic evaluations of pharmacist-led MRF acting on HTN, T2DM and DLP. Recommendations drawn from the systematic review of the literature, contributed to the development of a cRCT for field work. The trial, named Polaris, aimed to evaluate clinical and economic impact of pharmacist-led MRF in CVD risk factors. As a product of this trial, and focus of this thesis, two economic evaluations were performed. The first analysis, a trial-based evaluation, yielded the intervention as cost-effective with low uncertainty. The second evaluation was performed through a decision-analytic model and confirmed the results over a lifetime time horizon.

8.1 Systematic Review

The systematic review found that there is international evidence that pharmacist-led MRF is cost-effective in outpatients with HTN, DLP and T2DM. Two of the evaluations deemed MRF as dominant, eight as cost-effective, and one had higher costs with no benefits. All these studies were trial-based economic evaluations and did not evaluate long-term outcomes. Transferability issues arose from these evaluations. It was recommended to perform a cost-utility analysis from the societal perspective, to identify all relevant resources, to perform uncertainty analysis and to extrapolate results to long-term outcomes using modelling techniques.

8.2 The Polaris Trial

There was evidence that MRF was clinically effective and value for money in HTN, T2DM and DLP. A cRCT that studied MRF in the local primary care setting was instituted. A method of MRF was adapted to the local setting and had three main components: pharmacists' training, a Polaris adapted MRF and the PCF.

8.3 Trial-based Economic Evaluation

A cost-utility analysis alongside the trial was performed. It deemed the addition of MRF to usual care as cost-effective gaining QALYs at higher costs from the public third-party payer perspective. Low uncertainty was observed in the cost-effectiveness plane and acceptability curve. When patients that had hospitalisation data available and more than nine medications prescribed were evaluated, a cost saving trend was observed increasing the number of dominant iterations in the uncertainty analysis.

8.4 Decision-analytic Model

A decision-analytic model was developed with a state-transition microsimulation approach to account for populations' heterogeneity and extrapolate outcomes to lifetime time horizon. This is the first published model that uses this analytic approach in the professional pharmacy services field on CVD. Extrapolated results over a lifetime time horizon deemed the intervention as cost-effective driven mainly by a 5.9% difference in mortality due to myocardial infarction and stroke. This conclusion was not changed in sensitivity analyses.

MRF was deemed as cost-effective through different analyses, with more benefits, and at costs below the cost-effectiveness threshold. Policy-makers should evaluate the implementation of MRF in CVD prevention at a national level using these results as inputs to hold an accountable decisions. If this approach is followed, it should be done through an implementation framework, using PCFs as a resource to aid in the program adoption with the final objective of reaching sustainability. Pragmatic clinical and economic studies should be carried out to evaluate clinical and economic outcomes.

References

1. Roth GA, Abate D, Abate KH, et al. Global, regional, and national age-sex-specific mortality for 282 causes of death in 195 countries and territories, 1980–2017: a systematic analysis for the Global Burden of Disease Study 2017. *Lancet*. 2018;392(10159):1736-1788. doi:10.1016/S0140-6736(18)32203-7

2. Mendis S, Puska P, Norving B. Global Atlas on Cardiovascular disease prevention and control. *World Heal Organ*. 2011.

3. Network GB of DC. Global Burden of Disease Study 2017 (GBD 2017) Results. http://ghdx.healthdata.org/gbd-results-tool. Accessed January 26, 2020.

4. Kyu HH, Abate D, Abate KH, et al. Global, regional, and national disability-adjusted life-years (DALYs) for 359 diseases and injuries and healthy life expectancy (HALE) for 195 countries and territories, 1990-2017: A systematic analysis for the Global Burden of Disease Study 2017. *Lancet*. 2018;392(10159):1859-1922. doi:10.1016/S0140-6736(18)32335-3

5. NICE. Hypertension in adults : diagnosis and management. *Natl Inst Heal Care Excell*. 2019;(August 2019).

6. NICE. Managing blood glucose in patients with type 2 diabetes. *Natl Inst Heal Care Excell*. 2019;(July):1-29.

7. NICE. Lipid modification ther therap apy y for pre prev venting cardio cardiovascular vascular disease. *Natl Inst Heal Care Excell*. 2017:1-20. doi:10.1177/1933719117732165

8. Benjamin EJ, Muntner P, Alonso A, et al. *Heart Disease and Stroke Statistics-2019 Update: A Report From the American Heart Association*. Vol 139.; 2019. doi:10.1161/CIR.0000000000000659

9. World Health Organization (WHO). Global Health Observatory data repository. http://apps.who.int/gho/data/node.main.A867?lang=en. Accessed January 28, 2020.

10. Wilkins E, Wilson L, Wickramasinghe K, et al. European Cardiovascular Disease Statistics 2017. *Eur Hear Network, Brussels*. 2017.

11. Adolfo R, Vilma I, Matias C, Natalia E. Multiple Cardiometabolic Risk Factors in the Southern Cone of Latin America: A Population-based Study in Argentina, Chile, and Uruguay. *Int J Cardiol*. 2015;183:82-88.

12. Rubinstein AL, Irazola VE, Calandrelli M, et al. Prevalence, awareness, treatment, and control of hypertension in the southern cone of Latin America. *Am J Hypertens*. 2016;29(12):1343-1352. doi:10.1093/ajh/hpw092

13. Irazola V, Rubinstein A, Bazzano L, et al. Prevalence, awareness, treatment and control of diabetes and impaired fasting glucose in the Southern Cone of Latin America. *PLoS One*. 2017;12(9):1-13. doi:10.1371/journal.pone.0183953

14. Bloom DE, Cafiero ET, Jané-Llopis E, et al. *The Global Economic Burden of Non-Communicable Diseases*.; 2011.

15. Organization WH. Cardiovascular diseases fact sheet. https://www.who.int/news-room/fact-sheets/detail/cardiovascular-diseases-(cvds). Published 2017. Accessed January 3, 2020.

16. Khavjou O, Phelps D, Leib A. Projections of Cardiovascular Disease Prevalence and Costs: 2015-2035. *RTI Int*. 2016;(0214680):1-54.

17. Chile M de S de. Mortality Causes. http://www.deis.cl/wp-content/2017/gobCL-sitios-1.0/assets/SerieDefunciones_2000_2015.html. Accessed January 4, 2020.

18. Chile ministry of health. *Chilean National Health Survey 2016-2017 V1*.; 2017. http://web.minsal.cl/wp-content/uploads/2017/11/ENS-2016-17_PRIMEROS-RESULTADOS.pdf.

19. Chile ministry of health. *Chilean National Health Survey 2016-2017 V2*.; 2018. https://www.minsal.cl/wp-content/uploads/2018/01/2-Resultados-ENS_MINSAL_31_01_2018.pdf.

20. Valdivia G. *Chilean National Health Survey 2009-2010*.; 2010.

21. Icaza G, Núñez L, Marrugat J, et al. Estimation of coronary heart disease risk in Chilean subjects based on adapted Framingham equations. *Rev Med Chil*. 2009;137(10):1273-1282. doi:10.4067/s0034-98872009001000001

22. Bossert TJ, Leisewitz T. Innovation and Change in the Chilean Health System. *N Engl J Med*. 2016;374(1):1-5. doi:10.1056/nejmp1514202

23. Chilean Health Superintendency. *Private Insured Patients Report 1990-2017*.; 2018. http://www.supersalud.gob.cl/documentacion/666/w3-propertyvalue-3724.html. Accessed January 29, 2020.

24. FONASA. Statistics Bulletin. 2017. https://www.fonasa.cl/sites/fonasa/documentos. Accessed January 29, 2020.

25. Benavides P, Jones I. *Sistema de Pensiones y Otros Beneficios Pecuniarios de Las Fuerzas Armadas y de Orden y Seguridad Pública y Gendarmería de Chile: Situación Actual y Proyecciones Fiscales 2012-2050*.; 2012.

26. Castillo-Laborde C, Aguilera-Sanhueza X, Hirmas-Adauy M, et al. Health insurance scheme performance and effects on health and health inequalities in Chile. *MEDICC Rev*. 2017;19(2-3):57-64. doi:10.1590/medicc.2017.1902030011

27. Cid C, Uthoff A. La reforma a la salud pendiente en Chile: reflexiones en torno a una propuesta de transformación del sistema. *Rev Panam Salud Pública*. 2017;41:1. doi:10.26633/rpsp.2017.170

28. PAHO/WHO. *Renewing Primary Health Care in the Americas*. Washington DC; 2007.

29. Chile ministry of health. *Implementation Guidelines of the Family Medicine Model*.; 2012. http://web.minsal.cl/portal/url/item/e7b24eef3e5cb5d1e0400101650128e9.pdf.

30. Chile ministry of health. Cardiovascular Health Program Guidelines 2017. 2017:1-85. http://www.redcronicas.cl/wrdprss_minsal/wp-content/uploads/2017/08/OT-PROGRAMA-DE-SALUD-CARDIOVASCULAR_03.pdf.

31. OECD. OECD Reviews of Public Health: Chile. *OECD Rev Public Heal Chile*. 2019. doi:10.1787/9789264309593-en

32. Seron P, Irazola V, Rubinstein A, et al. Ideal Cardiovascular Health in the southern cone of Latin America. *Public Health*. 2018;156(56):132-139.

doi:10.1016/j.puhe.2017.12.017

33. Chile ministry of health. *Guidelines for the Pharmacy Fund for Non-Communicable Diseases in Primary Care*.; 2019.

34. FERRER-LUES M, MARÍA LUISA D, IVAN V. *RESUMEN EJECUTIVO EVALUACIÓN PROGRAMAS GUBERNAMENTALES: PROGRAMA FONDO DE FARMACIA PARA ENFERMEDADES CRÓNICAS NO TRANSMISIBLES EN ATENCIÓN PRIMARIA DE SALUD*.; 2018. https://www.dipres.gob.cl/597/articles-177366_r_ejecutivo_institucional.pdf.

35. PAHO/WHO. *Primary Care Based Pharmacy Services. Position Paper of the PAHO/WHO*. Washington DC; 2013.

36. Griese-Mammen N, Hersberger KE, Messerli M, et al. PCNE definition of medication review: reaching agreement. *Int J Clin Pharm*. 2018;40(5):1199-1208. doi:10.1007/s11096-018-0696-7

37. Pharmaceutical Care Network Europe Foundation. PCNE statement on medication review 2013. https://www.pcne.org/upload/files/150_20160504_PCNE_MedRevtypes.pdf. Published 2013.

38. Jokanovic N, Hons BP, Tan ECK, et al. Pharmacist-led medication review in community settings : An overview of systematic reviews. *Res Soc Adm Pharm*. 2016. doi:10.1016/j.sapharm.2016.08.005

39. Martínez-Mardones F, Fernandez-Llimos F, Benrimoj SI, et al. Systematic Review and Meta-Analysis of Medication Reviews Conducted by Pharmacists on

Cardiovascular Diseases Risk Factors in Ambulatory Care. *J Am Heart Assoc*. 2019;8(22):e013627. doi:10.1161/JAHA.119.013627

40. Drummond M, Sculpher M, Claxton K, Stoddart G, Torrance G. *Methods for the Economic Evaluation of Health Care Programmes.* 4th ed. Oxford University Press; 2015.

41. Manca A, Hawkins N, Sculpher MJ. Estimating mean QALYs in trial-based cost-effectiveness analysis: The importance of controlling for baseline utility. *Health Econ*. 2005;14(5):487-496. doi:10.1002/hec.944

42. Rabin R, Gudex C, Selai C, Herdman M. From translation to version management: A history and review of methods for the cultural adaptation of the euroqol five-dimensional questionnaire. *Value Heal*. 2014;17(1):70-76. doi:10.1016/j.jval.2013.10.006

43. Zarate V, Kind P, Valenzuela P, Vignau A, Olivares-Tirado P, Munoz A. Social valuation of EQ-5D health states: The chilean case. *Value Heal*. 2011;14(8):1135-1141. doi:10.1016/j.jval.2011.09.002

44. Black WC, Magnuson WG. The CE Plane: A Graphic Representation of Cost-Effectiveness from the Diagnostic Radiology Depart-ment. *Med Decis Mak*. 1990;10(c):212-214. http://journals.sagepub.com/doi/pdf/10.1177/0272989X9001000308.

45. L. V-T, B. G-L, I. C, et al. On the Estimation of the Cost-Effectiveness Threshold: Why, What, How? *Value Heal*. 2016;19(5):558-566. doi:10.1016/j.jval.2016.02.020

46. Petrou S, Gray A. Economic evaluation alongside randomised controlled trials: Design, conduct, analysis, and reporting. *Bmj*. 2011;342(7806):1-6. doi:10.1136/bmj.d1548

47. Roberts M, Russell LB, Paltiel AD, Chambers M, McEwan P, Krahn M. Conceptualizing a model: A report of the ISPOR-SMDM modeling good research practices task force-2. *Med Decis Mak*. 2012;32(5):678-689. doi:10.1177/0272989X12454941

48. Glick H, Doshi JA, Sonnad SS, Polsky D. *Economic Evaluation in Clinical Trials*. Second. Oxford University Press; 2015.

49. Sculpher MJ, Claxton K, Drummond M, McCabe C. Whither trial-based economic evaluation for health care decision making? *Health Econ*. 2006;15(7):677-687. doi:10.1002/hec.1093

50. Caro JJ, Briggs AH, Siebert U, Kuntz KM. Modeling good research practices - Overview: A report of the ISPOR-SMDM modeling good research practices task force-1. *Value Heal*. 2012;15(6):796-803. doi:10.1016/j.jval.2012.06.012

51. Altowaijri A, Phillips CJ, Fitzsimmons D. A systematic review of the clinical and economic effectiveness of clinical pharmacist intervention in secondary prevention of cardiovascular disease. *J Manag Care Pharm*. 2013;19(5):408-416. doi:https://doi.org/10.18553/jmcp.2013.19.5.408

52. Wang Y, Yeo QQ, Ko Y. Economic evaluations of pharmacist-managed services in people with diabetes mellitus: A systematic review. *Diabet Med*. 2016;33(4):421-427. doi:10.1111/dme.12976

53. Jacob V, Chattopadhyay SK, Thota AB, et al. Economics of Team-based Care in Controlling Blood Pressure: A Community Guide Systematic Review. *Am J Prev Med*. 2015;49(5):772-783. doi:10.1016/j.amepre.2015.04.003

54. Higgins J, Green S. Cochrane handbook for systematic reviews of interventions version 5.1. 0 [updated March 2011]. *Cochrane Collab*. 2011. www.cochrane-handbook.org.

55. Simpson SH, Lier DA, Majumdar SR. Cost-effectiveness analysis of adding pharmacists to primary care teams to reduce cardiovascular risk in patients with Type 2 diabetes: Results from a randomized controlled trial. *Diabet Med*. 2015;32(7):899-906.

56. Simpson SH, Majumdar SR, T.Tsuyuki R, Lewanczuk RZ, Spooner R, A.Johnson J. Effect of Adding Pharmacists to Primary Care Teams on Blood Pressure Control in Patients With Type 2 Diabetes A randomized controlled trial. *Diabetes Care*. 2011;34(1):20-26. doi:10.2337/dc10-1294.

57. Fishman PA, Cook AJ, Anderson ML, et al. Improving BP Control Through Electronic Communications: An Economic Evaluation. *Am J Manag Care*. 2013;19(9):709-716.

58. Green BB, Cook A, Ralston J, et al. Effectiveness of Home Blood Pressure Monitoring, Web Communication, and Pharmacist Care on Hypertension Control. *J Am Med Assoc*. 2008;299(24):2857-2867. doi:10.1001/jama.299.24.2857

59. Shireman TI, Svarstad BL. Cost-effectiveness of Wisconsin TEAM model for improving adherence and hypertension control in black patients. *J Am Pharm*

Assoc. 2016;56(4):389–396. doi:10.1016/j.japh.2016.03.002

60. Svarstad BL, Kotchen JM, Shireman TI, et al. The Team Education and Adherence Monitoring (TEAM) Trial: Pharmacy Interventions to Improve Hypertension Control in Blacks. *Circ Cardiovasc Qual Outcomes*. 2009;2(3):264-271. doi:10.1161/CIRCOUTCOMES.109.849992

61. The Community Pharmacy Medicines Management Project Evaluation Team. The MEDMAN study: A randomized controlled trial of community pharmacy-led medicines management for patients with coronary heart disease. *Fam Pract*. 2007;24(2):189-200. doi:10.1093/fampra/cml075

62. Chen J-H, Huang-Tz O, Tzu-Chieh L, Chia-Cheng Lai E, Yang Kao Y-H. Pharmaceutical care of elderly patients with poorly controlled type 2 diabetes mellitus: a randomized controlled trial. *Int J Clin Pharm*. 2016;38(1):88-95. doi:10.1007/s11096-015-0210-4

63. Polgreen LA, Han J, Carter BL, et al. Cost-Effectiveness of a Physician-Pharmacist Collaboration Intervention to Improve Blood Pressure Control. *Hypertension*. 2015;66(6):1145-1151. doi:10.1161/HYPERTENSIONAHA.115.06023

64. Carter BL, Coffey CS, Ardery G, et al. Cluster-randomized trial of a physician/pharmacist collaborative model to improve blood pressure control. *Circ Cardiovasc Qual Outcomes*. 2015;8(3):235-243. doi:10.1161/CIRCOUTCOMES.114.001283

65. Adibe MO, Aguwa CN, Ukwe C V. Cost-utility analysis of pharmaceutical care intervention versus usual care in management of nigerian patients with type 2

diabetes. *Value Heal Reg Issues*. 2013;2(2):189-198. doi:10.1016/j.vhri.2013.06.009

66. Okamoto MP, Nakahiro RK. Pharmacoeconomic Evaluation of a Pharmacist-Managed Hypertension Clinic. *Pharmacotherapy*. 2001;21(11):1337-1344. doi:10.1016/j.jval.2011.02.542

67. Borenstein JE, Graber G, Saltiel E, et al. Physician-pharmacist comanagement of hypertension: A randomized, comparative trial. *Pharmacotherapy*. 2003;23(2):209-216. doi:10.1592/phco.23.2.209.32096

68. Chan C-W, Siu S-C, Wong CKW, Lee VWY. A Pharmacist Care Program: Positive Impact on Cardiac Risk in Patients With Type 2 Diabetes. *J Cardiovasc Pharmacol Ther*. 2012;17(1):57-64. doi:10.1177/1074248410396216

69. Obreli-Neto PR, Marusic S, Guidoni CM, et al. Economic evaluation of a pharmaceutical care program for elderly diabetic and hypertensive patients in primary health care: A 36-month randomized controlled clinical trial. *J Manag Care Pharm*. 2015;21(1):66-75. doi:10.18553/jmcp.2015.21.1.66

70. Polgreen LA, Han J, Carter BL. Cost-Effectiveness of a Physician-Pharmacist Collaboration Intervention to Improve Blood Pressure Control. *Hypertension*. 2015;66(6):1145-1151.

71. Shireman TI, Svarstad BL. Cost-Effectiveness of Wisconsin TEAM Model for Improving Adherence and Hypertension Control in Black Patients. 2016;56(4):389–396. doi:10.1016/j.japh.2016.03.002

72. Ahumada-Canale A, Quirland C, Martinez-Mardones F, Plaza-Plaza JC,

Benrimoj S, Garcia-Cardenas V. Economic evaluations of pharmacist-led medication review in outpatients with hypertension, type 2 diabetes mellitus, and dyslipidaemia: a systematic review. *Eur J Heal Econ*. 2019;20(7):1103-1116. doi:10.1007/s10198-019-01080-z

73. Martinez-Mardones FJ, Plaza-Plaza JC. *Development and Implementation of a Medication Review with Follow-up Program for Older Adults with Polypharmacy in a Primary Care Centre*. Santiago; 2016.

74. Chile ministry of health. *Preventive Examination for Older Adults*.; 2010.

75. Hemming K, Girling AJ, Sitch AJ, Marsh J, Lilford RJ. Sample size calculations for cluster randomised controlled trials with a fixed number of clusters. *BMC Med Res Methodol*. 2011;102(11). doi:10.1186/s12874-017-0292-x

76. Blenkinsopp A, Bond C, Raynor DK. Medication reviews. *Br J Clin Pharmacol*. 2012;74(4):573-580. doi:10.1111/j.1365-2125.2012.04331.x

77. Martinez F, Farragher T, Dader M, et al. *Medida Del Impacto Clínico, Económico y Humanístico Del Servicio de Seguimiento Farmacoterapéutico En Mayores Polimedicados, En La Farmacia Comunitaria Española*.; 2014.

78. Grupo de Investigación en Atención Farmacéutica U de G. Pharmacotherapy follow-up: The Dader method (3rd revision: 2005). *Pharm Pract*. 2006;4(1):44-53. http://scielo.isciii.es/scielo.php?script=sci_arttext&pid=S1885-642X2006000100008.

79. Jódar-Sánchez F, Malet-Larrea A, Martín JJ, et al. Cost-Utility Analysis of a Medication Review with Follow-Up Service for Older Adults with Polypharmacy

in Community Pharmacies in Spain: The conSIGUE Program. *Pharmacoeconomics*. 2015;33(6):599-610. doi:10.1007/s40273-015-0270-2

80. Scottish Government. *Polypharmacy Guidance*. 3rd Editio.; 2018. http://dghstatistiques.ci/assets/documents/annuaire/Annuaire-DGH-2018-v3.pdf.

81. Cipolle R, Strand L, Morley P. *Pharmaceutical Care Practice. The Clinician's Guide*. (McGraw-Hill, ed.). NewYork; 2004.

82. Foundation A pharmacists A and the NA of chain DS. Medication therapy management in pharmacy practice: Core elements of an MTM service model (version 2.0). *J Am Pharm Assoc*. 2008;48(3):341-353. doi:10.1331/JAPhA.2008.08514

83. Hoffmann TC, Glasziou PP, Boutron I, et al. Better reporting of interventions: Template for intervention description and replication (TIDieR) checklist and guide. *BMJ*. 2014;348(March):1-12. doi:10.1136/bmj.g1687

84. Garcia-Cardenas V, Perez-Escamilla B, Fernandez-Llimos F, Benrimoj SI. The complexity of implementation factors in professional pharmacy services. *Res Soc Adm Pharm*. 2018;14(5):498-500. doi:10.1016/j.sapharm.2017.05.016

85. Matza LS, Stewart KD, Gandra SR, et al. Acute and chronic impact of cardiovascular events on health state utilities Utilization, expenditure, economics and financing systems. *BMC Health Serv Res*. 2015;15(1):1-11. doi:10.1186/s12913-015-0772-9

86. Brooks R, De Charro F. EuroQol: The current state of play. *Health Policy (New York)*. 1996;37(1):53-72. doi:10.1016/0168-8510(96)00822-6

87. Castillo Riquelme M, Castillo Laborde C, Loayza Saldivia S, Aravena Pastén M. *Methodological Guideline of Economic Evaluations of Health Technologies in Chile*.; 2013.

88. Chile congress library. Municipal Primary Health Care Law. https://www.leychile.cl/Navegar?idNorma=30745. Published 2016. Accessed November 14, 2019.

89. FONASA. Institucional Care Modality. https://www.fonasa.cl/sites/fonasa/mobile/prestadores/normativa/aranceles. Published 2019. Accessed February 1, 2020.

90. Chile ministry of health. CENABAST updated prices. https://www.cenabast.cl/precios-vigentes-en-contratos/. Published 2019. Accessed July 3, 2019.

91. Chile ministry of health. *Chilean Refined Diagnosis Related Groups Guideline*.; 2014.

92. Shemilt I, Thomas J, Morciano M. A web-based tool for adjusting costs to a specific target currency and price year. *Evid Policy*. 2010;6(1):51-59. doi:10.1332/174426410X482999

93. IMF IMF. World Economic Outlook Database. https://www.imf.org/external/pubs/ft/weo/2019/01/weodata/index.aspx. Published 2018. Accessed April 23, 2019.

94. Evers S, Goossens M, de Vet H, van Tulder M, Ament A. Criteria list for assessment of methodological quality of economic evaluations: Consensus on

Health Economic Criteria. *Int J Technol Assess Health Care*. 2005;21(2):240-245. doi:10.1017.S0266462305050324

95. Cochrane Effective Practice and Organisation of Care (EPOC). Suggested risk of bias criteria for EPOC reviews. EPOC Resources for review authors. 2017:1-4. http://epoc.cochrane.org/resources/epoc-resources-review-authors.

96. Chen J-H, Huang-Tz O, Tzu-Chieh L, Chia-Cheng Lai E, Yang Kao Y-H. Pharmaceutical care of elderly patients with poorly controlled type 2 diabetes mellitus: a randomized controlled trial. *Int J Clin Pharm*. 2016;38(1):88-95. doi:10.1007/s11096-015-0210-4

97. Piepoli MF, Hoes AW, Agewall S, et al. 2016 European Guidelines on cardiovascular disease prevention in clinical practice. *Eur Heart J*. 2016;37(29):2315-2381. doi:10.1093/eurheartj/ehw106

98. Fenwick E, O'Brien BJ, Briggs A. Cost-effectiveness acceptability curves - Facts, fallacies and frequently asked questions. *Health Econ*. 2004;13(5):405-415.

99. Garcia-Cardenas V, Benrimoj SI, Ocampo CC, Goyenechea E, Martinez-Martinez F, Gastelurrutia MA. Evaluation of the implementation process and outcomes of a professional pharmacy service in a community pharmacy setting. A case report. *Res Soc Adm Pharm*. 2017;13(3):614-627. doi:10.1016/j.sapharm.2016.05.048

100. Uwe, Siebert, Alagoz O, Bayoumi AM, et al. State-Transition Modeling: A Report of the ISPOR-SMDM Modeling Good Research Practices Task Force-3. *Value Heal*. 2012;15:812-820. doi:10.1016/j.jval.2012.06.014

101. D'Agostino RB, Vasan RS, Pencina MJ, et al. General cardiovascular risk profile for use in primary care: The Framingham heart study. *Circulation*. 2008;117(6):743-753.

102. Wilson PWF, D'Agostino R, Bhatt DL, et al. An international model to predict recurrent cardiovascular disease. *Am J Med*. 2012;125(7):695-703.e1. doi:10.1016/j.amjmed.2012.01.014

103. Van Wilder L, Rammant E, Clays E, Devleesschauwer B, Pauwels N, De Smedt D. A comprehensive catalogue of EQ-5D scores in chronic disease: results of a systematic review. *Qual Life Res*. 2019;28(12):3153-3161. doi:10.1007/s11136-019-02300-y

104. Ministerio de Salud C. *Prioritized Health Problems Cost Verification Study*.; 2019.

105. Vegter S, Oosterhof P, van Boven JFM, Stuurman Bieze AGG, Hiddink EG, Postma MJ. Improving adherence to lipid-lowering therapy in a community pharmacy intervention program: A cost-effectiveness analysis. *J Manag Care Pharm*. 2014;20(7).

106. Marra C, Johnston K, Santschi V, Tsuyuki RT. Cost-effectiveness of pharmacist care for managing hypertension in Canada. *Can Pharm J*. 2017;150(3):184-197. doi:10.1177/1715163517701109

107. Kulchaitanaroaj P, Brooks JM, Chaiyakunapruk N, Goedken AM, Chrischilles EA, Carter BL. Cost-utility analysis of physician-pharmacist collaborative intervention for treating hypertension compared with usual care. *J Hypertens*. 2017;35(1):178-187. doi:10.1097/HJH.0000000000001126

108. Fried TR, O'Leary J, Towle V, Goldstein MK, Trentalange M, Martin DK. Health outcomes associated with polypharmacy in community-dwelling older adults: A systematic review. *J Am Geriatr Soc*. 2014;62(12):2261-2272. doi:10.1111/jgs.13153

109. Davies EA, O'Mahony MS. Adverse drug reactions in special populations - The elderly. *Br J Clin Pharmacol*. 2015;80(4):796-807. doi:10.1111/bcp.12596

110. Chiatti C, Bustacchini S, Furneri G, et al. The economic burden of inappropriate drug prescribing, lack of adherence and compliance, adverse drug events in older people a systematic review. *Drug Saf*. 2012;35(SUPPL. 1):73-87. doi:10.1007/BF03319105

111. Malet-Larrea A, García-Cárdenas V, Sáez-Benito L, Benrimoj SI, Calvo B, Goyenechea E. Cost-effectiveness of professional pharmacy services in community pharmacy: a systematic review. *Expert Rev Pharmacoecon Outcomes Res*. 2016;16(6):747-758. doi:10.1080/14737167.2016.1259071

112. Siebert U, Alagoz O, Bayoumi AM, et al. State-transition modeling: A report of the ISPOR-SMDM modeling good research practices task force-3. *Value Heal*. 2012;15(6):812-820. doi:10.1016/j.jval.2012.06.014

113. Salive ME. Multimorbidity in older adults. *Epidemiol Rev*. 2013;35(1):75-83. doi:10.1093/epirev/mxs009

114. van der Laan DM, Elders PJM, Boons CCLM, Beckeringh JJ, Nijpels G, Hugtenburg JG. Factors associated with antihypertensive medication non-adherence: a systematic review. *J Hum Hypertens*. 2017;31(11):687-694. doi:10.1038/jhh.2017.48

115. Ministerio de Salud de Chile. *Supplemental Material: Demand Files, Prices and Technical Files*.; 2018.

116. Cid Pedraza C, Bastías S. G. Evaluation of financial status of public hospitals considering the updated costs of their services. *Rev Med Chil*. 2014;142(2):161-167.

117. Krol M, Brouwer W, Rutten F. Productivity costs in economic evaluations: Past, present, future. *Pharmacoeconomics*. 2013;31(7):537-549. doi:10.1007/s40273-013-0056-3

118. Huter K, Kocot E, Kissimova-Skarbek K, Dubas-Jakóbczyk K, Rothgang H. Economic evaluation of health promotion for older people-methodological problems and challenges. *BMC Health Serv Res*. 2016;16(Suppl 5). doi:10.1186/s12913-016-1519-y

119. Drummond M, Barbieri M, Cook J, et al. Transferability of economic evaluations across jurisdictions: ISPOR good research practices task force report. *Value Heal*. 2009;12(4):409-418. doi:10.1111/j.1524-4733.2008.00489.x

120. Supapaan T, Low BY, Wongpoowarak P, Moolasarn S, Anderson C. A transition from the BPharm to the PharmD degree in five selected countries. *Pharm Pract (Granada)*. 2019;17(3):1-9. doi:10.18549/PharmPract.2019.3.1611

121. Donovan J, Tsuyuki RT, Al Hamarneh YN, Bajorek B. Barriers to a full scope of pharmacy practice in primary care: A systematic review of pharmacists' access to laboratory testing. *Can Pharm J*. 2019;152(5):317-333. doi:10.1177/1715163519865759

122. Tam-Tham H, Clement F, Hemmelgarn BR, et al. A Cost Analysis and Cost-Utility Analysis of a Community Pharmacist–Led Intervention on Reducing Cardiovascular Risk: The Alberta Vascular Risk Reduction Community Pharmacy Project (RxEACH). *Value Heal*. 2019;22(10):1128-1136. doi:10.1016/j.jval.2019.05.012

123. Moullin JC, Sabater-Hernández D, Benrimoj SI. Qualitative study on the implementation of professional pharmacy services in Australian community pharmacies using framework analysis. *BMC Health Serv Res*. 2016;16(1):1-13. doi:10.1186/s12913-016-1689-7

124. Crespo-Gonzalez C, Garcia-Cardenas V, Benrimoj SI. The next phase in professional services research: From implementation to sustainability. *Res Soc Adm Pharm*. 2017;13(5):896-901. doi:10.1016/j.sapharm.2017.05.020

125. Chile ministry of health. *TECHNICAL GUIDELINES FOR THE IMPLEMENTATION OF MEDICATION REVIEWS IN PRIMARY CARE*.; 2018.

126. Health ministry of health. *MANUAL FOR CONDUCTING MEDICATION REVIEWS WITH FOLLOW-UP IN PRIMARY CARE CENTERS*.; 2019. http://quimica.uc.cl/images/noticias/2019/2019_07_12_MANUAL-SEGUIMIENTO-FARMACO-TERAPEUTICO1_compressed.pdf.

127. Marra C, Johnston K, Santschi V, Tsuyuki RT. Cost-effectiveness of pharmacist care for managing hypertension in Canada. *Can Pharm J*. 2017;150(3):184-197. doi:10.1177/1715163517701109

128. Al Hamarneh YN, Johnston K, Marra CA, Tsuyuki RT. Pharmacist prescribing and care improves cardiovascular risk, but is it cost-effective? A cost-

effectiveness analysis of the RxEACH study. *Can Pharm J*. 2019;152(4):257-266. doi:10.1177/1715163519851822

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Appendix
Public protocol for the Polaris trial (https://clinicaltrials.gov/ct2/show/NCT03502109)

ClinicalTrials.gov Protocol Registration and Results System (PRS) Receipt
Release Date: January 23, 2020

ClinicalTrials.gov ID: NCT03502109

Study Identification

Unique Protocol ID:	PUCUTS1
Brief Title:	Pharmacist-led Medication Review With Follow-up on Primary Care Cardiovascular Older Adult Patients. (POLARIS)
Official Title:	Randomized Controlled Trial of Pharmacist-led Medication Review With Follow-up on Cardiovascular Older Adult Patients in Primary Care. POLARIS
Secondary IDs:	

Study Status

Record Verification:	January 2020
Overall Status:	Completed
Study Start:	January 5, 2018 [Actual]
Primary Completion:	June 30, 2019 [Actual]
Study Completion:	July 31, 2019 [Actual]

Sponsor/Collaborators

Sponsor:	Pontificia Universidad Catolica de Chile
Responsible Party:	Principal Investigator Investigator: Cristián Plaza [cplaza] Official Title: Director Affiliation: Pontificia Universidad Catolica de Chile
Collaborators:	University of Technology, Sydney

Oversight

U.S. FDA-regulated Drug:	No
U.S. FDA-regulated Device:	No
U.S. FDA IND/IDE:	No
Human Subjects Review:	Board Status: Approved Approval Number: 2886 Board Name: Comité ético-científico Board Affiliation: Servicio de Salud Metropolitano Sur Oriente Phone: +56225765163 Email: comiteeticocientifico@ssmso.cl Address:

Concha y Toro Avenue, 3459, Puente Alto, Santiago, Chile.

Data Monitoring: No

FDA Regulated Intervention: No

Study Description

Brief Summary: Hypothesis: Medication Review with follow-up can improve clinical, health related quality of life and economic outcomes. To prove this hypothesis a cluster randomized controlled trial will be held in primary care centres of the public health system of Chile. Patients of the cardiovascular disease prevention program, older than 65 years and with poly pharmacy (more than 5 drugs) will be recruited. Control group will receive usual care and the intervention arm will have medication review consultations by a pharmacist every 4 months for one year. Clinical interventions will be made with physician authorisation. Participating pharmacist will be trained in cardiovascular prevention pharmacotherapy in the elderly, interview skills and educational techniques. A practice change facilitator will assist the pharmacist in any matters regarding the methodology and will asses barriers and facilitators to the implementation of the medication review with follow-up service. A personalised plan will be developed for every pharmacist. Clinical outcomes (blood pressure, HbA1c, LDL cholesterol, overall cardiovascular risk, among others), number of medications, adherence rate and health-related quality of life will be evaluated. A cost-utility analysis will be made through the health ministry of Chile perspective.

Detailed Description: This study was approved by the ethics committee from the Metropolitan Southeastern health service and the University of Technology Sydney (UTS)'s Human Research Ethics Committee (HREC). All patients are compelled to sign an informed consent document before the first interview, explaining that they can leave the study whenever they want without punishment or justification. All data will be coded and stored without any personal information, to comply with the Chilean law 19,628 for protection of personal data and 20,584 for rights and duties of the patients.

Sample size and losses

Sample size was calculated with data from the pilot study conducted between March and July of 2017. The effect size was determined by the reduction of CHD risk (0.324). Cluster size was of 24, clustering effect of 1.57, control-intervention relationship of 1:1, with an 80% of statistical power and type I error of 5%. A 20% attrition rate was assumed. With this data the calculated sample size was 576, with 288 patients and 11-12 clusters in each study group.

In addition, primary care centers will recruit participants following the proportion of older adults (OA) in the Cardiovascular disease care program (PSCV in spanish) of each one . If a center gathers more than 10% of the total population, that center must recruit 10% of the sample in that group.

Study structure

This study will have two stages: stage one is the preparation of the participating pharmacist in the intervention group and stage two is the development of the fieldwork.

Training of pharmacists in the intervention group will consist of 15 hours of topics developed in theory and practice, focusing on the resolution of clinical cases. The topics will be:

- Study methods.
- Pharmacist-physician and pharmacist-patient relationship.

- Measurement of vitals (blood pressure, cardiac frequency, weight and height determination, waist circumference, and capillary glycaemia).
- Communication abilities and health education.
- Geriatrics pharmacotherapy in hypertension, type 2 diabetes mellitus and dyslipidemias.

Control group will only be prepared in control of vitals and survey application.

Facilitator pharmacist

Facilitator Pharmacists (FAPHA) are pharmacists trained in MRF and implantation of professional pharmaceutical services. Its main objective is to conduct a systematic evaluation of implantation factors of the MRF service in the Polaris program, being positive –facilitators- or negative –barriers- and to support the pharmacists that provide the service in each individual center and municipality. Each Pharmacist will be supervised by a FAPHA, who will conduct weekly evaluations in the initial phase and monthly thereafter during the followup period.

Each FAPHA will be trained in:

- Medication review with follow-up.
- Pharmacotherapy of chronic diseases in the elderly.
- Analysis of implantation factors of a pharmaceutical service.
- Intervention strategies to overcome barriers and increase facilitators.

Main functions of the FAPHA are:

- To promote the collaborative work between each pharmacist and authorities of the Family health care center (CESFAM in spanish) or municipality..
- To detect causes of barriers and facilitators of the service in the primary care center.
- To increase and spread facilitators between primary care centers.
- To overcome barriers by implementing specific action plans in each primary care center.
- To establish the implementation of MRF service according to the Polaris method.
- To register the process and analysis in the corresponding data sheet.

Medication review with follow-up (MRF)

MRF will be conducted according to the Polaris methods developed for this study. Each participant will be interviewed at least seven times, and possibly more in the intervention group.

Service offer

The MRF service will be offered in two levels:

- Health Service and municipalities: the investigation team will introduce the program to each health service authorities and to each municipality (managers of each health care center and health authorities).
- CESFAM: the program will be presented to all health care professionals in each CESFAM by the pharmacist of that center. If needed, the assigned FAPHA can support this with the help of the pharmacist in chief.

Invitation to the service

Different methods can be used and will be compared to perform patient recruitment. This will be defined by each health care center's availability of resources. Each method requires that the participants of the study to go to each interview with all their medications.

The suggested methods are:

- Primary care center customer service: the invitation to participate in the study will be made by each center customer service. The investigator team will prepare a script for the administrative personal to use for recruiting and a list of patients to be recruited by phone call.
- Pharmacy unit: patients will be recruited in the pharmacy unit by each participant pharmacist. This will be conducted with spontaneous recruitment, at the moment of dispensation. In that instance, each participant should sign the informed consent document.
- Referral of other professionals: patients could be invited to the service through referral to the pharmacist if they meet the inclusion and exclusion criteria.

It is suggested to make the community aware of the service by making presentations of the program in different community instances, like the council of users of each primary care centre where the patients show their problems and participate in designing and proposing health practices and services.

Intervention group

Initial interview:

With the data obtained during the pilot study, this interview should last maximum 30 minutes. The following structure will be followed:

- Review of clinical records and pharmacy registry. This should be conducted previously by the pharmacist, and should be used to complete before the interview some of the patient information in the registry like health problems, prescriptions, laboratory tests and any other relevant information.
- During the first interview, pharmacist will apply the Morisky-green survey of four questions to determine medication adherence and the EuroQoL 5D-3L survey to determine perceived quality of life.
- Complete review of medications brought by the patient, including prescription and self-administered drugs. In addition, information about the use of each medication will be assessed while interviewing, like drug adherence, knowledge about the medication, reason of the prescription, signs or symptoms of Adverse Drug Reactions (ADR), among other information.
- Any other relevant information will be registered, and the pharmacist must perform a review of the interview to summarize the topics of interest and to receive any additional information that the patient considers relevant and has not been spoken previously.

Invitation to next interviews should be made at the end of every session and scheduled according their prescription refill, to increase adherence to the program and to confirm the appointment with the patient. All information gathered in the first interview will be registered in the MRF profile. After the initial analysis, patient will be classified in compensation or follow-up stage.

Compensation stage

All patients will be classified in this stage if they are not controlled in their Hypertension, Type 2 Diabetes Mellitus or Dyslipidemias, to assess the greater risk of cardiovascular complications. These patients will have a greater number of interviews and interventions, until they accomplish control of their diseases or the pharmacist decides that the problem can't be resolved in primary health care. The frequency of appointments will be the following:

- Uncontrolled Hypertension: interviews and interventions will be every 7-14 days until achievement of blood pressure goal. This will require close work with physicians and nurses. Once the goal has been reached, the patient will continue on the follow-up stage.

- Uncontrolled Type 2 Diabetes Mellitus: interviews and interventions will be every 7-14 days until achievement of the glycaemic target, controlled by fasting values and capillary glycaemia in the following 7 days. After an initial achievement normal values, the patient will have an appointment every 30 days. Only with confirmation of an HbA1c value in the bellow the accepted limit, the patient will continue on the follow-up stage.
- Uncontrolled Dyslipidemias: interviews and interventions every 4-6 weeks, until achievement of lipid goals. Once the goal has been reached, the patient will be derived to the follow-up stage.
- Special cases: patients in which a moderate or severe ADR is suspected, or those who present a pharmacological interaction defined as relevant by the literature, will receive interviews and interventions every 7-14 days until the issue has been tackled. After that, the patient will be derived to the follow-up stage.

Follow-up stage

All patients that are controlled in the previously described health problems will be classified in the follow-up stage, with interviews every four months.

Patients can be moved between both stages when necessary and will be constantly evaluated in their laboratory results, vitals and clinical signs and symptoms. Independently of the stage of the patient, all surveys must be completed every two months.

Study and evaluation phase

This phase consists of a comprehensive analysis of the medications used by the patient, reviewing aspects of necessity, efficacy and safety.

According to the data of the pilot study, this phase should last about 30 minutes. After an analysis of the pharmacotherapy of the patient, an action plan must be developed. If it requires a prescription change it must be discussed with a physician. If an educational plan is developed, it can be implemented directly. This process should last about 30 minutes, and it could be developed through a designated physician of the health center or through appointments with each physician in charge of each patient.

Adverse drug reactions (ADR)

A screening to identify ADR will be conducted in each interview by therapeutic group and expected ADR in the patient. In this study, ADR will be classified by the following:

Type according to the World Health Organization (WHO):

- A: Augmented, exaggerated effects from the pharmacological action of the drug (like hypotension with anti-hypertensive medication).
- B: Bizarre, ADR that can't be explained by the drugs mechanism of action (like allergic reactions or Steven-Johnson syndrome).
- C: Chronic, associated with a prolonged use of the drug (like benzodiazepine dependence).
- D: Delayed, like malignancy or teratogenic effects.
- E: End-use, associated with a residual effect after suspension of the drug (like rebound effect).

Causality through Naranjo's Algorithm:

- Definite
- Probable
- Possible
- Unlikely

Severity classified by the WHO:

- Mild: mild clinical manifestations that does not require a therapeutic intervention or suspension of the drug.
- Moderate: significant clinical manifestations that do not put in risk the life of the patient, but that require suspension of the drug or additional therapeutic interventions.
- Severe: important clinical manifestations that threatens the life of the patient and requires immediate suspension of the drug and urgent therapeutic interventions.

Each suspected ADR must be reported to the Chilean pharmacovigilance online system (RED-RAM) of the Public Health Institute of Chile.

Follow-up interviews

Follow-up interviews are defined as any interview after the first, and could be in compensation or follow-up stage. With the data from the pilot study, follow-up interviews should last about 20 minutes.

Registry of phase times

All phases should be timed and must be registered by the pharmacist to determine the duration of the process of MRF. The minimum timed activities should be:

- Previous review of the clinical records.
- Each interview.
- Time to register all data.
- Time spent while studying the patient and elaborating the action plan.
- Time of the meeting with the physician.

Laboratory exams will be considered as valid if they are not older than six weeks –three months to HbA1c-. Each pharmacist must manage the exams orders by their own primary care center policies.

Control group

Control group will receive usual care, with clinical attention of health professionals like nurses, physicians and dietitians, dispensation of medications from technicians in the pharmacy unit, and consultation of the pharmacist if required by the patient. If there is a detection of a medication issue with a patient, it will be reported to the health center managers so it could receive usual care. Each patient must have interviews every two months, with seven points of comparison with the intervention group. In each interview, pharmacist will register the patient's vitals, medications and health problems; medication adherence will be measured through the four questions Morisky-Green test and QoL by the EuroQoL 5D-3L tests. Time spent in the interview must be registered. According to the pilot study it should be about 15 minutes.

Economic evaluation

Study perspective The study will be analyzed from the Chilean Ministry of Health (MINSAL) perspective. We elected to use this, because CESFAM are public funded institutions and should develop their services following the public policies of MINSAL.

Therefore, all the intervention related costs that will be included should be the ones related to public budget, for example, cost of implementation of the service, cost of development the intervention and any other cost related with public funding.

Comparators MRF will be compared with usual care as defined above. Time horizon The costs and benefits will be evaluated for a year to avoid any season-related bias and to obtain significant changes in QoL, number of medical appointments, emergency unit visits and hospitalizations, among others.

Discount rate

Discount won't be applied because of the extension of the study (one year); therefore the discount rate will be 0%.

Choice of health outcomes

The benefits will be measured through QALY (Quality Adjusted Life Year) . This analysis is widely used because it reflects the personal perception of patient's QoL through survey considering also the quantity of life gained with those values. For the calculation of QALYs we will use the regression-adjusted area under curve (AUC) method to control for differences in the initial mean values.

This approach allows comparison with other health technologies that also use QALY as a measure of benefit.

Measurement of effectiveness

The measurement of effectiveness is described above. Measurement and valuation of preference based outcomes The QoL of the patients will be estimated using the survey EuroQoL 5D test. Patients will determinate their own QoL perception, both in a descriptive and a general system with a Visual Analog Scale (VAS). The descriptive system has five dimensions (mobility, personal care, daily activities, pain and anxiety/depression); each one has three levels of gravity. In this section of the survey, the patient must select the level of gravity according to his/her perception in that day. In the VAS system, the patient must define his/her personal health perception, ranging it in a scale between 0 and 100, being 0 death and 100 the best health status possible.

Estimation of resources and costs

The resources and cost will be evaluated along the year of study. In accordance with MINSAL perspective approach, we will evaluate the following:

- Initial investment:
    - Resource: pharmacists training time for the study.
    - Costs: value by hour spent in the training program (determined by the academic entity).
- Pharmacist´s working time (minutes), measured in Chilean pesos (CLP). • Resource: time spent in the service.

Time spent in each phase of the service:

- Initial interview.
- Study and evaluation.
- Intervention with the physician.
- Intervention with the patient.
- Follow-up interviews.
- Anything else. o Cost: Pharmacist salary.

Pharmacists are paid according to the Chilean law number 19.378, which refers and involves primary health care professionals, and determines different categories and levels for a full-time job (44 hours a week):

- Categories:
- A: Physicians, Pharmacists, Biochemists and Dentists.
- B: Other professionals like Nurses, Dietitians, and Physiotherapists among others.
- C: superior-level technicians.
- D: mid-level technicians.
- E: Administrative staff.
- F: cleaning staff and others.
- Each employee begins in level 15 with a fixed salary that can be increased by two requirements: time (every two years) and training –by doing

courses in a related area-. When an employee meets these two requisites, advances to the upper level.
- Employees with diplomas get an increase on their wage. It varies depending on the duration of the diploma (between 5 and 15%).

Chilean government fixes the minimum wage every year, but allows each municipality to determinate their own salaries as long as they are higher than de minimum. Therefore, the wage of each municipality will be used for the analysis.

There are bonifications given by the municipalities for different responsibilities. This bonifications will not be considered because they don´t represent extra cost for the intervention.

- Medications:
- Resource: quantity of medications dispensed during the study time obtained from the records from each primary care center.
- Cost: prices of medications are determined according to the Chilean national supply center (CENABAST in Spanish).
- Emergency visits: registered the year before the study and during the intervention.
- Resource: Hospital urgency records, obtained from each hospital.
- Hospital admissions: registered the year before the study and during the intervention.
- Resource: number of hospital admissions, obtained from each hospital.
- Costs: MINSAL has fixed prices according to diagnosis called GRD (group-related diagnosis).

This information will be used to determine if the patient was admitted by a drug-related problem (DRP). The evaluation will be conducted by three physicians, specialists in internal medicine according to Malet-Larrea et.al methods. The following information of the patient will be provided to the evaluators:

- Age.
- Gender.
- Health problems.
- Status of the health problems.
- Prescribed medication.
- GRD.

The specialists in internal medicine will answer yes or no; if he/she considers that the cause of the hospitalization was a DRP. Two yes answers are required to establish a positive causality. Cohen´s kappa index will determine the inter-rater agreement and Fleiss´s kappa index will be used for reliability of agreement between all raters

- Facilitator Pharmacist
- Resource: time spent in transport between visits, planning and intervening with each pharmacist participant in the study and registration of the process.
- Cost: FAPHA costs will be determined by their own salaries.

Currency, price date, and conversion The costs and resources will be measured during 2017 and 2018. All the analysis will be conducted in CLP. Year 2019 will be used as baseline year.

The ICER (incremental cost-effectiveness ratio) will be determined for each scenario, discounting the cost and benefits of usual care from the intervention group according to the following formula: ICER = (Intervention Costs – Control Costs) / (QALY of intervention – QALY of control) Uncertainty will be determined through bootstrapping to evaluate the variability of the outcomes by conducting non-parametric estimations in 5000 different cases. Bootstrapping results will be visualized in a cost-effectiveness plot, and an acceptability curve for different

QALY prices. All patients who complete the four interviews will be considered in the analysis.

Conditions

Conditions:	Cardiovascular Diseases Medication Adherence Drug Use Hypertension Type 2 Diabetes Mellitus Dyslipidemias
Keywords:	Medication review Pharmacist Medication therapy management Cardiovascular diseases Economics Elderly Primary Care

Study Design

Study Type:	Interventional
Primary Purpose:	Health Services Research
Study Phase:	N/A
Interventional Study Model:	Parallel Assignment
Number of Arms:	2
Masking:	Single (Participant) Each participant will sign an informed consent, without knowing that there is another group of patients.
Allocation:	Randomized
Enrollment:	340 [Actual]

Arms and Interventions

Arms	Assigned Interventions
Experimental: Intervention group Medication review with follow-up every 2 months, conducted by a trained pharmacist.	Medication review with follow-up Medication review with follow-up: trained pharmacists will conduct consecutive medication reviews by detecting and resolving drug related problems, educational interventions and applying pharmacotherapy changes made in collaboration with physicians. Other Names: • Pharmaceutical care • Pharmacotherapy follow-up
No Intervention: Control group Usual care by physicians, nurses and dietitians.	

Outcome Measures

Primary Outcome Measure:

1. Patients with controlled hypertension, type-2 diabetes or dyslipidemia
   Proportion of patients with controlled diseases by the chilean government treatment goals. Results will be presented for each disease as Odds ratio for achieving goals in control and intervention group.

   [Time Frame: 12 months]

2. Quality of Life (QoL) by 5 dimensions.
   Measured by the EuroQol-5D-3L five dimension test. Each dimension will be presented individually.

   [Time Frame: 12 months]

3. Incremental Cost-Effectiveness ratio (ICEr)
   Calculated by the difference in costs between groups, divided by the difference in effects.

   [Time Frame: 12 months]

4. Quality of Life (QoL) by visual analog scale (VAS)
   Measured by the EuroQol-5D-3L VAS test, where 0 is the worst and 100 is the best possible health status by personal perception.

   [Time Frame: 12 months.]

Secondary Outcome Measure:

5. Blood pressure (SBP and DBP).
   Mean systolic and diastolic blood pressure levels in each group (in mmHg).

   [Time Frame: 12 months]

6. Fasting glycemia (FG)
   Mean blood glucose levels with at least 8 hours of fasting (in mg/dL).

   [Time Frame: 12 months]

7. Glycated hemoglobin (HbA1c)
   Percentage of glycated hemoglobin in diabetic patients (in %).

   [Time Frame: 12 months]

8. Lipid profile
   Mean total cholesterol, LDL-C, HDL-C and Triglycerides (TG) levels in blood (in mg/dL).

   [Time Frame: 12 months]

9. Serum electrolytes
   Mean K+ and Na+ serum levels in each group (in milliEquivalent/L).

   [Time Frame: 12 months]

10. Glomerular filtration rate (GFR)
    Mean GFR values by the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) equation.

    [Time Frame: 12 months]

11. Costs of the interventions
    Calculated costs in the intervention group versus the control group.

    [Time Frame: 12 months]

12. ACR (albumin-creatinine ratio)
    Mean ACR values in each group (in mg/g).

    [Time Frame: 12 months]

Eligibility

Minimum Age:	65 Years
Maximum Age:	
Sex:	All
Gender Based:	No
Accepts Healthy Volunteers:	No
Criteria:	Inclusion Criteria:

- Age 65 or older.
- Polypharmacy, defined as five or more chronic prescribed medications.
- Independent or independent at risk, classified by the chilean scale of autonomy for older adults (EFAM in spanish).
- Included in the Cardiovascular Primary Care Program.

Exclusion Criteria:

- Low Cardiovascular Disease Risk (CVDR).
- Participants of the pilot study.
- Risk of dependency or dependent by the EFAM.

Contacts/Locations

Central Contact Person: Cristian Plaza, PhD
Telephone: 56226864034
Email: jplaza@uc.cl

Central Contact Backup:

Study Officials:

Locations: **Chile**
Pontificia Universidad Católica de Chile, Facultad de Química.
Santiago, Chile, 7820436
Contact: Francisco Martínez Mardones, Mr. 56224854198 fjmarti3@uc.cl
Sub-Investigator: Francisco J Martínez Mardones, Mr.
Sub-Investigator: Antonio O Ahumada Canale, Mr.
Principal Investigator: Shalom C Benrimoj, PhD
Principal Investigator: Victoria García-Cárdenas, PhD
Sub-Investigator: Roberto Ebensperguer, PhD

IPDSharing

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References

Citations:

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Available IPD/Information:

Paper	Author	Contribution	Signature
Economic evaluations of pharmacist-led medication review in outpatients with hypertension, type 2 diabetes mellitus, and dyslipidaemia: a systematic review	**Ahumada-Canale A**	Collaborated in the design, data extraction, analysis, drafting, and manuscript editing.	Production Note: Signature removed prior to publication.
	Quirland C	Collaborated analysis, and manuscript editing.	Production Note: Signature removed prior to publication.
	Martinez-Mardones FJ	Collaborated in the design, and data extraction.	Production Note: Signature removed prior to publication.
	Plaza-Plaza JC	Collaborated in the design, and manuscript editing	Production Note: Signature removed prior to publication.
	Benrimoj S	Collaborated in the design, analysis, and manuscript editing	Production Note: Signature removed prior to publication.
	Garcia-Cardenas V	Collaborated in the design, analysis, and manuscript editing	Production Note: Signature removed prior to publication.
Cost-utility Analysis of a Medication Review for Cardiovascular Outcomes: A Microsimulation Model	**Ahumada-Canale A**	Collaborated in the design, analysis, drafting, and manuscript editing	Production Note: Signature removed prior to publication.
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Paper	Author	Contribution	Signature
Medication Review with follow-up for Cardiovascular Outcomes: A Trial-based Cost-utility Analysis	**Ahumada-Canale A**	Collaborated in the design, analysis, drafting, and manuscript editing	Production Note: Signature removed prior to publication.
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