Economic impact and health outcomes of a community pharmacist-led medication review with follow-up service in elderly patients with polypharmacy

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Universidad del País Vasco
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CAMPUS OF INTERNATIONAL EXCELLENCE

Economic impact and health outcomes of a community pharmacist-led medication review with follow-up service in elderly patients with polypharmacy

Impacto económico y resultados en salud del servicio de seguimiento farmacoterapéutico realizado a pacientes mayores polimedicados en farmacia comunitaria

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“It always seems impossible until it´s done”

Nelson Mandela

Resumen (Summary)

El gasto en salud ha aumentado considerablemente durante los últimos años en los países occidentales. El envejecimiento de la población es uno de los factores que genera ese aumento del gasto sanitario y se prevé un incremento constante tanto del envejecimiento poblacional como del gasto en salud en el futuro. Por lo tanto, la inversión en estrategias focalizadas en la prevención y en el control de las enfermedades crónicas pueden frenar el coste sanitario y contribuir a la sostenibilidad de los sistemas sanitarios.

Los recursos son escasos en comparación con las necesidades, por lo que es necesario elegir aquellas alternativas que maximicen el bienestar social. Las nuevas tecnologías que se incorporen al sistema sanitario deben demostrar una relación positiva entre los resultados obtenidos y los recursos utilizados; es decir, deben ser eficientes. Las evaluaciones económicas, definidas como el análisis comparativo de acciones alternativas tanto en términos de costes como de beneficios, evalúan la eficiencia de las tecnologías sanitarias e informan a los gestores sanitarios del valor que generaría la financiación de las mismas.

Los medicamentos representan actualmente la tecnología sanitaria más utilizada para controlar y resolver problemas de salud y consumen gran parte

del presupuesto sanitario. Sin embargo, el uso inefectivo e inseguro de los medicamentos genera importantes costes clínicos y económicos prevenibles. Diversos procesos fisiológicos y patológicos asociados a la edad aumentan el riesgo de sufrir problemas relacionados con los medicamentos en los pacientes mayores polimedicados. Por tanto, es necesario realizar un seguimiento individualizado de la respuesta de estos pacientes al uso de los medicamentos.

La atención farmacéutica es la provisión responsable de la farmacoterapia con el propósito de alcanzar unos resultados concretos que mejoren la calidad de vida del paciente. Existen diferentes tipos de servicios profesionales farmacéuticos que se realizan en el ámbito de la atención farmacéutica y que han demostrado ser efectivos evitando problemas relacionados con los medicamentos. Sin embargo, además de los resultados de proceso, es necesario evaluar los resultados en salud en relación a los recursos necesarios. La evidencia hallada respecto al efecto de los servicios profesionales farmacéuticos en resultados en salud y su coste-efectividad varía considerablemente, probablemente porque los servicios difieren en el objetivo, complejidad y responsabilidad asumida por el farmacéutico. De ahí que cada servicio profesional farmacéutico deba ser evaluado individualmente.

El seguimiento farmacoterapéutico (SFT) es un servicio profesional farmacéutico desarrollado en España y cuyo objetivo consiste en la detección de problemas relacionados con los medicamentos, para la prevención y resolución de resultados negativos asociados a la medicación. La presente tesis doctoral está englobada dentro del Programa conSIGUE, trabajo de investigación que se ha llevado a cabo con el objetivo de evaluar el impacto clínico, económico y humanístico del servicio de SFT realizado en farmacia comunitaria a pacientes mayores polimedicados. El estudio consistió en un ensayo controlado aleatorizado por conglomerados, de 6 meses de duración, realizado en 178 farmacias de 4 provincias españolas entre 2011 y 2013. Las farmacias se aleatorizaron en los grupos de intervención (GI), que realizaron SFT, y control (GC), que continuaron con la atención habitual.

El objetivo principal de la presente tesis doctoral consistió en evaluar el impacto económico y los resultados en salud del SFT en farmacia comunitaria a pacientes mayores polimedicados.

Para la consecución de este objetivo, el trabajo se dividió en tres fases:

En primer lugar se llevó a cabo una **revisión sistemática de evaluaciones económicas para determinar si los servicios profesionales farmacéuticos realizados a pacientes ambulatorios que acuden a la**

farmacia comunitaria son coste-efectivos en comparación con la atención habitual.

El estudio incluyó las evaluaciones económicas basadas en ensayos controlados aleatorizados o ensayos controlados aleatorizados por conglomerados realizadas hasta septiembre de 2015. La búsqueda se efectuó en MEDLINE, Scopus, Centre for Reviews and Dissemination databases, Web of Knowledge y Cochrane Library y se incluyeron un total de 17 evaluaciones económicas correspondientes a 13 estudios.

Tras evaluar el riesgo de sesgo de los ensayos y la calidad metodológica de las evaluaciones económicas, siete estudios obtuvieron una puntuación correspondiente a alta calidad, tres a media y tres a baja calidad. Los servicios profesionales farmacéuticos resultaron ser más efectivos y menos costosos que la atención habitual en cuatro de los estudios. Siete estudios concluyeron que los servicios eran más efectivos y más costosos que la atención habitual. En dos de los estudios, los servicios resultaron ser igual de efectivos que la atención habitual, con mayor y menor coste en cada caso. A pesar de la limitada comparabilidad de los estudios incluidos y la incertidumbre relacionada con algunos de los ratios de coste-efectividad incremental, se observó una tendencia general hacia el coste-efectividad de los servicios profesionales farmacéuticos.

Así, en segundo lugar y con el fin de **cuantificar el impacto económico del SFT realizado en farmacia comunitaria a pacientes mayores polimedicados, se llevó a cabo un análisis de costes y un análisis de coste-beneficio del Programa conSIGUE.**

El análisis se realizó desde la perspectiva del sistema sanitario con un horizonte temporal de 6 meses. Se incluyeron los costes directos médicos relativos a la medicación, visitas a urgencias, ingresos hospitalarios relacionados con la medicación, tiempo de los farmacéuticos para la realización del servicio, tiempo del formador colegial (farmacéutico que asistió a la provisión del servicio de SFT y al desarrollo del estudio) y la inversión de la farmacia necesaria para la provisión del servicio.

En el análisis se incluyeron 1403 pacientes (GI: n=688 vs. GC: n=715). El análisis de costes mostró que el SFT ahorró 97€ por paciente a lo largo de los 6 meses de estudio (€, 2014). Extrapolando los resultados a un año y asumiendo que la farmacia recibiera un pago por servicio de 22€ por paciente y mes, los ahorros ascenderían a 273€ por paciente y año. En el análisis de coste-beneficio, los beneficios en salud se estimaron asignando un valor monetario a los años de vida ajustados por calidad obtenidos durante el estudio. El ratio de coste-beneficio mostró que por cada euro invertido en SFT, se obtuvo un beneficio entre 3,3€ y 6,2€. El análisis de sensibilidad

univariante mostró que el SFT ahorraba costes en la mayoría de los escenarios considerados y una dominancia del SFT en todos los casos del análisis de coste-beneficio. Lo cual permite concluir que el SFT proporciona beneficios clínicos a los pacientes y ahorros sustanciales al sistema sanitario, y por tanto invertir en este servicio supondría un uso eficiente de los recursos sanitarios.

En tercer lugar, **se cuantificó el impacto del SFT realizado en farmacia comunitaria a pacientes mayores polimedicados en el número de ingresos relacionados con la medicación y se estimó el efecto en los costes hospitalarios.**

Para llevar a cabo este estudio, se realizó un sub-análisis de la muestra total de pacientes del Programa conSIGUE, en el que un panel de tres expertos en medicina interna cribaron los ingresos hospitalarios ocurridos durante los 6 meses de duración del Programa conSIGUE para determinar si estaban relacionados con la medicación.

Entre los 1.403 pacientes del Programa conSIGUE, se produjeron 83 ingresos hospitalarios. El 50,6% (n=42) estaban relacionados con la medicación, alcanzando un nivel de acuerdo sustancial entre los expertos medido a través de la Kappa de Fleiss. El número de ingresos relacionados con la medicación resultó ser significativamente menor entre los pacientes

que recibían SFT, y la probabilidad de ser ingresado fue 3,7 veces mayor en el grupo comparación (odds ratio: 3,7; p=0,021). Los costes se estimaron a través de los grupos relacionados con el diagnóstico y el coste medio de un ingreso relacionado con la medicación fue de 6.672€. El coste medio por paciente de los ingresos relacionados con la medicación fue menor para los pacientes que recibían SFT (GI: 94€ vs. GC: 301€; p=0,018). Este estudio permitió concluir que el SFT realizado por farmacéuticos comunitarios puede ser una estrategia efectiva para optimizar el beneficio del uso de medicamentos y evitar los ingresos relacionados con la medicación en pacientes mayores polimedicados.

La presente tesis doctoral ha generado evidencia sobre resultados económicos y en salud del seguimiento farmacoterapéutico realizado en el ámbito de la farmacia comunitaria a pacientes mayores polimedicados. Se ha demostrado a través de la revisión sistemática, que los servicios profesionales realizados por farmacéuticos comunitarios son en general coste-efectivos, y por tanto sería recomendable que se considerase la viabilidad de implantar y financiar estos servicios en los sistemas sanitarios. Ha permitido demostrar que el SFT es una intervención dominante que mejora la salud de los pacientes mientras genera ahorros para el sistema sanitario y que tiene un impacto positivo en los ingresos hospitalarios relacionados con la medicación,

en tanto que disminuye la probabilidad de ser hospitalizado y los costes asociados. El SFT realizado por farmacéuticos comunitarios parece ser una estrategia coste-efectiva para responder a las necesidades sanitarias de la población mayor, evitar el coste clínico y económico prevenible causado por los problemas relacionados con los medicamentos y a largo plazo, promover la sostenibilidad de los sistemas sanitarios occidentales.

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Glossary

AUD	Australian dollars	**BMI**	Body mass index
CAD	Canadian dollars	**CEA**	Cost-effectiveness analysis
CG	Comparison group	**CHD**	Coronary heart disease
CMA	Cost-minimisation analysis	**c-RCT**	Cluster randomised controlled trial
CUA	Cost-utility analysis	**CV(D)**	Cardiovascular (disease)
DRG	Diagnosis related group	**DRP**	Drug related problem
ED visits	Emergency department visits	**EE**	Economic evaluations
EQ-5D	EuroQoL 5D	**GC**	Grupo comparación
GI	Grupo intervención	**GP**	General practitioner
HbA1c	Glycated haemoglobin	**ICC**	Intracluster correlation coefficient
ICER	Incremental cost-effectiveness ratio	**ICUR**	Incremental cost-utility ratio
IG	Intervention group	**IRR**	Inter-rater reliability
LYG	Life years gained	**MRF**	Medication review with follow-up
MTM	Medication therapy management	**NA**	Not applicable

NCOM	Negative clinical outcomes related to medicines	**NHS**	National health system
NICE	National Institute for Health and Clinical Excellence	**OECD**	Organisation for Economic Co-operation and Development
OR	Odds ratio	**P**	p-value
PPS	Professional pharmacy services	**QALY**	Quality-adjusted life years
QoL	Quality of life	**RCT**	Randomised controlled trial
SD	Standard deviation	**SE**	Standard error
SFT	Seguimiento farmacoterapéutico	**UC**	Usual care
USD	United States dollar	**VAS**	Visual analogue scale
WTP	Willingness to pay	**95% CI**	95% Confidence interval
€	Euros	**£**	Pounds
$	US Dollars		

Introduction

1. Health systems and sustainability

In recent decades total expenditure on health has increased significantly in Western countries, with a percentage of gross domestic product in Organisation for Economic Co-operation and Development (OECD) countries growing from 7.2% in 2000 to 9% in 2015[1]. Although health spending fell across the European Union in 2010 for the first time since 1975[2], it is projected to continue rising even assuming cost-containment policies[3]. Population ageing and increased life expectancy is one of the factors that will drive healthcare spending in the coming years, along with technology innovation to meet new demands, rising prices, and consumer expectations in healthcare quality[3].

Increasing life expectancy is leading to an ageing of the European population. In countries belonging to the OECD, the population aged 65 or over was 8.5% in 1960, 13.8% in 2005 and is projected to grow to 25.2% by

1 OECD Health Statistics 2016 - Frequently Requested Data. Available from: http://www.oecd.org/els/health-systems/health-data.htm. [Accesed August 2, 2016].
2 OECD Newsroom. Health spending in Europe falls for the first time in decades, 16/11/12. Availabe from: http://www.oecd.org/newsroom/healthspendingineuropefallsforthefirsttimeindecades.htm. [Accesed 14 April 2016].
3 OECD (2013), "What Future for Health Spending?", OECD Economics Department Policy Notes, No. 19 June 2013. Available from: http://www.oecd.org/economy/health-spending.pdf. [Accesed 14 April 2016].

2050[4]. In the context of ageing population and the increased prevalence of chronic illness, healthcare needs are changing[5]. Population´s health needs must be identified in order to effectively use health resources, and health systems must adapt to effectively and efficiently meet these needs. Therefore, the investment in strategies focused on prevention and improving the control of chronic diseases, might lower future healthcare costs and contribute to the sustainability of health systems[4].

Addressing financial sustainability of health systems and responding efficiently to healthcare needs of the ageing population are key priority areas for European countries. The sustainability of health systems relies on the ability of policy makers adequately to manage and finance healthcare resources to meet population needs[6].

A high percentage of these healthcare needs can be met by primary care services[6]. Since costs in primary care are lower than in secondary, care should

[4] Rechel B, Doyle Y, Grundy E, McKee M. How can health systems respond to population ageing? WHO Regional Office for Europe, on behalf of the European Observatory on Health Systems and Policies. Copenhagen, 2009. Available from: http://www.euro.who.int/__data/assets/pdf_file/0004/64966/E92560.pdf. [Accessed July 28, 2016].

[5] Nolte E, McKee M. Caring for people with chronic conditions : a health system perspective. Maidenhead: Open University Press; 2008.

[6] Thomson S, Foubister T, Figueras J, Kutzin J, Permanand G, Bryndová L. Addressing financial sustainability in health systems. WHO Regional Office for Europe on behalf of the European Observatory on Health Systems and Policies. Copenhagen, 2009. Available from: http://www.euro.who.int/__data/assets/pdf_file/0005/64949/E93058.pdf?ua=1. [Accessed July 27, 2016].

be delivered in the primary level when possible. The breadth and scope of services that can be provided in primary care should be expanded, and the better coordination across different healthcare settings is crucial[7].

Policies intended to ensure the sustainability of health systems can be directed to one of the following three key points: to define the amount to be spent on healthcare, to decide the level of coverage to be provided by the health system and how to increase the value from existing health system resources. The last approach is based on the optimization of the outcomes gained by healthcare and the efficiency of the new financed technologies while outweighing the opportunity cost[6].

[7] Figueras J, McKee M, Lessof S, Duran A, Menabde N. Health systems, health and wealth: assessing the case for investing in health systems. WHO Regional Office for Europe on behalf of the European Observatory on Health Systems and Policies. Copenhagen, 2008. Available from: http://www.euro.who.int/__data/assets/pdf_file/0009/83997/E93699.pdf. [Accessed July 28, 2016].

2. Economic evaluations

There is no perfect competition in medical care markets and the intervention of non-market institutions is needed to enhance the efficiency of the systems[8]. The funding of health systems in OECD countries is mainly public, thus governments and health authorities make decisions on funding health technologies based on equity, accessibility and efficiency of health technologies[9].

Resources are scarce relative to the needs, and decisions must be made to choose the alternative which maximizes social welfare[10]. Efficiency is the relationship between the outcomes achieved and the resources used, and measures whether healthcare resources are getting the best value for money[11]. Lower costs do not imply more efficiency, neither higher costs better outcome. Therefore, any new technology incorporated into the health system must demonstrate a positive relationship between resources required and

[8] Arrow KJ. Uncertainty and the welfare economics of medical care. 1963. Bull World Health Organ. 2004;82(2):141-9.
[9] Pinto JL, Sánchez FI. [Methods for the economic evaluation of new technologies]. Ministry of Health and Consumer Affairs: Madrid; 2003. Available from: http://www.msssi.gob.es/estadEstudios/estadisticas/docs/metodos_evaluacion.pdf. [Accessed April 14, 2016].
[10] Liss PE. Allocation of scarce resources in health care: values and concepts. Texto Contexto. Enferm. 2006;15:125-34.
[11] Palmer S, Torgerson DJ. Economic notes: definitions of efficiency. BMJ. 1999;318(7191):1136.

outcomes achieved. Distributing available resources using the efficiency criterion, allows health outcomes to be optimised and to minimize the opportunity cost[12].

The economic evaluation (EE) is one of the methodologies that have been proposed to select those efficient medical technologies[9]. EE is defined as "the comparative analysis of alternative courses of action in terms of both their costs and consequences"[13]. It compares all the necessary resources for the provision of a health technology and the consequences with the best or most widely used alternative. This facilitates the process of decision making for a rational choice among alternative technologies. EE are needed to inform decision makers on the value of financing new technologies.

[12] Culyer AJ. Encyclopedia of Health Economics. 1st edition. UK: Oxford. Elsevier; 2014.
[13] Drummond MF, Sculpher MJ, Torrance GW, O'Brien BJ, Stoddart GL. Methods for the Economic Evaluation of Health Care Programmes. 3rd edition. Oxford: Oxford University Press; 2005.

3. Medicines and drug related problems

Medicines are the most widely used technology to manage and resolve health problems. They improve patients´ clinical outcomes and quality of life, as well as extend the overall life expectancy. An important percentage of healthcare budget is spent in medicines. For instance, prescription drugs consume 10% of the healthcare spending in the U.S.[14]. However, the clinical and economic burden associated with the ineffective and unsafe use of medicines is widely documented, as well as the preventability of a substantial proportion of drug related problems (DRPs).

A high percentage of DRPs result in emergency department (ED) visits or/and hospital admissions. Systematic reviews of studies undertaken in the hospital setting found a median prevalence of 5.3% adverse drug reactions[15] and 10% of adverse events in hospital admissions, with 50% of them being preventable[16]. A series of three studies undertaken in Spanish hospital emergency departments found that between 24.4% and 35.7% of the ED

[14] Baker D, Fugh-Berman A. Do New Drugs Increase Life Expectancy? A Critique of a Manhattan Institute Paper. J Gen Intern Med. 2009;24(5):678-82.
[15] Kongkaew C, Noyce PR, Ashcroft DM. Hospital admissions associated with adverse drug reactions: a systematic review of prospective observational studies. Ann Pharmacother. 2008;42(7):1017-25.
[16] Vries EN, Ramrattan MA, Smorenburg SM, Gouma DJ, Boermeester MA. The incidence and nature of in-hospital adverse events: a systematic review. Qual Saf Health Care. 2008;17(3):216–23.

visits were caused by negative clinical outcomes related to medicines (NCOMs), of which from 73% to 83.9% were preventable[17,18,19].

An ageing population and the use of polypharmacy are well documented risk factors for DRPs and medication-related hospital admissions[18,20]. The study carried out by Chan *et al.* with aged patients using eight or more medications found that 87% of the analysed patients had at least one DRP[21]. When analysing patients with a mean age of 81 and using 15 medicines, the prevalence of DRPs per patient was 8.9[22]. The main reasons for the higher risk of DRPs in the elderly are the changes in pharmacokinetics and pharmacodynamics parameters due to the physiological and pathological changes related to the age and the chronic use of medicines, the higher prevalence of co-morbidity of chronic illness, and the complex therapeutic management due to the polypharmacy for chronic diseases. Additionally,

17 Baena MI, Fajardo PC, Pintor-Marmol A, Faus MJ, Marin R, Zarzuelo A et al. Negative clinical outcomes of medication resulting in emergency department visits. Eur J Clin Pharmacol. 2014;70(1):79-87.
18 Baena MI, Faus MJ, Fajardo PC, Luque FM, Sierra F, Martinez-Olmos J, et al. Medicine-related problems resulting in emergency department visits. Eur J Clin Pharmacol 2006; 62(5): 387–93.
19 García V, Marquina I, Olabarri A, Miranda G, Rubiera G, Baena MI. [Negative results associated with medication in the emergency department of a hospital]. Farm Hosp 2008;32(3):157-62.
20 Rogers S, Wilson D, Wan S, Griffin M, Rai G, Farrell J. Medication-related admissions in older people: a cross-sectional, observational study. Drugs Aging. 2009;26(11):951-61.
21 Chan DC, Chen JH, Kuo HK, We CJ, Lu IS, Chiu LS, et al. Drug-related problems (DRPs) identified from geriatric medication safety review clinics. Arch Gerontol Geriatr. 2012;54(1):168-74.
22 Farrell B, Szeto W, Shamji S. Drug-related problems in the frail elderly. Can Fam Physician 2011;57(2):168-9.

geriatric patients have a greater incidence of cognitive and functional disabilities, which increases the risk of using medicines incorrectly, affecting for instance the adherence[23].

DRPs use social and health resources and generate costs to the healthcare system. In the U.S., the cost of treating drug-related morbi-mortality in ambulatory care was estimated to be $177.4 billion in 2000 year[24] and avoidable healthcare costs generated by DRPs amounted to $200 billion in 2012[25]. In Spain, the cost in ED visits caused by preventable NCOMs was estimated to be €14.5 million during the 2003 year[19]. In the Netherlands potentially preventable medication-related hospital admissions cost more than €94 million in 2006[26]. The annual cost of outpatients' drug-related morbidity was estimated to be €6,600 million in 2012 for the Swedish healthcare system, with 45% of this morbidity being preventable[27]. Therefore, an individualized

[23] Malet-Larrea A, Calvo B. [Impact of the Medication Review with Follow-up in the polymedicated elderly. The conSIGUE Program in Gipuzkoa]. Masters dissertation. Vitoria: University of the Basque Country; 2013.
[24] Ernst FR, Grizzle AJ. Drug-related morbidity and mortality: updating the cost-of-illness model. J Am Pharm Assoc (Wash). 2001;41(2):192-9.
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[26] Leendertse AJ, Bemt PM, Poolman JB, Stoker LJ, Egberts AC, Postma MJ. Preventable hospital admissions related to medication (HARM): cost analysis of the HARM study. Value Health. 2011;14(1):34-40.
[27] Gyllensten H, Hakkarainen KM, Jonsson AK, Andersson Sundell K, Hagg S, Rehnberg C et al. Modelling drug-related morbidity in Sweden using an expert panel of pharmacists'. Int J Clin Pharm. 2012;34(4):538-46.

follow-up of patients´ response to medicines is required, especially in aged patients using polypharmacy, in order to avoid the preventable clinical and economic burden caused by DRPs.

4. Professional pharmacy services

"Pharmaceutical care" concept promoted by Hepler & Strand in 1990 was defined as "the responsible provision of drug therapy for the purpose of achieving definite outcomes that improve a patient's quality of life"[28], highlighting the transition of a product-oriented to patient-oriented pharmacy practice. However the adoption and implementation of this professional role has been patchy between and within countries[29].

The concept of pharmaceutical care has been crystallised into a more acceptable, understandable and practical construct i.e. a professional pharmacy services (PPSs). Several definitions and concepts have been developed for the pharmaceutical care[30,31] and PPSs (for instance, clinical pharmacy services[32] or cognitive pharmaceutical services[33]). All these

[28] Hepler CD, Strand LM. Opportunities and responsibilities in pharmaceutical care. Am J Hosp Pharm. 1990;47(3):533-43.
[29] van Mil JWF, Schulz M. A Review of Pharmaceutical Care in Community Pharmacy in Europe. Harv Health Pol Rev. 2006;7(1):155-68.
[30] Allemann SS, van Mil JW, Botermann L, Berger K, Griese N, Hersberger KE. Pharmaceutical care: the PCNE definition 2013. Int J Clin Pharm. 2014; 36(3):544-55.
[31] Pharmaceutical Care Forum. Expert panel. Consensus document. Madrid: Spanish General Council of Official Colleges of Pharmacists; 2010 (ISBN: 9788469112434).
[32] Perez A, Doloresco F, Hoffman JM, Meek PD, Touchette DR, Vermeulen LC, et al. ACCP: economic evaluations of clinical pharmacy services: 2001-2005. Pharmacotherapy. 2009;29(1):128.
[33] Benrimoj SI, Feletto E, Gastelurrutia MA, Martinez-Martinez F, Faus MJ. A holistic and integrated approach to implementing cognitive pharmaceutical services. Ars Pharm 2010;51: 69-87.

definitions, although with minor variations, address the same underlying philosophy.

PPSs are provided in community, hospital and long-term care settings. They are mainly aimed at optimising medication therapy and managing chronic diseases, although the prevention and resolution of acute conditions is also considered. Some services are focused in one health problem whereas other services analyse patients from a holistic approach. The "Hierarchical model of cognitive pharmaceutical services" classifies PPSs in ten different levels of pharmacists´ interventions, according to their complexity of clinical decision making (Table 1). Level 1 is the simplest intervention, provision of information about medicines, and level 10 is the most complex, medication prescribing[33]. Medication review with follow-up (MRF) is a service included in the level 7, focused on both medication use process and health outcomes, and requires a commitment to follow-up.

Table 1: Hierarchical model of professional pharmacy services[33]

1. Medicines information
2. Compliance, adherence and/or concordance
3. Disease screening
4. Disease prevention
5. Clinical intervention or identification and resolving drug related problems
6. Medication use reviews
7. Medication management/medication therapy management 7.a Home medication reviews 7.b Residential care home medication reviews 7.c Medication reviews with continuance follow-up
8. Disease state management for chronic conditions
9. Participation in therapeutic decisions with medical practitioners 9.a In clinical setting 9.b In the pharmacy
10. Prescribing 10.a Supplementary 10.b Independent

4.1 Clinical and economic impact of professional pharmacy services

There is a growing evidence of the positive effect of several PPSs on improving pharmacotherapy and reducing DRPs such as the number of medicines used by patient and improving the appropriateness of the medication in elderly patients[34,35]. However, their effectiveness on reducing hospital admissions in aged patients has not been clearly established[34].

[34] Saez-Benito L, Fernandez-Llimos F, Feletto E, Gastelurrutia MA, Martinez-Martinez F, Benrimoj SI. Evidence of the clinical effectiveness of cognitive pharmaceutical services for aged patients. Age Ageing. 2013;42(4):442-9.
[35] Spinewine A, Fialova D, Byrne S. The role of the pharmacist in optimizing pharmacotherapy in older people. Drugs aging. 2012;29(6):495-510.

Different and inconclusive findings have been found in several systematic reviews addressing this topic[36,37].

Diverse findings have been found not only in health outcomes but also in the cost-effectiveness of PPSs. Some studies concluded that PPSs were more effective and less costly than usual care (UC)[38] while others found higher costs for PPSs[39,40.] Several systematic reviews conclude that PPSs provided in different settings generally provide positive economic benefits, although the variability in both health outcomes and the subsequent cost-effectiveness analysis (CEA) is high[32,41,42,43].

[36] Holland R, Desborough J, Goodyer L, Hall S, Wright D, Loke YK. Does pharmacist-led medication review help to reduce hospital admissions and deaths in older people? A systematic review and meta-analysis. Br J Clin Pharmacol. 2008;65(3):303–16.
[37] Thomas R, Huntley AL, Mann M, Huws D, Elwyn G, Paranjothy S, et al. Pharmacist-led interventions to reduce unplanned admissions for older people: a systematic review and meta-analysis of randomised controlled trials. Age ageing. 2014;43(2):174-87.
[38] Elliott RA, Barber N, Clifford S, Horne R, Hartley E. The cost effectiveness of a telephone-based pharmacy advisory service to improve adherence to newly prescribed medicines. Pharm World Sci. 2008;30(1):17-23.
[39] RESPECT Trial Team. Cost-effectiveness of shared pharmaceutical care for older patients: RESPECT trial findings. Br J Gen Pract. 2010;60(570):e20-7.
[40] Gordois A, Armour C, Brillant M, Bosnic-Anticevich S, Burton D, Emmerton L, et al. Cost-Effectiveness Analysis of a Pharmacy Asthma Care Program in Australia. Dis-Manage-Health-Outcomes. 2007;15:387-96.
[41] Gallagher J, McCarthy S, Byrne S. Economic evaluations of clinical pharmacist interventions on hospital inpatients: a systematic review of recent literature. Int J Clin Pharm. 2014;36(6):1101-14.
[42] Schumock GT, Butler MG, Meek PD, Vermeulen LC, Arondekar BV, Bauman JL, et al. Evidence of the economic benefit of clinical pharmacy services: 1996-2000. Pharmacotherapy. 2003;23(1):113-32.
[43] Schumock GT, Meek PD, Ploetz PA, Vermeulen LC. Economic evaluations of clinical pharmacy services:1988-1995. Pharmacotherapy. 1996;16(6):1188-208.

Settings in which PPSs are provided, variability in assessing complex interventions[44] or strengths and flaws of different studies may explain different findings. However, the main reason could be that every service differs widely in its aims, methodology, complexity, collaboration with other healthcare providers and level of responsibility assumed by the pharmacist[33] and therefore logically the same outcomes cannot be assumed for different types of PPSs.

4.2 Medication review with follow-up and conSIGUE Program

MRF is a service developed in Spain and defined according to Spanish national guidelines as "the professional pharmacy service aimed at identifying drug related problems in order to prevent and resolve negative clinical outcomes related to medicines. It requires a commitment, and it must be delivered in a continuous, systematic and registered way, in collaboration with the patient and other health professionals, with the aim of achieving definite outcomes that will improve patient´s quality of life"[31].

[44] Craig P, Dieppe P, Macintyre S, Michie S, Nazareth I, Petticrew M, et al. Developing and evaluating complex interventions: the new Medical Research Council guidance. BMJ. 2008;337:a1655.

MRF starts with the pharmacist´s interview undertaken in a private area of the pharmacy. The pharmacist collects relevant information about patient's health problems, medicines used, clinical and biological parameters (gathered through medical records provided by the patient or measured in the pharmacy), medication use, lifestyle habits and concerns about diseases and medications. The pharmacist records this information in a tool called "situational analysis". After undertaking the study phase for all the health problems and medicines, a comprehensive medication review is undertaken. The pharmacist identifies drug related problems and negative clinical outcomes related to medicines. Subsequently an action plan is agreed with the patient and the physician if required. Pharmacist´s interventions follow the action plan. Monthly patient visits to the pharmacy are used for patient´s monitoring and performing new interventions[45] (see Figure 1).

[45] Malet-Larrea A, Goyenechea E, Garcia-Cardenas V, Calvo B, Arteche JM, Aranegui P, et al. The impact of a medication review with follow-up service on hospital admissions in aged polypharmacy patients. Br J Clin Pharmacol. 2016; 82(3):831-8.

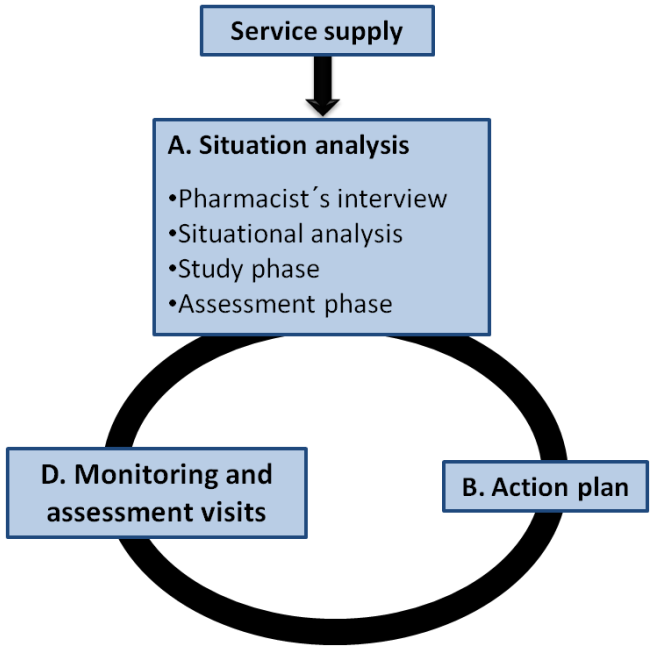


Figure 1: Process of the medication review with follow-up

The aim of the conSIGUE Program[46], carried out between 2009 and 2013, was to assess the clinical, economic and humanistic impact of the MRF provided to aged patients with polypharmacy in community pharmacy. A cluster randomized controlled trial (c-RCT) was carried out in 178 community

[46] Martínez-Martínez F, Gastelurrutia MA, Benrimoj SI, García-Cárdenas V, Saez-Benito L, Varas R. [conSIGUE: clinical, economic and humanistic impact of the Medication Review with Follow-up service in aged polypharmacy patients in Spanish community pharmacy]. Madrid: Spanish General Council of Official Colleges of Pharmacists; 2014. ISBN: 978-84-87276-83-5.

pharmacies in four Spanish provinces (Guipúzcoa, Granada, Las Palmas and Tenerife) between November 2011 and July 2013, with 6 months fieldwork in each province. All the community pharmacies located in the four provinces received an invitation to participate in the study from the provincial official associations of pharmacists, with all the respondents enrolled. Each pharmacy was required to recruit up to 10 patients with the following criteria: aged patients (65 years or older), using polypharmacy (five or more medications for at least 6 months) and with the ability to complete the EuroQol 5D (EQ-5D) questionnaire. Pharmacies were the cluster unit of randomization in order to minimize contamination bias, and they were randomly allocated into either the intervention group (IG) or comparison group (CG). Pharmacists in the IG provided MRF whereas pharmacists in the CG provided the UC in Spanish community pharmacies, which consists of dispensing medicines prescribed by physicians and minor ailments advice[47].

A specifically trained pharmacist called a practice change facilitator[48] assisted pharmacists of the IG in the provision of the MRF, identifying barriers and facilitators specific to each pharmacy and providing solutions. Additionally, the practice change facilitator ensured fidelity using process

[47] Gastelurrutia MA, Faus MJ, Fernandez-Llimos F. Providing patient care in community pharmacies in Spain. Ann Pharmacother. 2005;39(12):2105-10.

[48] Harvey G, Loftus-Hills A, Rycroft-Malone J, Titchen A, Kitson A, McCormack B, et al. Getting evidence into practice: the role and function of facilitation. J Adv Nurs. 2002;37(6):577-88.

indicators to the intervention and supported pharmacists of both study groups on doubts about documentation forms. Pharmacists in the IG received a 3 day training course covering the following topics: clinical management of aged patients, the MRF method, communication with patients and doctors, study protocol and documentation forms. Study variables, including variables used in the economic evaluation of the MRF presented in this thesis, were collected on a monthly basis during the c-RCT. The study was approved by the Clinical Research Ethics Committee of the Hospital Virgen de las Nieves of Granada (Spain) in November 2009. All patients were provided with an information sheet prior to the beginning of the study and informed consent was obtained. Detailed methods and preliminary results of the study can be accessed in Spanish in the report published by the Spanish General Council of Official Colleges of Pharmacists[46].

Objectives

Health expenditure in western countries is steadily increasing and it could lead to unsustainable health systems in the coming years. Developing and implementing efficient technologies to meet ageing population´s demands should be a key health investment area.

The incorrect use of medicines causes significant and preventable clinical and economic burden. Ensuring the effective and safe use of medication would improve patients´ health and quality of life, as well as avoid unnecessary costs to the health system.

Professional pharmacy services have shown promising results and could be one of the strategies to ensure the correct use of medicines, meet aged population´s health needs and promote the sustainability of health systems.

The main aim of this thesis was to assess the economic impact and health outcomes of the community pharmacist-led medication review with follow-up to aged patients using polypharmacy. The specific goals were the following:

1. To systematically and critically analyse the existing evidence to determine whether professional pharmacy services provided to ambulatory patients attending community pharmacies are cost-

effective compared with usual care. Furthermore, the methodological quality of individual studies was assessed and cost-effectiveness data were synthesized to facilitate the consideration of implementing professional pharmacy services in health systems (addressed through Chapter 1).

2. To assess the economic impact of the medication review with follow-up provided in community pharmacy to aged patients using polypharmacy compared with usual care, through a cost-analysis and a cost-benefit analysis based on the conSIGUE cluster randomized trial (addressed through Chapter 2).

3. To analyse the effect of community pharmacy-led medication review with follow-up provided to aged polypharmacy patients on the number of medication-related hospital admissions, using an expert panel to ascertain whether the hospital admissions of the conSIGUE Program were medication related. Additionally, the impact of the medication review with follow-up on hospital costs was estimated (addressed through Chapter 3).

Objetivos

El aumento continuo del gasto sanitario en los países occidentales podría dar lugar en los próximos años a sistemas sanitarios insostenibles. El desarrollo e implantación de tecnologías eficientes que cubran las necesidades de la población mayor debería ser un área prioritaria de inversión sanitaria.

El uso incorrecto de los medicamentos causa daños clínicos y económicos significativos y prevenibles. Garantizar el uso efectivo y seguro de la medicación podría mejorar la calidad de vida de los pacientes, así como evitar costes innecesarios al sistema sanitario.

Los servicios profesionales farmacéuticos han mostrado resultados prometedores y podrían ser una de las estrategias para asegurar el uso correcto de los medicamentos, cubrir las necesidades sanitarias de los pacientes mayores y promover la sostenibilidad de los sistemas sanitarios.

El objetivo principal de la presente tesis doctoral consistió en evaluar el impacto económico y los resultados en salud del seguimiento farmacoterapéutico realizado en farmacia comunitaria a pacientes mayores polimedicados.

Los objetivos específicos que se propuso alcanzar este trabajo fueron los siguientes:

1. Analizar sistemática y críticamente la evidencia existente para determinar si los servicios profesionales farmacéuticos realizados a pacientes ambulatorios que acuden a la farmacia comunitaria son coste-efectivos en comparación con la atención habitual. Además se evaluó la calidad metodológica de los estudios individuales y se sintetizaron los resultados de coste-efectividad, para facilitar la consideración de implantar servicios profesionales farmacéuticos en los sistemas sanitarios (abordado en el Capítulo 1).

2. Evaluar el impacto económico del seguimiento farmacoterapéutico realizado en farmacia comunitaria a pacientes mayores polimedicados en comparación con la atención habitual, mediante un análisis de costes y un análisis de coste-beneficio basados en el ensayo clínico aleatorizado por conglomerados del Programa conSIGUE (abordado en el Capítulo 2).

3. Analizar el efecto del seguimiento farmacoterapéutico realizado en farmacia comunitaria a pacientes mayores polimedicados sobre el

número de ingresos relacionados con la medicación, utilizando un panel de expertos para determinar la relación de los ingresos hospitalarios del Programa conSIGUE con la medicación. Asimismo se estimó el efecto del seguimiento farmacoterapéutico en los costes hospitalarios (abordado en el Capítulo 3).

Methods and results

1. Chapter 1:

Cost-effectiveness of professional pharmacy services in community pharmacy: a systematic review

1.1 Introduction

Clinical and economic burden of DRPs has been widely documented. DRPs including medication nonadherence, inappropriate polypharmacy in older adults and medication errors generated $200 billion of avoidable healthcare costs in the U.S. in 2012 year[49]. The annual cost of outpatients' drug-related morbidity was estimated to be €6,600 million for the Swedish health system for the same year, with 45% of this morbidity being preventable[27]. A systematic review of observational studies concluded that the median prevalence of adverse drug reactions in hospital admissions was 5.3%[15]. The prevalence of NCOMs in nine Spanish hospital emergency department visits was 35.7%, of which 81% could have been prevented[17].

PPSs are "any activity in which the pharmacists would use their professional knowledge and abilities to improve pharmacotherapy and disease management by means of interacting with the patient or with other health professional"[50]. A systematic review showed that PPSs are an effective strategy to prevent and resolve drug related problems, such as medication

[49] Aitken, M. Valkova, S. Avoidable costs in U.S. healthcare: the $200 billion opportunity from using medicines more responsibly. USA: IMS Institute for Healthcare Informatics; 2013. Availabe from: http://www.imshealth.com/files/web/IMSH%20Institute/Reports/Avoidable_Costs_in%20_US_Healthcare/IHII_AvoidableCosts_2013.pdf. [Accessed May 10, 2016].

[50] Cipolle J, Strand LM, Morley PC. A Reimbursement System for Pharmaceutical Care: Pharmaceutical Care Practice. New York: McGraw-Hill, 1998.

non-adherence or inappropriate medications[34]. PPSs have been shown to decrease medication-related hospital admission rates in aged polypharmacy patients[45], as well as to improve clinical outcomes and reduce hospitalisation rates, general practice and ED visits in a systematic review including studies conducted in low and middle-income countries[51]. The economic implications of clinical pharmacy services have been reported[32,42,43,52]. While the cost-effectiveness of clinical pharmacist interventions on hospital inpatients has already been specifically analysed[41], there are no systematic reviews analysing their cost-effectiveness in the community pharmacy setting.

Therefore, the objective of this systematic review was to determine whether PPSs provided to ambulatory patients attending community pharmacies are a cost-effective strategy to improve patients´ clinical and humanistic outcomes compared to UC. We provide data in a visual and simple method for decision makers to assess whether they should evaluate the feasibility of implementing PPSs in their specific health systems.

[51] Pande S, Hiller JE, Nkansah N, Bero L. The effect of pharmacist-provided non-dispensing services on patient outcomes, health service utilisation and costs in low- and middle-income countries. Cochrane Database Syst Rev. 2013;2:CD010398.
[52] Touchette DR, Doloresco F, Suda KJ, Perez A, Turner S, Jalundhwala Y, et al. Economic evaluations of clinical pharmacy services: 2006-2010. Pharmacotherapy. 2014;34(8):771-93.

1.2 Methods

The Cochrane Handbook for Systematic Reviews of Interventions[53] and the NHS Economic Evaluation Database Handbook[54] methodology were followed. The reporting of this systematic review followed the guidelines provided by PRISMA statement[55,56].

1.2.1 Selection criteria

A systematic review of full EE based on randomised or cluster randomised controlled trials (RCT/c-RCT) of professional pharmaceutical services provided to ambulatory patients attending community pharmacy was conducted.

[53] Higgins JPT, Green S (editors). Cochrane Handbook for Systematic Reviews of Interventions Version 5.1.0 [updated March 2011]. The Cochrane Collaboration, 2011. Available from www.cochrane-handbook.org. [Accesed 8 Sept 2015].
[54] NHS Centre for Reviews and Dissemination. NHS Economic Evaluation Database Handbook. UK: University of York; 2007. Available from: http://www.york.ac.uk/inst//crd/pdf/nhseed-handbook2007.pdf. [Accessed September 20, 2015].
[55] Liberati A, Altman DG, Tetzlaff J, Mulrow C, Gotzsche PC, Ioannidis JPA, et al. The PRISMA statement for reporting systematic reviews and meta-analyses of studies that evaluate healthcare interventions: explanation and elaboration. BMJ. 2009;339:b2700.
[56] Moher D, Liberati A, Tetzlaff J, Altman DG, The PRISMA Group. Preferred Reporting Items for Systematic Reviews and Meta-Analyses: The PRISMA Statement. BMJ. 2009;339:b2535.

Full EE were included, as they allow assessing the efficiency of health technologies. Drummond´s definition for full EE was adopted ("studies reporting both costs and consequences of at least two alternatives")[13]. These full EEs were subcategorized as cost-effectiveness, cost-minimization, cost-utility, cost-consequence or cost-benefit analysis, depending on the units used to measure outcomes. PPSs were defined using Cipolle's definition[50] and categorized using the "Hierarchical model of cognitive pharmaceutical services", which comprises 10 different levels of pharmacists´ interventions, according to their complexity of clinical decision making[33]. For the purpose of this study, we combined level 6 (medication use review) and level 7 (medication therapy management) leading to a category of "medication therapy management with/without follow-up".

The exclusion criteria were: (i) studies assessing interventions that were not considered PPSs based on Cipolle's definition[50] and on the hierarchical model[33]; (ii) studies in which the service was not exclusively provided by a pharmacist to ambulatory patients recruited in the community pharmacy; (iii) not full EE based on Drummond's definition[13]; (iv) studies in which the main cost and effectiveness data were not gathered from a single RCT/c-RCT study, (v) studies not including the main types of costs from the perspective of the society, government, health system or third party; (vi) studies not

comparing a PPS with the UC; (vii) letters, study protocols, notes, commentaries, guidelines, conference abstracts, pilot studies, literature reviews, meta-analysis and papers without abstract; and (viii) papers not written in languages with Latin alphabet.

1.2.2 Article retrieval and screening

The databases searched from inception to 2015 were MEDLINE, Web of Knowledge, Centre for Reviews and Dissemination Database, the Cochrane Library and Scopus.

Queries were built by examining the Mesh terms of potentially relevant studies and combining them with keywords. Publication date filter was not used. Previously published filters for EE and gathered by the InterTASC Information Specialists' Sub-Group Search Filter Resource were consulted to ensure the inclusion of all the relevant terms[57].

The search strategy used in MEDLINE was: ("Economic evaluation"[TIAB] OR "cost"[TIAB] OR "costs and cost analysis"[MH] OR "economic impact"[TIAB] OR "pharmacoeconomic"[TIAB] OR "economic

[57] The InterTASC Information Specialists' Sub-Group Search Filter Resource. Filters to find Economic Evaluations [internet]. UK. Available from: https://sites.google.com/a/york.ac.uk/issg-search-filters-resource/filters-to-find-i. [Accessed Sept 20, 2015].

outcomes"[TIAB] OR "cost-effectiveness"[TW] OR "cost-utility"[TW] OR "cost-benefit"[TW] OR "cost-minimization"[TW] OR "quality adjusted life years"[MH] OR "quality of life"[MH]) AND ("community pharmacy services"[MH] OR "medication review"[TIAB] OR (pharmacist* [TW] AND ("drug utilization review"[MH] OR "cognitive services"[TIAB])) OR "pharmaceutical services"[MH] OR "pharmaceutical care"[TW] OR "cognitive services"[TW] OR intervention*[TIAB] OR "professional role"[MH]) AND ("pharmacists"[MH] OR "pharmacies"[MH] OR pharmaci*[TW] OR "pharmacy"[TIAB]) NOT (review[PT] OR comment[PT] OR "newspaper article") AND HASABSTRACT. The search strategy was adapted for other databases using the appropriate syntax and terms (all search strategies are available from authors). Search strategy was tested by screening selected citations for relevance. The references of the retrieved papers were reviewed for additional relevant studies and two experts in PPSs checked their libraries (CB & VGC).

The literature selection process was undertaken and discussed by two researchers on PPSs (AML and LSB). This process was over inclusive. Discrepancies between reviewers were resolved with the opinion of a third researcher (EG).

1.2.3 Data extraction, quality assessment and analyses

A tailored data extraction form based on Cochrane[53] and NHS handbook[54] data extraction forms was developed and piloted for data retrieval and analysis. It included information about the study characteristics (citation, objective, study design, randomization, follow-up and sample size), the PPS (type of service according to the hierarchical model, description of the intervention and the comparator, remuneration and training of pharmacists), clinical and humanistic outcomes (differences between groups, tools used to measure the outcomes), costs (currency and year, direct medical costs, direct non-medical costs, indirect costs), economic evaluation (type of economic evaluation, perspective, time horizon, discount rate, incremental analysis, sensitivity analysis) and miscellaneous (conclusions, limitations, funding source and references to other relevant studies). Data extraction was also undertaken and discussed between two researchers (AML and VGC), and discrepancies resolved by a third researcher (EG).

A single extraction table was completed to avoid the duplication of the impact of various papers reporting the same EE study in the systematic review. The most complete paper was chosen to extract the information and if any detail about methods or results was missing, it was complemented with the second paper. In cases where in the retrieved paper the methods section

was incomplete, the referenced effectiveness study or study protocol was retrieved to extract the missing information.

The main outcome variables were the costs incurred and outcomes of the PPS and the UC, and the primary outcome or summary measure was the incremental cost-effectiveness ratio (ICER) of the PPS compared with UC. When the incremental analysis was not provided in the original studies, we estimated the ICER when statistically significant differences were found in the effectiveness of the PPS vs. UC. Cost-effectiveness results of these studies were treated separately.

The "Suggested risk of bias criteria for EPOC reviews"[58] tool was used to assess the risk of bias of the RCT/c-RCT, whereas the "Evers' Checklist"[59] was used to assess the EE. In the studies where a decision analytic model was used to extrapolate the short-term results obtained in the RCT/c-RCT to long-term results, the "Phillips' checklist"[60] was additionally used to assess the model. The study was classified as high quality if there was low risk of bias in

[58] Cochrane. EPOC Guidance on Risk of Bias. EPOC. Suggested risk of bias criteria for EPOC reviews. UK. Available from: https://epoc.cochrane.org/sites/epoc.cochrane.org/files/uploads/Suggested%20risk%20of%20bias%20criteria%20for%20EPOC%20reviews.pdf. [Accesed 11 May 2016].

[59] 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):240-5.

[60] Philips Z, Ginnelly L, Sculpher M, Claxton K, Golder S. Review of guidelines for good practice in decision-analytic modelling in health technology assessment. Health Technol Assess. 2004;8(36):1-158.

at least 6 criteria of the "Suggested risk of bias criteria for EPOC reviews" tool; it was classified as low quality if the risk of bias was high in at least 5 criteria; the other situations were considered medium quality. The EE was classified as high quality if at least 75% of Evers' (all the papers) and 75% of Philips' criteria (only in decision analytic models) were fulfilled. If less than 50% of criteria were fulfilled it was classified as low quality, and between 51%-74% were classified as medium quality. If any criterion was not applicable in individual studies, it was not taken into account when calculating the percentage. When the score in the risk of bias and the quality of the EE was different, the lowest classification was accepted as the overall quality of the study.

To allow direct comparisons across countries and years, costs were converted to a common year and currency (USD, 2015 prices) through an online tool which uses Purchasing Power Parities (PPP) to convert currencies and the Gross Domestic Product deflation index to adjust the years[61]. The PPP values given by the International Monetary Fund were chosen.

The validity and interpretation of meta-analyses of EE is a widely discussed topic mainly due to the low generalisability among health

[61] Shemilt I, Thomas J, Morciano M. A web-based tool for adjusting costs to a specific target currency and price year. Evidence & Policy. 2010;6(1):51-9.

systems[53,62]. Therefore, we synthesized the results through the permutation matrix proposed by Nixon *et al.*[63]. The matrix shows the nine possible outcomes in terms of costs and effectiveness and the shading indicates if the decision is strongly or less favoured or if there is no obvious decision. Studies were represented in the matrix depending on the ICER point estimates. We added a symbol system to indicate the quality of each study when represented in the permutation matrix ([+]: low quality, [++]: medium quality and [+++]: high quality).

The protocol of the systematic review was registered in PROSPERO (registration number: CRD42016032540) where a detailed protocol of the review can be found.

[62] Anderson R. Systematic reviews of economic evaluations: utility or futility? Health Econ. 2010;19(3):350-64.
[63] Nixon J, Khan KS, Kleijnen J. Summarising economic evaluations in systematic reviews: a new approach. BMJ. 2001;322(7302):1596-8.

1.3 Results

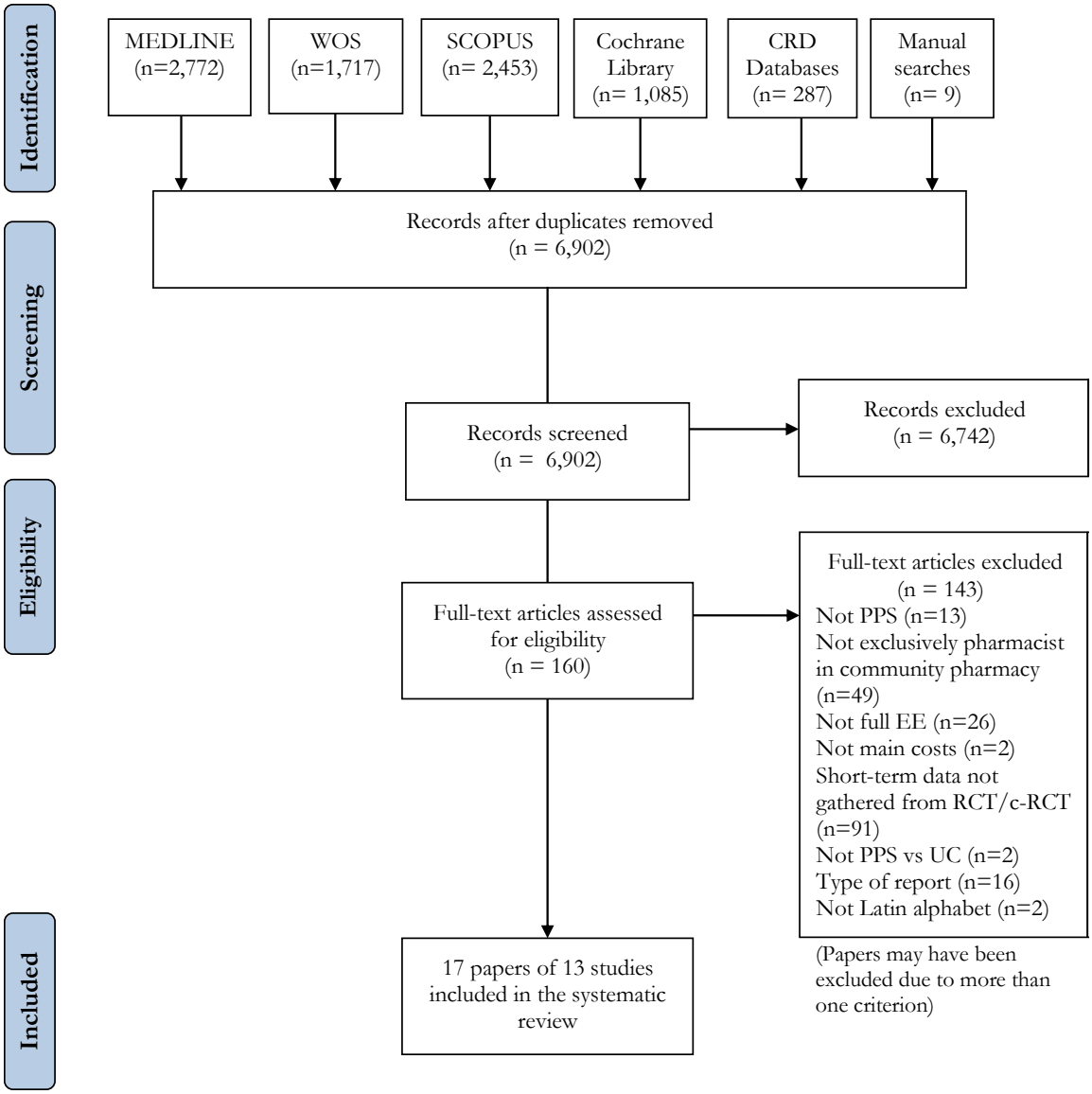
1.3.1 Study selection

8,314 potential papers were identified through different databases and nine through manual searches. After deleting duplicities, 6,902 papers were screened using the title and abstract. The 160 papers that met the inclusion criteria were assessed in full-text for eligibility. The main exclusion reasons were the setting and the study design. Seventeen EE[38,40,46,64,65,66,67,68,69,70,71,72,73,74,75,76,77] corresponding to 13 studies were included

[64] Bernsten C, Bjorkman I, Caramona M, Crealey G, Frokjaer B, Grundberger E, et al. Improving the well-being of elderly patients via community pharmacy-based provision of pharmaceutical care: a multicentre study in seven European countries. Drugs Aging. 2001;18(1):63-77.
[65] Bond CM, Fish A, Porteous TH, Reid JP, Scott A, Antonazzo E. A randomised controlled trial of the effects of note-based medication review by community pharmacists on prescribing of cardiovascular drugs in general practice. Int J Pharm Pract. 2007;15(1):39-46.
[66] Bosmans JE, Brook OH, van Hout HP, de Bruijne MC, Nieuwenhuyse H, Bouter LM, et al. Cost effectiveness of a pharmacy-based coaching programme to improve adherence to antidepressants. Pharmacoeconomics. 2007;25(1):25-37.
[67] 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.
[68] Jodar-Sanchez F, Malet-Larrea A, Martin JJ, Garcia-Mochon L, Lopez Del Amo MP, Martinez-Martinez F, 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.
[69] Krass I, Armour C, Taylor S, Mitchell B, Brillant M, Stewart K et al. Pharmacy Diabetes Care Program. Final Report. The University of Sydney. Australia, 2005. Available from: http://6cpa.com.au/wp-content/uploads/Pharmacy-Diabetes-Care-Program-final-report.pdf. [Accessed April 18, 2016].
[70] McLean W, Gillis J, Waller R. The BC Community Pharmacy Asthma Study: A study of clinical, economic and holistic outcomes influenced by an asthma care protocol provided by specially trained community pharmacists in British Columbia. Can Respir J. 2003;10(4):195-202.

since the economic analysis of the MEDMAN study[67,72], the conSIGUE Program[46,68], the PHARMACOP-intervention[76,77] and a multicentre study carried out in seven European countries[64,74] were published in two different papers (Figure 2).

[71] Rubio-Valera M, Bosmans J, Fernandez A, Penarrubia-Maria M, March M, Trave P, et al. Cost-effectiveness of a community pharmacist intervention in patients with depression: a randomized controlled trial (PRODEFAR Study). PLoS One. 2013;8(8):e70588.
[72] Scott A, Tinelli M, Bond C, Community Pharmacy Medicines Management Evaluation Team. Costs of a community pharmacist-led medicines management service for patients with coronary heart disease in England: healthcare system and patient perspectives. Pharmacoeconomics. 2007;25(5):397-411.
[73] Simpson SH, Johnson JA, Tsuyuki RT. Economic impact of community pharmacist intervention in cholesterol risk management: an evaluation of the study of cardiovascular risk intervention by pharmacists. Pharmacotherapy. 2001;21(5):627-35.
[74] Sturgess IK, McElnay JC, Hughes CM, Crealey G. Community pharmacy based provision of pharmaceutical care to older patients. Pharm World Sci. 2003;25(5):218-26.
[75] RESPECT Trial Team. Cost-effectiveness of shared pharmaceutical care for older patients: RESPECT trial findings. Br J Gen Pract. 2010;60(570):e20-7.
[76] van Boven JF, Tommelein E, Boussery K, Mehuys E, Vegter GS, Brusselle GG, et al. Optimalisation de la pharmacothérapie en pharmacie d'officine chez des patients atteints de Bronchopneumopathie Chronique Obstructive (BPCO): une analyse coût-efficacité. J Pharm Belg. 2014;96(3):15-6.
[77] van Boven JF, Tommelein E, Boussery K, Mehuys E, Vegter S, Brusselle GG, et al. Improving inhaler adherence in patients with chronic obstructive pulmonary disease: a cost-effectiveness analysis. Respir Res. 2014;15:66.



WOS: Web of Science; CRD: Centre for Reviews and Dissemination databases; PPS: professional pharmacy service; EE: economic evaluation; RCT/c-RCT: randomized controlled trial/cluster randomized controlled trial; UC: usual care.

Figure 2: Flow diagram of the search, screening, excluded and included articles

1.3.2 Characteristics of individual studies

Thirteen individual studies were included in the systematic review (Table 2). Nine (69%) studies were conducted in Europe, two in North America (Canada) and two in Australia. Publication years range from 2001 to 2015. Seven (54%) of the EE were based on a RCT, four (31%) in a c-RCT, one was a combination of c-RCT and RCT and one a randomised multiple interrupted time-series. This study was included since it compares groups randomised by clusters and therefore shares the main characteristics of c-RCTs. The follow-up period was one year or longer for five of the studies (38%), and less than one year in the remaining eight studies (62%). The time horizons of the EE were the same as the randomised controlled trial follow-up length except for three studies extrapolating beyond these periods by modelling techniques[40,69,77].

Table 2: Characteristics and results of the studies

Author	Title, year, country	Study design, sample size	Intervention and control group description	Follow-up and time horizon	Clinical and humanistic outcomes assessed	Cost data reported	Cost and consequence (USD, 2015)
Compliance, Adherence and/or Concordance							
Bosmans *et al*[36]	Cost effectiveness of a pharmacy-based coaching programme to improve adherence to antidepressants, 2007. The Netherlands	RCT 151 patients (IG: 70; CG: 81)	IG: 1st visit: pharmacists gave information about the use of antidepressants (verbal, written, video). Two additional visits to stimulate adherence and evaluate safety and effectiveness of the treatment. CG: UC	Study follow-up: 6 months EE time horizon: 6 months	Clinical outcomes: **Adherence**: IG: 88%, CG: 86%; (p>0.05). Diff. between groups in **depressive symptoms**: -0.15; p>0.05). Humanistic outcomes: NA	Currency, year: €, 2002 Perspective: Societal Included costs: **Direct medical costs**: intervention and UC, primary and secondary care, medication, alternative therapies, company doctor. **Indirect costs**: productivity losses Total cost per patient: IG: €3,275 ($4,616); CG: €2,961 ($4,173); (p>0.05).	Type of EE: CEA Incremental analysis: €149 ($210)/1% improvement in adherence €2,550 ($3,594)/point improvement in the SCL depression mean item score
Elliott *et al* [38]	The cost effectiveness of a telephone-based pharmacy advisory service to improve adherence to newly prescribed medicines, 2008.	RCT 492 patients (IG: 255; CG: 237)	IG: Pharmacists made a semi structured interview by phone, enquiring about medicine related problems and adherence to the new medicine. CG: UC	Study follow-up: 2 months EE time horizon: 2 months	Clinical outcomes: **Non-adherence**: IG: 10/87, 11%. CG: 23/118, 19% (p<0.05) Humanistic outcomes: NA	Currency, year: £, 2004/2005 Perspective: Healthcare system Included costs: **Direct medical costs**: intervention (time of pharmacists, call tariff), GP and ED visits, outpatient, hospitalisations. Total cost per patient: IG:	Type of EE: CEA Incremental analysis: The intervention is dominant (cost/extra adherent patient)

Author	Title, year, country	Study design, sample size	Intervention and control group description	Follow-up and time horizon	Clinical and humanistic outcomes assessed	Cost data reported	Cost and consequence (USD, 2015)
	United Kingdom					£188 ($347); CG: £283 ($523); (p<0.05).	
Rubio-Valera *et al* [71]	Cost-Effectiveness of a Community Pharmacist Intervention in Patients with Depression: A Randomized Controlled Trial (PRODEFAR Study), 2013. Spain	RCT 179 patients (IG: 87; CG: 92)	IG: Intervention when patients picked up their first prescription of antidepressants, + reminder when refilling prescriptions. Focused on antidepressants, compliance, side-effects and carrying out GPs' advice. CG: UC	Study follow-up: 6 months EE time horizon: 6 months	Clinical outcomes: Diff. between groups in **adherence:** 0.04 (p>0.05), **severity of depression:** -0.01 (p>0.05). Humanistic outcomes: Diff. between groups in **QALY: 0.01** (p>0.05) (EQ-5D).	Currency, year: €, 2009 Perspective: Societal and healthcare system Included costs: **Direct medical costs**: intervention (training of pharmacists, pharmacy time), medication, diagnostic tests, ED visits, hospital admissions, other visits to primary and secondary care. **Indirect costs**: sick leave (only in societal perspective). Total cost per patient: IG: €1,091 ($1,547); CG: €767 ($1,088); (p>0.05).	Type of EE: CEA and CUA Incremental analysis: **Societal perspective**: €1,866 ($2,647)/adherent patient €9,872 ($14,002)/QALY **Healthcare perspective**: €962 ($1,364)/adherent patient €3,592 ($5,095)/QALY *Cost/depressive symptoms: UC dominated the intervention.

Author	Title, year, country	Study design, sample size	Intervention and control group description	Follow-up and time horizon	Clinical and humanistic outcomes assessed	Cost data reported	Cost and consequence (USD, 2015)
van Boven *et al* [77]	Improving inhaler adherence in patients with Chronic Obstructive Pulmonary Disease: a cost-effectiveness analysis, 2014. Belgium	RCT 734 patient (IG: 371; CG: 363)	IG: Visit 1: structured education about COPD pathophysiology, medication, self-management and smoking cessation (written+verbal). Visit 2: verbal reminder of the education provided in visit 1. CG: UC	Study follow-up: 3 months EE time horizon: 12 months	Clinical outcomes: **Hospital-treated exacerbation**: IG: 0.177/patient; CG: 0.244/patient ($p<0.05$). Humanistic outcomes: Diff. between groups in **QALY** less than 0.001 ($p>0.05$) (EQ-5D).	Currency, year: €, 2013 Perspective: Healthcare system Included costs: **Direct medical costs**: intervention (training and pharmacy time), medication, community/ED/hospital treated exacerbation. Total cost per patient: IG: €2,221 ($2538); CG: €2,448 ($2,797); ($p<0.05$).	Type of EE: CUA and CEA Incremental analysis: The intervention is dominant (Cost/QALY and cost/hospital treated exacerbations avoided)
Medication Therapy Management services							
Bernsten *et al* [64]	Improving the well-being of elderly patients via community pharmacy-based provision of pharmaceutical care: a multicentre study in seven European countries, 2001. Denmark,	c-RCT 190 pharmacies (IG: 104; CG: 86) 2,454 patients (IG: 1290; CG: 1164)	IG: Pharmacists identified drug-related problems and formulated an intervention + monitoring plan. Education on drug regimen and medical conditions, compliance-improving	Study follow-up: 18 months EE time horizon: cost data given for 3 periods of 6 months	Clinical outcomes: **Hospitalisations**: IG: 35.6% of patients and CG: 40.4% reported one or more hospitalisations ($p>0.05$). **Clinical Signs and Symptom Control**: better control within IG (diff. between groups not given). **Knowledge of medicines, compliance,**	Currency, year: €, 1999 Perspective: Healthcare system (not given in the paper) Included costs: **Direct medical costs**: intervention (pharmacy time), medication, hospitalisations, GP/specialists/nurse visits. Total cost per patient:	Type of EE: Cost-consequence analysis. Incremental analysis: NA (no differences in effectiveness were assumed)

Author	Title, year, country	Study design, sample size	Intervention and control group description	Follow-up and time horizon	Clinical and humanistic outcomes assessed	Cost data reported	Cost and consequence (USD, 2015)
	Germany, The Netherlands, Northern Ireland, Portugal, Republic of Ireland and Sweden		strategies and rationalising drug regimens (with GP). Continuous visits. CG: UC		**contacts with GP, drug use and number of changes in therapy**: overall, p>0.05 between groups. Humanistic outcomes: **Health-related quality of life**: no differences between groups (p<0.05) (SF-36). **Patient satisfaction**: some indicators higher in IG.	IG: €19,212 ($40,054); CG: € 21,480 ($44,782) (estimated by reviewers).	
Bojke *et al* [75]	Cost-effectiveness of shared pharmaceutical care for older patients: RESPECT trial findings, 2010. United Kingdom	Randomised multiple interrupted time-series Patients: 760 5 primary care trusts	IG: Medication review focused on appropriate prescription and use. Collaboration among pharmacist, patient and GP. Drug related problems are resolved through continuous	Study follow-up: 12 months EE time horizon: 12 months	Clinical outcomes: NA Humanistic outcomes: **Utility scores**: Highest scores obtained in intervention months; IG: 0.614; CG: 0.595; p>0.05) (EQ-5D).	Currency, year: £, 2004-2005 Perspective: Healthcare system Included costs: **Direct medical costs**: Intervention (pharmacy time), medications (acute+ repeat), laboratory tests, visits to the general practice/ primary care clinic/home visits and telephone consultations (GP/nurse), outpatient and inpatient admissions.	Type of EE: CUA Incremental analysis: £10,000 ($18,507)/QALY

Author	Title, year, country	Study design, sample size	Intervention and control group description	Follow-up and time horizon	Clinical and humanistic outcomes assessed	Cost data reported	Cost and consequence (USD, 2015)
			visits. CG: UC			Total cost per patient: IG: £2,001 ($3,703); CG: £1,809 ($3,348); (p>0.05).	
Bond *et al* a [67]	The MEDMAN study: a randomized controlled trial of community pharmacy-led medicines management for patients with coronary heart disease, 2007. United Kingdom	RCT 1493 patients (IG: 980; CG: 513)	IG: Initial consultation + follow-up visits. Consultations included assessments of therapy, medication compliance, lifestyle and social support. Recommendations sent to GP. CG: UC	Study follow-up: 12 months EE time horizon: 12 months	Clinical outcomes: **Proportion of patients receiving secondary prevention treatment for CHD/ cumulative score summarizing 'appropriate treatment' and advice/adherence**: no differences between groups. **5-year risk of CV death**: slightly better IG (p>0.05). Humanistic outcomes: **SF-36 and EQ-5D scores**: no differences between groups. **Patient satisfaction**: IG: 46.0; CG: 43.0; (p<0.01).	Currency, year: £, 2003/2004 Perspective: Healthcare system (and patient) Included costs: **Direct medical costs:** Intervention (training of pharmacists, pharmacy time), medicines, CHD related hospital visits/GP visits/ nurse visits. Total cost per patient: IG: £1,433 ($2,704); CG: £1,286 ($2,426); (p<0.05).	Type of EE: CMA Incremental analysis: NA
Bond *et al* b [65]	A randomised controlled trial of the effects of note-based medication review	RCT 2014 patients (Angina group: IG:	IG: Pharmacists conducted a single review of the	Study follow-up: 12 months EE time horizon:	Clinical outcomes: **Quality of prescribing/appropriateness of medication**: more IG patients were	Currency, year: £, 1999 Perspective: Healthcare system (not given) Included costs:	Type of EE: Cost-consequence analysis. Incremental

Author	Title, year, country	Study design, sample size	Intervention and control group description	Follow-up and time horizon	Clinical and humanistic outcomes assessed	Cost data reported	Cost and consequence (USD, 2015)
	by community pharmacists on prescribing of cardiovascular drugs in general practice, 2007. United Kingdom	340, CG: 366. Hypertension group: IG: 656, CG: 652).	patient's medical records, and recommended changes to GP. CG: UC	12 months (not given)	ordering antiplatelet drugs after the intervention (diff. between groups = 7.6% ($p<0.05$). *For angina patients only:* More patients in CG made fewer visits to an **outpatient department for CVD-related reasons** and to **GP surgery for CVD-related reasons**. More patients in IG received fewer **home visits for CVD-related reasons**. Humanistic outcomes: **EQ-5D scores**: no differences between groups.	**Direct medical costs**: intervention (pharmacy time), hospital admissions, home visits, outpatient/surgery attendance, tests, prescribing costs. Total cost per patient: IG: £230 ($480); CG: £187 ($390) (estimated by reviewers)	analysis: £4.8 ($10)/ patient with history of myocardial infarction ordering an antiplatelet (estimated by reviewers)
Jódar-Sánchez *et al* [68]	Cost-Utility Analysis of a Medication Review with Follow-Up Service for Older Adults with Polypharmacy	c-RCT 1403 patients (IG: 688; CG: 715) 178 pharmacies (IG: 88; CG: 90)	IG: comprehensive medication review in which the pharmacist identifies drug related problems and	Study follow-up: 6 months EE time horizon: 6 months	Clinical outcomes: **Number of medicines**: greater reduction in IG (diff. between groups: 0.21; $p>0.05$). **ED visits**: reductions in IG (before-after: $p<0.05$). **Number of hospital**	Currency, year: €, 2014 Perspective: Healthcare system Included costs: **Direct medical costs**: Intervention (pharmacy time, training of pharmacists, investment of the community pharmacy),	Type of EE: CUA Incremental analysis: The intervention is dominant (Cost/QALY)

Author	Title, year, country	Study design, sample size	Intervention and control group description	Follow-up and time horizon	Clinical and humanistic outcomes assessed	Cost data reported	Cost and consequence (USD, 2015)
	in Community Pharmacies in Spain: The conSIGUE Program, 2015. Spain		agrees an action plan with patient and GP if required. Continuous visits. CG: UC		**admissions**: IG: 0.03; CG: 0.06 ($p<0.05$). Humanistic outcomes: significant improvement in IG compared to CG (diff. between groups: 0.055 in **utility score** ($p<0.05$) and 5.87 in **VAS score** ($p<0.05$) (EQ-5D).	medication, ED visits, medication-related hospital admissions. Total cost per patient: IG: €978 ($1,364); CG: €1,173 ($1,638) ($p>0.05$).	
Disease State Management for Chronic Conditions services							
Gordois *et al* [40]	Cost-Effectiveness Analysis of a Pharmacy Asthma Care Program in Australia, 2007. Australia	c-RCT 396 patients (IG: 191; CG: 205) 57 pharmacies (IG: 29; CG: 28)	IG: Education on asthma, medication, lifestyle, inhaler technique, adherence and detection of drug-related problems. Referral to a GP as appropriate. Continuous visits. CG: UC	Study follow-up: 6 months EE time horizon: 5 years	Clinical outcomes: **Healthcare use resources**: No differences between groups ($p>0.05$). Humanistic outcomes: Six month study: 0.008 **QALY**/patient gained in IG. When modelling to 5 years, 0.131 QALYs are gained in IG compared to CG ($p>0.05$ mild and moderate asthma; $p<0.05$ severe asthma) (AQoL questionnaire).	Currency, year: AUD, 2006 Perspective: Healthcare system Included costs: **Direct medical costs**: intervention (pharmacy time, spirometers and consumables, software, promotional material, training resources), asthma medication, GP/ED visits, hospital admissions. Total cost per patient: Annual review scenario: IG: AUD 2,136 ($1,760); CG: AUD 1,514 ($1,248).	Type of EE: CUA Incremental analysis: Annual review scenario: AUD 4,753 ($3,918)/QALY No annual review scenario: AUD 2,869 ($2,365)/QALY

Author	Title, year, country	Study design, sample size	Intervention and control group description	Follow-up and time horizon	Clinical and humanistic outcomes assessed	Cost data reported	Cost and consequence (USD, 2015)
						No annual review scenario: IG: AUD 1,890 ($1,557); CG: AUD 1,514 ($1,248).	
Krass *et al* [69]	Pharmacy Diabetes Care Program. Final Report, 2005. Australia	c-RCT 335 patients (IG: 176; CG: 159) 58 pharmacies	IG: Pharmacists recorded patients' information and provided targeted counselling. Topics: lifestyle, blood glucose monitoring, adherence, reminders of follow-up checks for complications related to diabetes medicines. Continuous visits. CG: UC	Study follow-up: 6 months EE time horizon: 10 years	Clinical outcomes: **HbA1c:** IG: -0.97%; CG: -0.27%; p<0.05). **Blood pressure**: systolic decreased within IG (p<0.01). **Lipid profile and BMI**: no differences between groups (p>0.05). Humanistic outcomes: **Utility scores:** improvement from 0.75 to 0.79 within IG (p>0.05). CG: no changes (data at 6 months) (EQ-5D).	Currency, year: AUD, 2004 Perspective: Healthcare system Included costs: **Direct medical costs**: intervention (counter display unit, blood pressure monitor + software, pharmacists' fees, printouts, telephone calls), medication, GP, hospitalisations. Total cost per patient: IG: AUD 10,512 ($9,499); CG: AUD 7,148 (6,459); (p<0.05).	Type of EE: CUA and CEA Incremental analysis: Scenario A (0.35% HbA1c reduction) AUD 24,029 ($21,714) /LYG AUD 30,582 ($27,636) /QALY Scenario B (0.70% HbA1c reduction): AUD 17,752 ($16,042)/LYG AUD 22,486 ($20,320) /QALY
McLean *et al* [70]	The BC Community Pharmacy Asthma Study: A study of clinical,	Combination of a RCT and c-RCT 405 patients	IG: Teaching of asthma self-management: disease, medications, trigger identification and	Study follow-up: 12 months EE time horizon: 12 months	Clinical outcomes: **Peak expiratory flow rate/ Symptoms**: better results in IG than CG (p<0.05). **Medical visits**:	Currency, year: CAD, 1998 (not given) Perspective: Societal (not given) Included costs: **Direct medical costs**:	Type of EE: Cost-consequence analysis. Incremental analysis:

Author	Title, year, country	Study design, sample size	Intervention and control group description	Follow-up and time horizon	Clinical and humanistic outcomes assessed	Cost data reported	Cost and consequence (USD, 2015)
	economic and holistic outcomes influenced by an asthma care protocol provided by specially trained community pharmacists in British Columbia, 2003. Canada	(IG: 191; CG: 214) 27 pharmacies	avoidance. Development of asthma action plan. A comprehensive first visit + follow-up visits. CG: UC	(not given)	decrease in IG and increase in CG ($p<0.05$). **School or work days off, ED visits and hospitalisations**: no differences between groups. **Drug utilization**: significant drop in beta-agonist use in IG, no changes in corticosteroids. Humanistic outcomes: **QoL** (Juniper questionnaire) **/Knowledge**: greater increase in IG ($p<0.01$).	intervention (pharmacist fees), medical visits, ED visits, hospitalisations, prescription drugs. **Indirect costs**: days off from school or work Total cost per patient: IG: CAD 150 ($179); CG: CAD 351 ($418)	The intervention is dominant (Cost/peak expiratory flow rate (L/min), estimated by reviewers)
Simpson *et al* [73]	Economic Impact of Community Pharmacist Intervention in Cholesterol Risk Management: An Evaluation of the Study of Cardiovascular	RCT 675 patients (IG: 344; CG: 331)	IG: Screening and identification of CVD risk factors, individualised education on risk factor management (verbal + written), referral GPs. Continuous visits. CG: UC	Study follow-up: 4 months EE time horizon: 4 months	Clinical outcomes: **Number of cholesterol tests**: IG: 182 and CG: 96. **Number of cholesterol-lowering drugs**: IG: 34 and CG: 14. Humanistic outcomes: NA	Currency, year: CAD, 1999 Perspective: Provincial government (and community pharmacy managers) Included costs: **Direct medical costs**: intervention, physician visits, cholesterol-lowering	Type of EE: Cost-consequence analysis. Incremental analysis: CAD 1.4 ($1.6)/new prescription of cholesterol-

Author	Title, year, country	Study design, sample size	Intervention and control group description	Follow-up and time horizon	Clinical and humanistic outcomes assessed	Cost data reported	Cost and consequence (USD, 2015)
	Risk Intervention by Pharmacists, 2001. Canada					medication, cholesterol profile tests, liver function test, ED visits. Total cost per patient: IG: CAD 56 ($66); CG: CAD 28 ($33) (estimated by reviewers)	lowering drugs (estimated by reviewers)

RCT: randomised controlled trial; c-RCT: cluster randomised controlled trial; ED visits: emergency department visits; EQ-5D: EuroQoL-5D; GP visits: general practitioner visits; EE: economic evaluation; CEA: cost-effectiveness analysis; CUA: cost-utility analysis; CMA: cost-minimisation analysis; QALY: quality adjusted life years; LYG: life years gained; IG: intervention group; CG: comparison group; UC: usual care; NA: not applicable; BMI: body mass index; CV(D): cardiovascular (disease); HbA1c: glycated haemoglobin; VAS: visual analogue scale; CAD: Canadian dollars; AUD: Australian dollars; USD: United States dollars.

1.3.3 Professional pharmacy services

The service was always provided during a face to face interaction in the pharmacy, with the exception of one telephone-based study[38]. Nine (69%) of the studies were focused on patients with a single disease such as depression[66,71], type 2 diabetes[69], respiratory conditions[40,70,77] and cardiovascular diseases[65,67,73]. Other services were targeted at elderly using polypharmacy[64,68,75] and patients with one or more chronic conditions[38].

All the studies were classified in three of the nine categories considered in the hierarchical model. "Compliance, Adherence and/or Concordance" interventions were provided in four (31%) of the studies[38,66,71,77]. All of them where delivered to patients with a newly prescribed medication. Five (38%) studies assessed "medication therapy management services"[64,65,67,68,75]. Four of them were medication review with follow-up services[64,67,68,75] and the fifth service provided did not have follow-up[65]. Four (31%) services were "Disease state management for chronic conditions"[40,69,70,73]. Gordois *et al*[40] and Krass *et al*[69] assessed very similar services, provided in the same country (Australia), with a similar study design and economic evaluation. The most important characteristics of the services are described in Table 2.

1.3.4 Details of economic evaluations

The perspective was stated in ten (77%) of the studies and it was identifiable using the costs included in the remaining studies[64,65,70]. Nine (69%) of the evaluations were performed from the healthcare system perspective, two from the societal, one from the government and one from both the societal and the healthcare system (Table 2).

Some studies did not include potentially important cost components such as the cost of pharmacists' training[40,64,65,75] or general practitioner (GP) visits[68]. Additionally, a wide range of direct medical cost components were self-reported. In some studies all the costs were self-reported by patients[69,70,80], whereas in other studies some costs were self-reported by patients and some costs were extracted from the pharmacy and medical or hospital records[64,67,68,71,73,77]. Other studies did not clearly state how they retrieved this information[40,65,66]. The sources used for the cost valuation in all the studies were mainly official data of the country where the study was undertaken.

An incremental analysis was performed in nine (69%) studies: three studies performed a cost-utility analysis (CUA)[40,68,75], two studies performed a CEA[38,66] , three studies performed both CUA and CEA[69,71,77] and one study reported a cost-minimisation analysis (CMA)[67]. All of them used outcome

indicators to calculate ICERs. The remaining four studies were presented as cost-consequence analysis, and we estimated the incremental analyses. Outcome indicators were available in two studies[65,70] and only process indicators in the remaining one[73]. We decided not to calculate an incremental analysis in the study published by Bernsten *et al*[64] due to the lack of statistically significant difference in effectiveness between study groups. The clinical significance of some indicators was higher than others (i.e. "extra adherent patient"[38,71] vs. "1% improvement in adherence"[66]).

1.3.5 Risk of bias and quality of economic evaluations

The overall quality assessment yielded seven studies of high, three of medium and three of low quality (Table 3). According to the study design, the evidence level provided by all the studies was high (RCT/c-RCT). Seven studies had low risk of bias[40,67,68,69,71,75,77], whereas two studies had high risk of bias[65,70]. The most frequent high risk of bias was the risk of contamination bias among RCTs and the lack of reporting baseline characteristics of control and intervention providers among c-RCTs. The risks of bias related to the randomisation (allocation sequence and concealment) were low in all the studies.

The methodological quality of the EE assessed by Evers' checklist applied to all the EE, ranged from 39%[73] to 95%[77] with a mean score of 73%. The item "Are all future costs and outcomes discounted appropriately?" was not applicable to several studies as the time horizon did not exceed one year. None of the studies fulfilled the item "Are ethical and distributional issues discussed appropriately?" The methodological quality of the three decision analytic models[40,69,77] according to Philips' list was 87% in average. The EE carried out by van Boven *et al*[77] scored the highest punctuations in both Evers' and Philips' assessment tools.

Table 3: Quality assessment of the studies

Study	Risk of bias[a]		Quality of the EE[b]			Overall quality[c]
			Evers	Philips		
Bojke *et al* [75]	Low risk: 7 High risk: 1 Unclear risk: 1	High	15/18 = 83%	NA	High	High
Bond *et al* a [67]	Low risk: 8 High risk: 1 Unclear risk: 0	High	14/18 = 78%	NA	High	High
Gordois *et al* [40]	Low risk: 7 High risk: 1 Unclear risk: 1	High	16/19 = 84%	41/48 = 85%	High	High
Jodar-Sanchez *et al* [68]	Low risk: 7 High risk: 1 Unclear risk: 1	High	15/18 = 83%	NA	High	High
Krass *et al* [69]	Low risk: 7 High risk: 0 Unclear risk: 2	High	15/19 = 79%	38/47 = 80%	High	High
Rubio-Valera *et al* [71]	Low risk: 7 High risk: 2 Unclear risk: 0	High	16/18 = 89%	NA	High	High
van Boven *et al* [77]	Low risk: 6 High risk: 2 Unclear risk: 1	High	18/19 = 95%	45/47 = 96%	High	High
Bosmans *et al* [66]	Low risk: 5 High risk: 4 Unclear risk: 0	Medium	15/18 = 83%	NA	High	Medium
Bernsten *et al* [64]	Low risk: 3 High risk: 4 Unclear risk: 2	Medium	10/18 = 55%	NA	Medium	Medium
Elliott *et al* [38]	Low risk: 4 High risk: 2 Unclear risk: 3	Medium	13/18 = 72%	NA	Medium	Medium
McLean *et al* [70]	Low risk: 4 High risk: 5 Unclear risk: 0	Low	11/18 = 61%	NA	Medium	Low
Simpson *et al* [73]	Low risk: 3 High risk: 4 Unclear risk: 2	Medium	7/18 = 39%	NA	Low	Low
Bond *et al* b [65]	Low risk: 4 High risk: 5 Unclear risk: 0	Low	8/18 = 44%	NA	Low	Low

[a]Risk of bias: High quality: low risk ≥6; Low quality: high risk ≥ 5; Medium quality: others. [b]Quality of EE: High quality: ≥75%; Low quality: ≤50%; Medium quality: 51%-74% (Evers' checklist was used to assess all the EE, and additionally Philips' checklist in decision analytic models). [c]Overall quality: the study was classified with the lowest level of quality scored among all the assessments.

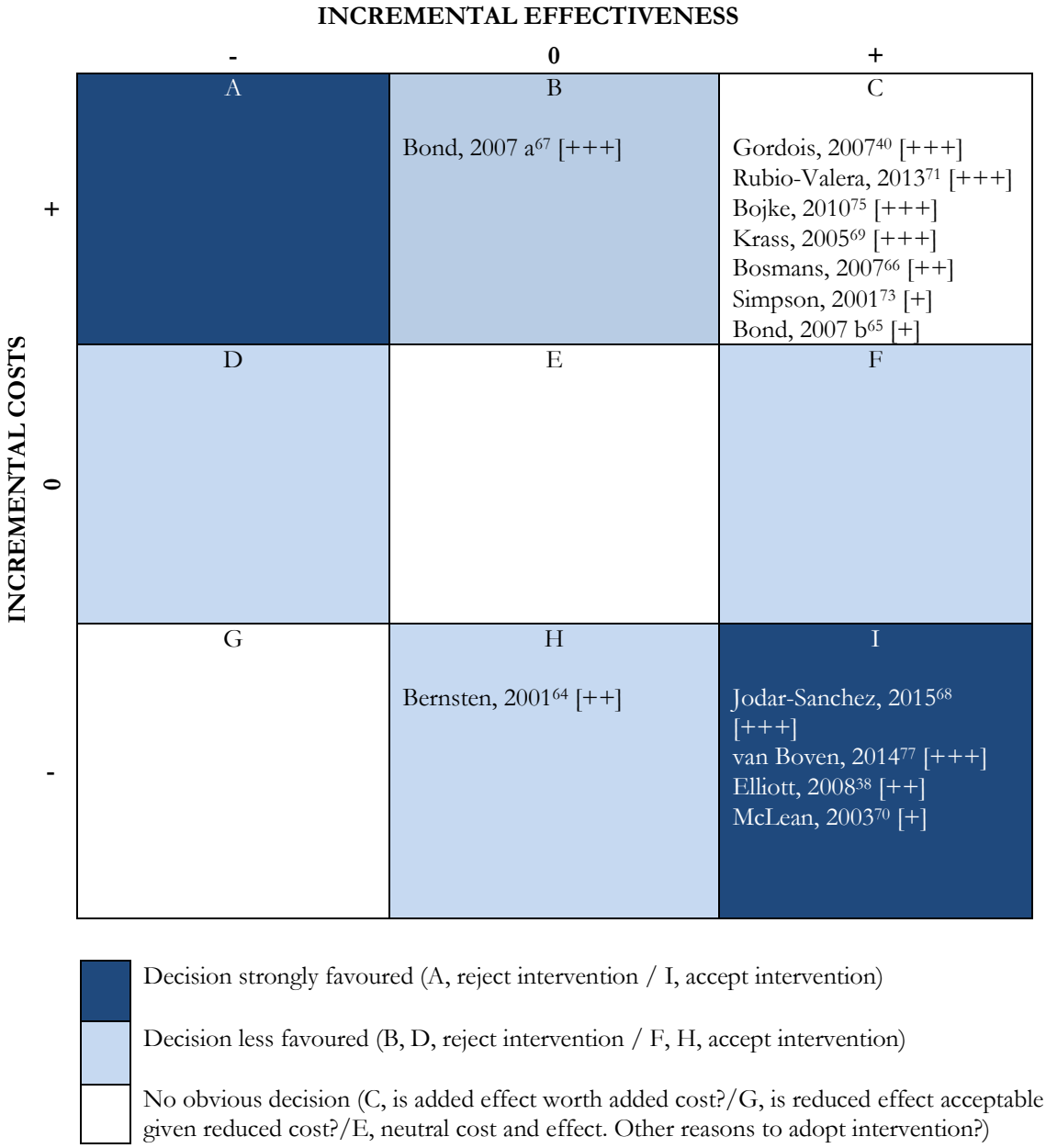
1.3.6 Cost-effectiveness of interventions

The cost-effectiveness of PPSs compared with UC is shown in the permutation matrix (Figure 3).

More effective and less costly interventions:

The intervention assessed was found to be dominant in four studies[38,68,70,77]. The permutation matrix showed that the decision of accepting these interventions was strongly favoured.

An incremental analysis was performed in three of the studies[38,68,77]. All of them found statistically significant improvements in the IG for humanistic and/or clinical outcomes, with lower associated costs. The uncertainty surrounding the ICER, represented by the cost-effectiveness plane and cost-effectiveness acceptability curves, was low. This is due to the probability for the services to be cost-effective at a willingness to pay (WTP) of $0 per unit of effectiveness was higher than 90% in the three studies. Specifically, probabilities were 96% at a WTP of €0 per QALY[68], 90% at a WTP of £0 per extra adherent patient[38], and 99.4% at a WTP of €0 per QALY[77]. The dominant situation of the intervention was retained in all the univariate, scenario and probabilistic sensitivity analyses performed by van Boven *et al*[77].



Effectiveness: +better, 0 same, - poorer; costs: + higher, 0 same, - lower. [+++]: high quality study; [++]: medium quality study; [+]: low quality study.

Figure 3: Permutation matrix summarising incremental cost and effectiveness findings of economic evaluations for professional pharmacy services in community pharmacy vs. usual care

Costs were lower in the IG, largely due to the decrease in hospitalisation costs[38,68]. The quality of the evidence provided by those studies was considered high[68,77] and medium[38]. The authors concluded that the implementation of the service was recommended or suggested[38,68,77].

McLean *et al*[70] also suggested the implementation of the service, since statistically significant improvements were found in IG compared to CG in most of the clinical and humanistic indicators at lower costs. The ICER calculated by reviewers showed savings of CAD 6.4 ($7.6) per one unit improvement in the peak expiratory flow rate (L/min).

Same effectiveness and less costly interventions:

Bernsten *et al*[64] assessed several clinical and humanistic outcomes. Statistically significant differences were not found between study groups and costs were lower in IG. Reviewers decided to assume equal effectiveness between both alternatives with less cost in IG, and we could not assess uncertainty. Although the decision of accepting or rejecting this intervention was less favoured, it should be accepted.

Same effectiveness and more costly interventions:

Bond *et al* a[67] only found statistically significant differences in the patient satisfaction. Therefore the authors presented a CMA, assuming equal effectiveness between the intervention and UC[72] and costs were significantly higher in IG. The decision of accepting or rejecting this intervention was less favoured according to the permutation matrix, but it should be rejected.

More effective and more costly interventions:

The decision of accepting or rejecting all these interventions was not obvious, and it should be considered if added effect was worth the added cost.

The two studies focused on antidepressants performed the EE from the societal perspective[66,71]. Costs were slightly higher in the IG, and the difference was driven by indirect costs. For this reason in the Rubio-Valera *et al* study[71] the ICER from the societal perspective was higher than the healthcare system perspective (societal perspective: €1,866 ($2,647) per adherent patient and €9,872 ($14,002) per QALY; healthcare system perspective: €962 ($1,364) per adherent patient and €3,592 ($5,095) per QALY). Bosmans *et al*[66] used only the societal perspective and the ICERSs

showed €149 ($210) per 1% improvement in adherence and €2,550 ($3,594) per point improvement in the Hopkins Symptom Checklist depression mean item score. Even though the point estimates of the ICERs/ICUR were not high, the implementation of the service was not recommended by the authors of both studies due to the high uncertainty evidenced by the cost-effectiveness plane and cost-effectiveness acceptability curve. In Bosmans *et al*, with a WTP of €1,000 ($1,468) the probability of the service of being cost-effective was 0.7[66] and ranged from 0.46 to 0.76 with a WTP ranging from €500 ($755) to €30,000 ($45,302) under the different scenarios considered by Rubio-Valera *et al*[71].

Two studies modelled the short-term outcomes achieved in the trials to a time horizon of five years through a Markov model[40] and to 10 years through a similar model[69]. Krass *et al*[69] found significant reductions in glycated haemoglobin (HbA1C) in the IG compared to CG but not in utility scores. ICERs and ICURs were presented for two scenarios, depending on the reduction of the HbA1C. Results ranged from AUD 17,752 ($16,042) per life years gained (LYG) to AUD 30,582 ($27,636) per QALY, with chances of being cost-effective ranging from 71% to 93% with a WTP of AUD 50,000 ($47,310). The service was cost-effective in almost all the scenarios studied in the one-way sensitivity analysis. The authors concluded that the intervention

was cost-effective compared with other healthcare programs that were routinely funded by the Commonwealth (interventions below AUD 37,000 ($35,009) to AUD 69,000 ($65,287) per life year).

Gordois *et al*[40] found that utility scores were significantly higher for patients with severe asthma in the IG compared with the CG. ICURs were calculated for two scenarios (with/without annual review to maintain the improvements in asthma) and ranged between AUD 4,753 ($3,918) per QALY and AUD 2,869 ($2,365) per QALY. The ICUR for the 6-month study was AUD 64,870 ($53,471) per QALY. The one-way sensitivity analysis showed that the cost-effectiveness of the program was sensitive to the time horizon and proportion of patients with severe asthma, and best-worst scenario that it could range from AUD 576 ($497) to AUD 7,189 ($6,198). Authors conclude that the service was cost-effective, and potentially implementable in the Australian healthcare system.

In the EE published by Bojke *et al*[75], the mean utility scores were higher during the intervention (IG: 0.614; CG: 0.595; p>0.05). A wide number of health service use costs extracted from GP records were included in the analysis. The ICUR was considered cost-effective by the authors, based on the thresholds of the National Institute for Health and Clinical Excellence (NICE) (ICUR: £10,000 ($18,507) per QALY; NICE thresholds: £20,000

($35,616) - £30,000 ($53,424) per QALY[78]). For these thresholds, the probability for the service being cost-effective was 0.775 and 0.812 respectively.

Simpson *et al*[73] and Bond *et al* b[65] had low scores in quality assessment. As they were cost-consequence analysis, we estimated the ICER using the intermediate outcomes reported, and the uncertainty was unknown. The ICER of Simpson *et al* was CAD 1.4 ($1.6) per new prescription of cholesterol-lowering drugs. The authors suggested that the reimbursement to pharmacies for providing this service would be justified. Bond *et al* b measured the quality of prescribing by the appropriateness of medication, and it showed significant improvements in the IG group compared to UC. Using this indicator the ICER turned out to be £4.8 ($10) per patient with history of myocardial infarction using an antiplatelet. The authors concluded that the improvements achieved by the intervention were limited, probably due to the characteristics of the service, the study being underpowered, or due to potential contamination bias as other projects with similar aims were being conducted in the same time.

[78] National Institute for Health and Clinical Excellence. Guide to the methods of technology appraisal. London: NICE, 2008.

1.4 Discussion

Thirteen studies were identified and seven were high quality EE based on c-RCT with low risk of bias. Two high quality studies provided evidence that PPSs delivered in community pharmacy can dominate UC, improving patients' clinical outcomes and health-related quality of life, while saving costs to the healthcare system. Four high quality studies suggested, with higher uncertainty, that PPSs could improve patients' outcomes with financial investment. The remaining high quality study assumed equal effectiveness between the PPS and UC, with the PPS as the most costly alternative. Results reported by studies with lower quality and subsequently less reliable information were mainly spread between the services being more effective at either higher or lower costs. Therefore, even though different outcomes were found among studies, an overall trend towards the cost-effectiveness of PPSs in community pharmacy could be observed.

The intervention was cost-effective in those studies in which the authors compared their ICURs with a specific cost-utility threshold[40,68,69,75]. A gross analysis without considering the quality of the studies and the uncertainty and reliability of the incremental analyses, showed that using the

arbitrary but commonly used figure of $50,000 per QALY[79], all six ICURs were far below the threshold: less than $0 in two of the studies[68,77], $2,365-$3,918[40], $18,507[75], $5,095-$14,002[71] and $27,636[69]. In those studies where the effectiveness of both alternatives was assumed to be equal, the intervention turned out to be either more costly[67] or less costly[64]. The remaining five ICERs were calculated using different and therefore incomparable variables; however two of them showed savings per one unit of improvement in effectiveness[38,70] and the maximum investment needed was $3,594 for improving one effectiveness unit in the remaining three[65,66,73].

Similar trends have been found in other recent systematic reviews of pharmacists providing PPSs in different settings, where services were generally considered cost-effective and cost saving[41,52]. Another review[80] concluded that the poor quality of the studies precluded from finding the cost-effectiveness of pharmacists interventions. However, the authors rigidly imposed CHEERS guidelines to assess the methodological quality of the studies, when CHEERS guidelines were developed to examine the quality of

[79] Grosse SD. Assessing cost-effectiveness in healthcare: history of the $50,000 per QALY threshold. Expert Rev Pharmacoecon Outcomes Res. 2008;8(2):165-78.
[80] Elliott RA, Putman K, Davies J, Annemans L. A review of the methodological challenges in assessing the cost effectiveness of pharmacist interventions. PharmacoEconomics 2014;32:1185-99.

reporting but not the methodological quality of the studies[81]. From our perspective, the low number of full EE based on RCT/c-RCT makes it difficult drawing firm conclusions about the cost-effectiveness of PPSs in community pharmacy; however it does not preclude from observing a trend towards the cost-effectiveness of this technology.

Due to the important concerns about the validity of pooled values of EE of different types of EE, costs and healthcare systems[53,62,82], the aim of the systematic review was not necessarily to establish a numeric incremental cost-effectiveness ratio for the PPS compared with the UC. The aim was to perform a mapping of the available evidence to ascertain if PPSs have been found to be cost-effective in specific countries and health systems. We aimed to generate evidence for decision makers to assess the feasibility of PPSs in their own health systems. Permutation matrix proposed by Nixon *et al*[63] was selected to summarise the ICER results in a qualitative way since the matrix is a visual and simple method to communicate complex health economic outcomes to non-expert audience and findings can be easily used to make decisions on healthcare resource allocation. The main limitation of the matrix

[81] Husereau D, Drummond M, Petrou S, Carswell C, Moher D, Greenberg D, et al. Consolidated Health Economic Evaluation Reporting Standards (CHEERS)--explanation and elaboration: a report of the ISPOR Health Economic Evaluation Publication Guidelines Good Reporting Practices Task Force. Value in health 2013;16:231-50.
[82] Drummond MF. Comparing cost-effectiveness across countries: the model of acid-related disease. Pharmacoeconomics. 1994;5(Suppl.3):60-7.

is that it loses important information to interpret the ICER, such as the uncertainty and quality of the studies. However in this review quality was assessed separately and symbols indicating the quality of each study were added in the matrix. Narrative results and tables summarizing the main information of individual studies are still needed to understand and interpret all the factors that affect the ICERs. In fact, we had several concerns when allocating a position in the matrix to the studies performed by Rubio-Valera *et al*[71] and Bosmans *et al*[66] due to the high uncertainty. Finally we followed the pre-specified criterion of allocating depending on the ICER point estimates since we were not able to systematically include the assessment of the sensitivity analysis when making this decision.

Limitations of this systematic review include a potential risk of publication bias, since grey literature was not specifically searched. However, the grey literature identified in manual searching was assessed for inclusion. Secondly, it was not possible to conduct subgroup analyses to investigate the impact of the type of PPS, EE, country or time horizon as a result of the relatively limited number of included studies. Findings cannot be extrapolated to underdeveloped or developing countries since all the included studies were carried out in developed countries. Another review with more relaxed exclusion criteria should be conducted to retrieve the studies carried out in

underdeveloped or developing countries. Finally, we acknowledge that including only full EE based on RCT/c-RCT, information given by other type of studies was not included. However, the inclusion of studies providing only the highest level of evidence was preferred.

Key recommendations arise from this review for future research. On one hand, the use of QALYs is recommended in ICER calculations. Besides increasing comparability among studies, QALYs are preference-based final outcomes. Additionally, although cost-benefit analyses were not found in this systematic review, their use should be considered since the cost-benefit ratio could give useful and easily manageable information to decision makers. Most of the EE were undertaken from the healthcare system perspective. However it would be interesting to complement these analyses with the societal perspective to assess the impact of PPSs on direct non-medical and indirect costs such as patients' time, transport or productivity loses. A better identification and measurement of costs is needed. Costs to perform the intervention should always be included, and costs that potentially can be affected as a result of the intervention depending on the perspective chosen should also be included. If any important cost could not be measured it should be discussed in limitations. Additionally, a higher level of reliability and validity could be achieved if the use of health resources could be

confirmed through medical records rather than being only self-reported by patients. The lack of concordance in hospital admissions when using self-reported data vs. medical records has been reported[45] and systems to ensure the appropriate recovery of these events are needed, since a single event has a high impact in total costs. Instead of the cost-consequence analysis used in some of the studies[64,65,70,73], when clinical and/or humanistic outcomes and economic data are measured in a RCT/c-RCT, calculations on the incremental cost-effectiveness and appropriate sensitivity analyses are strongly encouraged since cost-effectiveness data summarized in an incremental ratio are easier to manage than disaggregated cost and consequence outcomes.

Finally, only three studies used modelling techniques to lengthen the time horizon of the EEs based on RCT/c-RCT with short follow-up to allow capturing all the relevant cost and consequences[40,69,77]. The difference between ICERs for short vs. long-time horizons and sensitivity analyses[40,77] suggest that the costs associated with the intervention in short term, such as the cost of pharmacist training, had disappeared over time and the effectiveness of the service would be retained. It seems that if ICERs calculated for short time horizon were modelled to longer periods, the PPS would be more cost-effective. Nevertheless, the question of what is the appropriate time horizon for capturing all relevant cost and consequences of PPSs without relying on

too many assumptions still needs to be answered. It would probably need to be individualised for every EE depending on the type of PPS assessed and the length of time needed to see the change of the effect on measured outcomes.

1.5 Conclusions

In conclusion, the current systematic review performs a mapping of the studies assessing the cost-effectiveness of PPSs provided to patients attending the community pharmacy. Due to the limited comparability, low number of studies, few types of PPSs analysed and the uncertainty related to some ICERs, the actual evidence should be complemented with other high quality studies. From the available evidence it could be concluded that there was a general trend towards the cost-effectiveness of PPSs in community pharmacy compared to UC. Decision makers are encouraged to consider the feasibility of implementing and funding community pharmacist-led professional services in their specific health systems.

1.6 Reference

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. Accepted for publication in Expert Review of Pharmacoeconomics & Outcomes Research. DOI:10.1080/14737167.2016.1259071.

2. Chapter 2:

Cost analysis and cost-benefit analysis of a medication review with follow-up service in aged polypharmacy patients

2.1 Introduction

Drug related problems and negative clinical outcomes related to medicines have a significant clinical and economic burden[83,84] with the aged polypharmacy patients population being at high risk[21]. A direct positive correlation has been found between ageing, polypharmacy and an increased risk of DRPs and NCOMs. A recent study reporting the prevalence of DRPs in aged patients using eight or more medications, found that 87% of the analysed patients had at least one DRP[21]. Another study found 8.9 DRPs per patient with a mean age of 81 years and using 15 medicines[22].

These medication errors use social and health resources and generate costs to the healthcare system. Interestingly a high percentage of NCOMs are preventable, as evidenced in a Spanish study undertaken in a hospital setting[19]. These researchers estimated costs up to €14.5 million for ED visits caused by preventable NCOMs during the 2003 year. Johnson and Bootman[85] estimated that the cost associated with drug-related morbidity and mortality in

[83] Chiatti C, Bustacchini S, Furneri G, Mantovani L, Cristiani M, Misuraca C, 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.
[84] Beer C, Hyde Z, Almeida OP, Norman P, Hankey GJ, Yeap BB, et al. Quality use of medicines and health outcomes among a cohort of community dwelling older men: an observational study. Br J Clin Pharmacol. 2011;71(4):592-9.
[85] Johnson JA, Bootman JL. Drug-related morbidity and mortality. A cost-of-illness model. Arch Intern Med. 1995;155(18):1949-56.

ambulatory care in the U.S. was $76.6 billion (in 1995 values, only direct medical costs). Other authors[24] updated these estimates to the year 2000, reporting costs of $177.4 billion. They concluded that given the economic and medical burden associated with DRPs, the implementation of strategies for preventing drug-related morbidity and mortality are urgently needed.

An individualized review of patients' pharmacotherapy has been proven to be an effective strategy to avoid preventable NCOMs, reducing the clinical and economic burden[86]. A series of systematic reviews conclude that PPSs generally provide positive economic benefits, although there is high variability in both clinical outcomes and the subsequent cost-effectiveness analysis[32,42,43,52].

The conSIGUE Program was carried out to assess the impact of the MRF to aged patients with polypharmacy[46]. MRF has been shown to be a cost-effective strategy through a CUA[68]. However, policymakers requested other economic evidence different to the CUA in the process of considering a change in health policy and a payment for the service.

[86] Brummel A, Lustig A, Westrich K, Evans MA, Plank GS, Penso J, et al. Best practices: improving patient outcomes and costs in an ACO through comprehensive medication therapy management. JMCP. 2014;20(12):1152-8.

The aim of this paper was to ascertain the economic impact of the MRF service provided in community pharmacy to aged polypharmacy patients comparing MRF with UC, by undertaking a cost analysis and a cost benefit analysis.

2.2 Methods

2.2.1 Study design

The conSIGUE Program has been described previously in this thesis, and sampling and the research methodology was fully described in a report[46]. Briefly, a cluster randomized controlled trial was carried out in 178 community pharmacies in 4 Spanish provinces with 6 months fieldwork in each province. Following a request for participation for all community pharmacies within a province those willing to participate were randomly allocated into either the IG or CG. Each pharmacy was required to recruit up to 10 aged polypharmacy patients, defined as those aged ≥ 65 years and taking 5 or more medications for at least 6 months. Neither patients nor pharmacists could be blinded due to the characteristics of the intervention.

A piggyback cost-benefit analysis and a cost analysis were performed from the Spanish National Health System (NHS) perspective, with a time horizon of 6 months. Additionally, different extrapolations were made to estimate the outcomes depending on length of follow-up, number of patients receiving the MRF and a payment to pharmacies for delivering the service. The alternatives were a MRF service versus the usual care.

2.2.2 Medication review with follow-up service and study groups

Pharmacists allocated to MRF group delivered the service according to national guidelines[31]. MRF starts with a patient interview, in which the pharmacist collects relevant information about health problems, medicines used, clinical and biological parameters, medication use, lifestyle habits, and patient concerns about diseases and medications. After performing a comprehensive medication review, the pharmacist identifies NCOMs and DRPs. An action plan is agreed with the patient and the physician if required.

Patients included in the CG received UC. The UC in Spanish community pharmacy setting consists of dispensing medicines prescribed by physicians and minor ailments advice[47]. During the 6 months of follow-up, patients in both study groups attended the pharmacy on a monthly basis. Study variables were systematically collected at every patient visit to the pharmacy. Neither patients nor pharmacists received any incentives for participating in the study.

2.2.3 Costs

The economic evaluation was conducted from the health system perspective. The following direct medical costs were included in the analysis: medication costs, ED visits costs, hospital admission costs, the cost of pharmacists' time, pharmacists training and the cost of the practice change facilitator. Additionally, the investment of the pharmacy was also considered to establish the cost of the intervention. Costs are expressed in Euros at 2014 prices. Prices from previous years were updated using the Spanish consumer price index.

The information about medicines used was obtained from the records completed by pharmacists during the monthly visits with patients and validated by the practice change facilitators. Retail prices of the medicines were used[87]. All the products registered as medicines in Spain, involving prescribed and over the counter medications, were included.

[87] BotPLUS web database. Spanish General Council of Official Colleges of Pharmacists. Madrid. Available from: https://botplusweb.portalfarma.com/. [Accessed November 15, 2014].

Patients reported the number of times they had visited the emergency department throughout the follow-up. The reference sources for the unit costs of ED visits were the tariffs of the regional health services[88,89,90].

Patients were required to report the number of hospital admissions during the follow-up. The list of diagnosis related groups (DRGs) was requested from the regional health directorates and hospitals. When the information reported by patients and the one provided by official sources was discordant, the latter was accepted. Costs of DRG were taken from the Spanish NHS[91]. Three specialists in internal medicine independently assessed the causes of hospital admission and only those associated with DRPs were included in the analysis[45].

The time spent by pharmacists during the provision of MRF was obtained from pharmacists´ data collection forms. Missing data were replaced

[88] Order of 14 october 2005, which fixes public prices of health services provided by the Public Health System of Andalusia, BOJA 210. Available from: http://www.juntadeandalucia.es/boja/2005/210/d28.pdf. [Accessed June 12, 2014].
[89] Tariff book of public prices of the Public Health System of the Basque Country, 2014. Osakidetza. Available at: http://www.osakidetza.euskadi.net/r85-ckproc05/es/contenidos/informacion/libro_tarifas/es_libro/tarifas.html. [Accesed June 4, 2014].
[90] Decree 81/2009, 16 June, which fixes the public costs of health services of the Canarian Health Service. Available from: http://www.gobiernodecanarias.org/boc/2009/123/boc-2009-123-002.pdf. [Accessed June 10, 2014].
[91] Ministry of Health, Social Services and Equalty, Spanish Government. [Weights and costs of DRGs. Ministry rule APv27.0.] (2010). Available from: http://www.msssi.gob.es/estadEstudios/estadisticas/docs/SNS2011_PESOS_COSTES_AP27_DEF.pdf. [Accessed July 5, 2014].

with the median value of the variable, in order to avoid an underestimation of time costs. Costs for the pharmacist time were calculated multiplying the minutes spent during the provision of the service by the wage, depending on collective wage agreements in each province and the type of contract of employment[92]. Time spent providing UC was not recorded in conSIGUE Program, therefore it was estimated using data previously described in the literature[93].

The costs related to the investment of the pharmacy required to provide the MRF service during the 6 months of study were obtained through a questionnaire completed by pharmacy owners in the MRF group[92] (questionnaire available in reference[46]). Only the percentage of costs attributable to MRF was considered. Investment of pharmacies on fixed and variable costs besides the cost of attendance of the pharmacists to the three half-day training course were included.

In order to allocate the proportional part of the cost to every patient, the mean cost of investment per pharmacy was divided by the mean number of patients included in MRF service per pharmacy (7.9 ± 2.4 patients per

[92] Noain A, Garcia-Cardenas V, Gastelurrutia MA, Malet-Larrea A, Martínez-Martínez F, Sabater-Hernández D, Benrimoj SI. Cost analysis of a Medication Review with Follow-up service provided to elderly patients using polypharmacy. Submitted to Int J Clin Pharm.
[93] Casal-Sánchez C, Losada-Campa MJ. Necessary times for the dispensation of electronic prescriptions in Galicia: necessities and processes. Farmacéuticos Comunitarios. 2012;4(2):52-62.

pharmacy). The investment of pharmacies in the UC group was assumed to be null.

Costs of practice change facilitators were met by official pharmacists associations in each province. The cost for the practice change facilitator´s time was estimated multiplying the working hours by the wage depending on the type of contract of employment per province and adding the travel expenses to the pharmacies. Practice change facilitators were estimated to spend two-thirds of their time with pharmacists in the IG and one-third with pharmacists in the CG. The time spent in the CG was allocated to completing and validating data collection forms. However since this expenditure was not attributable to the provision of the MRF, the cost of practice change facilitator in the CG was considered to be null and the proportional part was discounted in the IG.

2.2.4 Benefits

Patient´s health-related quality of life was measured with the quality-adjusted life years (QALY). Patients in both study groups completed the EQ-5D questionnaire at every visit of the patient to the pharmacy[94], and utility

[94] EuroQol Group. Spanish (Spain) version version of EQ-5D-5L. Rotterdam, 2014.

index associated to each health state were estimated using the time trade off method[95].

In this cost-benefit analysis, a monetary value obtained through empirical research was assigned to the QALY. The assignment of a monetary value to the QALY has been the objective of several studies, and the study recently published by Robinson et al. collected data from 9 European countries, including Spain[96]. The authors adapted the "chained" approach, using first the time trade off and standard gamble methods to elicit utilities for health states and then estimating the willingness to pay (WTP) per QALY. They suggested that the WTP per QALY ranged from $18,247 to $34,097 (US dollars, 2013) and we assigned this monetary value to the QALYs obtained in our study.

2.2.5 Sensitivity analysis

One-way deterministic sensitivity analysis was undertaken in the base case of the cost-analysis in order to analyse the uncertainty and to explore the impact of varying the input parameters. The alternative values of the

[95] Ramos-Goñi JM, Rivero-Arias O. Eq5d: A command to calculate index values for the EQ-5D quality-of-life instrument. Stata Journal. 2011; 11(1):120-125.
[96] Robinson A, Gyrd-Hansen D, Bacon P, Baker R, Pennington M, Donaldson C, EuroVaQ Team. Estimating a WTP-based value of a QALY: the 'chained' approach. Soc Sci Med. 2013;92:92-104.

parameters were their upper and lower variations (for costs related to medication, ED visits, pharmacy time and investment of the pharmacy), logical values (hospital admissions without cause-effect screening and the number of patients that could be attended by each pharmacy in real practice) and arbitrary and conservative values in remaining ones (length of follow-up and practice change facilitator time). Fourteen scenarios were analysed through these alternative values.

The following assumptions were used to calculate the number of patients that could be included in the MRF in real practice: a community pharmacy in Spain serves a mean of 2500 patients[97]; 16% of the population are aged patients using polypharmacy[98,99], and 60% of these patients would accept the provision of service. The MRF service could be delivered to 240 patients per annum and 120 in 6 months.

[97] Statistics Collegiate and Community Pharmacies 2012. Spanish General Council of Official Colleges of Pharmacists. Madrid. Available from: http://www.portalfarma.com/Profesionales/infoestadistica/Documents/Estadisticas2012.pdf. [Accessed Feb 7, 2015].

[98] Abellán A, Esparza C. [A profile of the elderly in Spain, 2011. Basic statistical indicators.] (Informes Portal Mayores no. 127). Madrid. Available from: http://digital.csic.es/bitstream/10261/107721/1/pm-indicadoresbasicos11-1.pdf. [Accessed 7 Feb 2015].

[99] Cosby RH, Howard M, Kaczorowski J, Willan AR, Sellors JW. Randomizing patients by family practice: sample size estimation, intracluster correlation and data analysis. Fam Pract. 2003;20(1):77-82.

2.2.6 Statistical analysis

Student´s t-test was used to analyse the differences between IG and CG, and Chi Square test or Fisher's exact test to assess the differences in frequency distribution. The adjustment of the variables that were significantly different at baseline was performed through an analysis of covariance. All analyses were conducted using the Statistical Package for the Social Sciences (SPSS v. 18.0 for Windows XP, Microsoft, U.S.), Microsoft Excel 2010 and STATA version 12 (StataCorp LP, College Station, TX, USA).

2.3 Results

2.3.1 Study groups and patients

A total of 1474 patients were enrolled in the study. Patient recruitment, flow and dropouts are shown in Figure 4. Data on 1403 patients meeting the inclusion criteria and allocated into the IG (n=688) or CG (n=715) were included in the analysis. Patients were recruited by 178 community pharmacies with a mean number of 7.9 (SD 2.4) patients in each pharmacy.

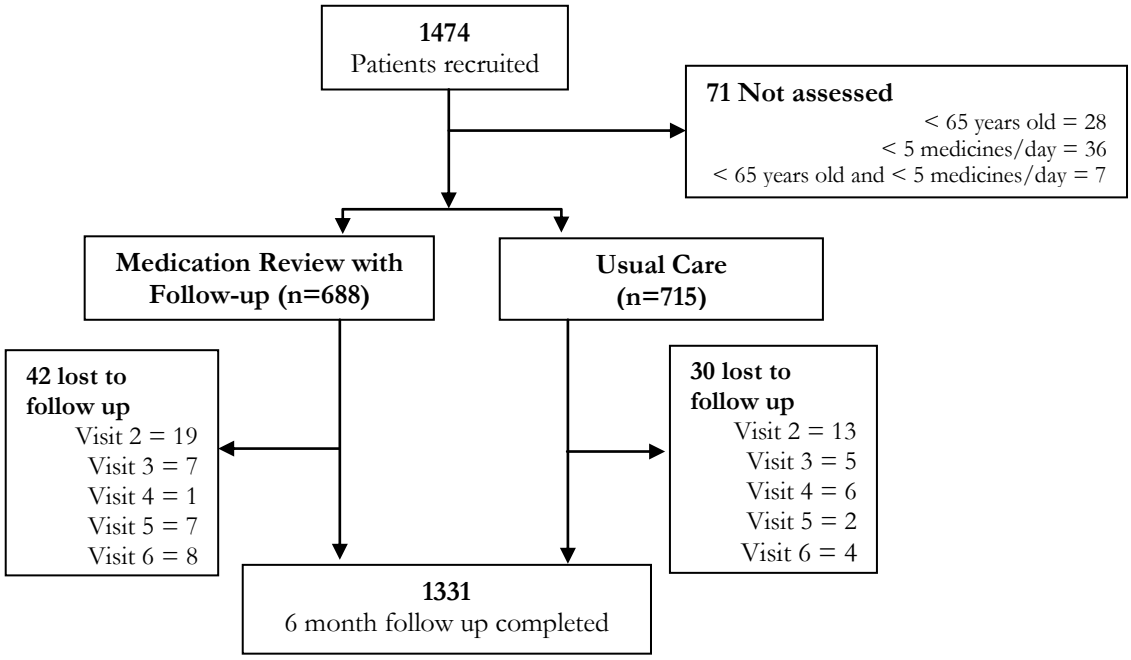


Figure 4: Participant recruitment, flow and dropouts

Table 4 shows the socio-demographic and clinical characteristics of patients at baseline and last study visits. Patients in IG used significantly more medicines, had more health problems and uncontrolled health problems than in CG at baseline ($p<0.05$). Every acute or chronic manifested health issues were considered health problems, and the level of control was assessed by pharmacists using information referred by patients' and/or clinical and biological parameters. At the end of the study the number of uncontrolled health problems had decreased in the IG more than 50% ($p<0.001$), becoming similar to the CG. The number of patients with visits to ED or being hospitalised decreased in the IG leading to significant differences between groups after the 6-month follow-up[45]. Utility scores were similar between groups at baseline; they remained constant in the CG while increased in IG, leading to significant differences between groups as well.

2.3.2 Costs and cost analysis

Pharmacists spent a median of 350 minutes (interquartile range: 265-490 minutes) in the provision of the service per patient for all phases of MRF during the 6 months study. Time required to provide the UC in Spain through the dispensing service with electronic prescription was estimated to be 4.2 minutes/patient´s visit to the pharmacy[93]. Taking into account the number of

patients lost to follow-up, pharmacists would need 25 minutes/patient to provide UC during the 6 months.

Table 4: Socio-demographic and clinical characteristics of the patients at baseline and at 6-month follow-up (mean (SD) unless otherwise reported)

	IG	CG	P-value
Age (years)	75.3 (6.5)	74.9 (6.6)	0.243
Gender (female); n (%)	409 (60.1)	441 (61.7)	0.535
Number of medicines used			
Period 1	7.7 (2.5)	7.4 (2.4)	0.009
Period 6	7.5 (2.4)	7.3 (2.4)	0.204
Health problems			
Period 1	4.9 (1.8)	4.3 (1.5)	<0.001
Period 6	4.9 (1.8)	4.3 (1.5)	<0.001
Uncontrolled health problems			
Period 1	1.5 (1.3)	0.7 (1.0)	<0.001
Period 6	0.6 (0.9)	0.7 (0.9)	0.217
Patients in emergency department; n (%)			
Period 1	193 (28.1)	211 (29.5)	0.556
Period 6	90 (13.1)	173 (24.2)	<0.001
Patients hospitalised; n (%)			
Period 1	89 (13.4)	68 (9.9)	0.044
Period 6	38 (6.2)	65 (9.8)	0.018
Utility scores			
Period 1	0.715 (0.3)	0.693 (0.3)	0.238
Period 6	0.768 (0.3)	0.693 (0.3)	<0.001

IG: intervention group. CG: comparison group. SD: standard deviation.

The investment needed by pharmacies to provide MRF service in the conSIGUE Program was 210.8 (SD: 32.8)[92] and the highest costs were associated with pharmacists´ attendance to the training course.

Amongst the 83 hospital admissions screened by the expert panel, 42 (50.6%) were related to medication (IG: 11, CG: 31; p=0.042).

Table 5: Unit and total costs of study groups (€, 2014) during 6 month follow-up

Item	Unit cost (€) and reference source	Number		Total cost (€)		% of total	
		IG	CG	IG	CG	IG	CG
Medication (nº packages)	Retail price[a]	29,353	29,974	425,460	459,157	63.3	62.7
Emergency department visits (nº visits)							
Andalusia	58.55[b]	30	59	1,756	3,454		
Basque Country	149.50[c]	41	58	6,129	8,671	2.7	6.7
Canary Islands	216.93[d]	47	173	10,195	37,528		
Drug related hospital admissions (nº admissions)	Diagnosis Related Group[e]	11	31	64,846.4	215,382	9.6	29.4
Pharmacy time (cost/min)	0.443[f]	240,800	17,426	106,674	7,719	15.8	1.0
Investment in MRF (per pharmacy)	210.8[g]	88	-	18,553	-	2.7	-
Practice change facilitator time (cost/min)	1.012[h]	37,661	-	38,112	-	5.6	
Total cost	-	-	-	**671,730**	**731,914**	100	100

[a]Spanish General Council of Colleges of Pharmacists[87]; [b]Tariffs of Andalusian health service[88]; [c]Tariffs of Basque Country health service[89]; [d]Tariffs of Canarian health service[90]; [e]Tariffs of Spanish National Health Service[91]; [f,g,h]Own data. IG: intervention group. CG: comparison group

The average costs of a practice change facilitator (wage plus travel expenses) was € 1616.6 per month. Taking into account that practice change facilitators worked 40h per week, the mean cost per practice change facilitator

was €0.169/min. Six practice change facilitators were employed with a total cost of €1.012/min.

Table 5 summarizes the unit and total costs for both groups. The highest cost was medication, with more than 60% of the total cost in both groups. The second most influential cost component was drug related hospital admissions for UC group and pharmacy time for MRF group, being the investment of the pharmacy the component having less weight.

Table 6: Mean costs per patient (€, 2014) during 6 month follow-up

Item	IG	CG	Mean difference[a]
Medication costs; mean (SE)[b]	615.5 (25.7)	661.3 (25.0)	-45.8
Emergency department visits; mean (SD)	26.3 (81.6)	69.5 (222.6)	-43.2
Hospital admissions; mean[c]	94.2	301.2	-207.0
Pharmacy time; MRF: median (Q_{25} – Q_{75})	155.1 (117.4 – 217.1)	11.1	144
Investment of pharmacy in MRF; mean (SD)	26.9 (3.8)	-	26.9
Practice change facilitator time; mean	27.7	-	27.7
Total	**945.7**	**1043.1**	**-97.4**

[a]Negative cost difference indicates cost saving related to MRF group [b]Adjusted by the number of used medicines in period 1 (ANCOVA) [c]Malet-Larrea *et al.*[45]. IG: intervention group. CG: comparison group. SE: Standard error; SD: standard deviation.

The cost savings per patient of the base case are shown in Table 6. Cost differences between groups in medication, ED visits and hospital admissions

were statistically significant ($p<0.001$ for medication and ED visits and 0.018 for hospital admissions). The difference between total costs in both groups showed a cost saving for the NHS of € 97 per patient in 6 months.

In order to obtain a profit margin of 30%, which is the current margin paid to pharmacies for each product supply by the NHS, pharmacies should receive €22 per patient-month for providing the MRF[92]. If health administration paid €22 per patient-month, the net saving of the MRF service would be € 273 per patient-year.

However, the saving obtained suggests that the service would be efficient even with a higher price than €22 per patient-month. Based on annual estimates, the threshold price for the efficiency of the MRF is expected to be €45 per patient-month. All the extrapolations are summarised in Table 7.

The sensitivity analysis showed that the MRF saved costs in 13 of 14 scenarios analysed. The MRF would achieve savings of €398 per patient in the scenario where 240 patients were included in the service per pharmacy during one year. In this case, if the service was remunerated, savings per patient-year would be €326 and each pharmacy would save €78,281 per year.

Table 7: Summary of calculations and extrapolations

Scenario	Time, unit of analysis and key assumptions	Variables and values	Cost-savings (€)
a) Base case scenario conSIGUE Program	*6 months, patient*	Medication: -45.8 ED visits: -43.2 Hospital admissions: -207.0 Pharmacy time: 144 Investment of pharmacy: 26.9 Practice change facilitator: 27.7	**-97**
b) Including fee for service	*1 year, patient* The fee for service calculation includes the cost of the intervention for the pharmacy; 22*12=264	Medication: -91.7 ED visits: -86.3 Hospital admissions: -413.9 Practice change facilitator: 55.4 Fee for service: 264	**-273**
c) Fee for service threshold analysis	*1 month, fee for service* Threshold: when cost-savings=0	Medication: -91.7 ED visits: -86.3 Hospital admissions: -413.9 Practice change facilitator: 55.4 = -536.58 / 12	**-45**
d) Including a real number of patients (n=240)	*1 year, patient* Intervention cost: share among 240 patients and extend follow-up visits time	Medication: -91.7 ED visits: -86.3 Hospital admissions: -413.9 Pharmacy time: 190.9 Investment of pharmacy: 0.9 Practice change facilitator: 1.8	**-398**
e) Including a real number of patients (n=240) and fee for service	*1 year, patient* Former scenario with fee for service including cost of the intervention for the pharmacy(22*12=264)	Medication: -91.7 ED visits: -86.3 Hospital admissions: -413.9 Practice change facilitator: 1.8 Fee for service: 264	**-326**
f) Including a real number of patients (n=240) and fee for service	*1 year, pharmacy* Former scenario, per pharmacy with 240 patients	Medication: -91.7 ED visits: -86.3 Hospital admissions: -413.9 Practice change facilitator: 1.8 Fee for service: 264	**-78,281**

[a]Negative cost difference indicates cost saving related to MRF group. ED visits: emergency department visits.

2.3.3 Cost-benefit analysis

The cost-benefit analysis considered the health benefits obtained by the provision of MRF in addition to the costs savings (Figure 5). The QALY obtained were 0.3721 (0.12) in the IG and 0.3488 (0.15) in the CG (p=0.002). Two scenarios were set up using the base case of the cost analysis and the upper and lower limit of the estimated range for the monetary value of QALY in the European study[96]. The cost-benefit ratio indicated that MRF benefits were from 3.3 to 6.2 times higher than costs. When benefits in health were added, every case considered in the sensitivity analysis provided positive results for the MRF.

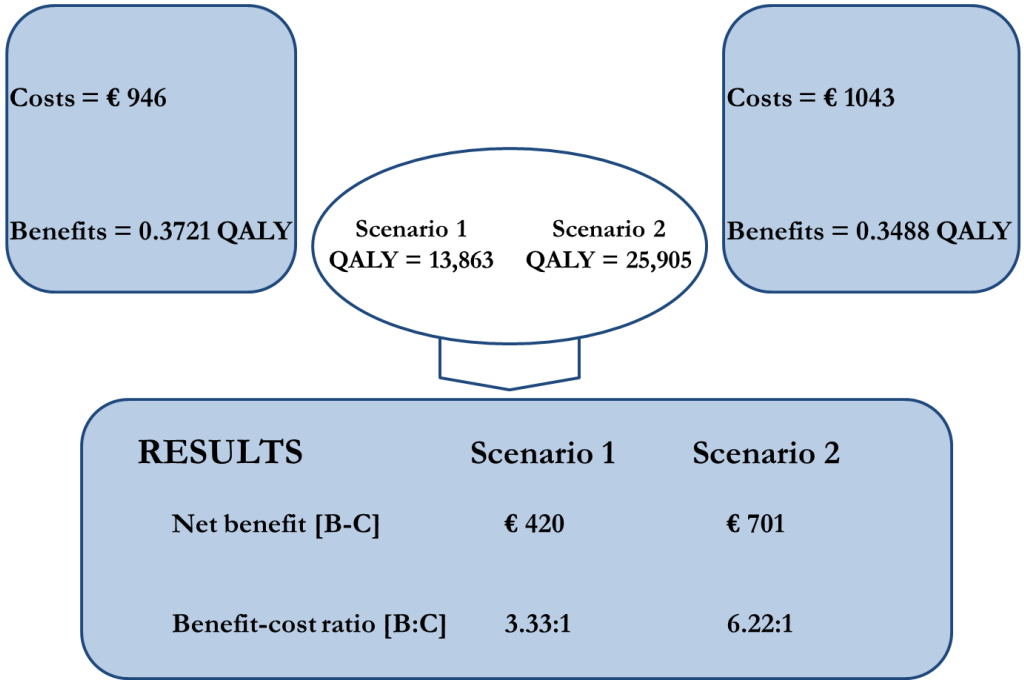


Figure 5: Cost benefit analysis (€, 2014) of the medication review with follow-up per patient in 6 months

The scenarios are given by the monetary value of QALY reported in the study by Robinson *et al.*[96]. IG: intervention group. CG: comparison group.

2.4 Discussion

The results of the present study show that MRF delivered in a community pharmacy setting targeted to aged polypharmacy patients has positive net benefits (between €420 and €700 per patient) and it saved €97 per patient in 6 months. For every €1 invested in MRF, the service returned a benefit from €3.3 to €6.2.

The analysis showed that if MRF was implemented in clinical practice, higher saving could be achieved. There were decreasing marginal costs of the intervention with the length of the follow-up and with the number of patients in the programme. Thus, the inclusion and maintenance of a higher number of patients during a longer period of time would generate more savings to the healthcare system. However, the sustainability of the service depends on its payment. Pharmacists would need a fee for service to deliver MRF to a higher number of patients and during a longer follow-up. Even if the health system remunerated pharmacists with €22 per patient-month, savings per patient-year would amount to €326.

Diverse results have been found when assessing the cost-effectiveness of PPSs[67,77]. Our results support the evidence suggesting that pharmacist

interventions might be cost-effective and cost-saving[100,101,102]. For example, a recent study carried out in a hospital setting[102] found a cost-benefit ratio of €1:8.64 for pharmacist interventions. Another study aimed at improving the quality of prescribing and the adherence to treatment by community pharmacists in patients with hypertension showed that benefits obtained were ten times higher than costs[101]. In the Asheville project a similar service to MRF was delivered by community and hospital pharmacists over 6 years in patients with different chronic conditions such as asthma[103], hypertension and/or dyslipidaemia[104]. Similar results to the ones found in our study were achieved. The pharmacy service provided allowed not only clinical improvements (supported by a decrease in ED visits and hospital admissions) but also cost savings (direct cost savings averaged $725 per patient-year). Findings of Asheville Project and conSIGUE Program are highly comparable due to the fact that the service provided was very similar, including the follow-up using scheduled consultations.

[100] Benrimoj SI, Langford JH, Berry G, Collins D, Lauchlan R, Stewart K, et al. Economic impact of increased clinical intervention rates in community pharmacy. A randomised trial of the effect of education and a professional allowance. Pharmacoeconomics. 2000;18(5):459-68.
[101] Cote I, Gregoire JP, Moisan J, Chabot I, Lacroix G. A pharmacy-based health promotion programme in hypertension: cost-benefit analysis. Pharmacoeconomics. 2003;21(6):415-28.
[102] Gallagher J, Byrne S, Woods N, Lynch D, McCarthy S. Cost-outcome description of clinical pharmacist interventions in a university teaching hospital. BMC Health Serv Res. 2014;14:177.
[103] Bunting BA, Cranor CW. The Asheville Project: long-term clinical, humanistic, and economic outcomes of a community-based medication therapy management program for asthma. J Am Pharm Assoc. 2006;46(2):133-47.
[104] Bunting BA, Smith BH, Sutherland SE. The Asheville Project: clinical and economic outcomes of a community-based long-term medication therapy management program for hypertension and dyslipidemia. J Am Pharm Assoc. 2008;48(1):23-31.

MRF is a well-defined service, which includes a comprehensive and systematic medication review and a follow-up commitment. The provision of MRF requires a considerable investment of time, clinical knowledge and effort, since pharmacists are responsible for not only the process of the use of medicines, but also patients´ health outcomes. Additionally, pharmacists in conSIGUE Program were supported by a practice change facilitator. Consequently, the MRF provided in conSIGUE Program achieved clinical results not found with other pharmacy services[34,105].

In fact, other studies showed even greater cost-benefit ratios such us those included in a series of systematic reviews 1:34.61, 1:17.0, 1:25.95, 1:75.84[32,42,43,52]. However these extreme values should be considered exceptional cases. The study design, included costs, type of pharmacy service and patients´ characteristics has an undeniable impact on the results. For instance, the study reporting a cost-benefit of 1:75.84 assessed the impact of a pharmacokinetic service in hospitalised patients receiving aminoglycosides, a specific service in ill patients treated with narrow therapeutic range medicines. These patients were at a very high risk of complications, so there was every chance of avoiding higher clinical and economic burden than services like MRF, provided to ambulatory patients with chronic comorbidities.

[105] Beaucage K, Lachance-Demers H, Ngo TT, Vachon C, Lamarre D, Guevin JF, et al. Telephone follow-up of patients receiving antibiotic prescriptions from community pharmacies. Am J Health Syst Pharm. 2006;63(6):557-63.

Nevertheless, the median values of cost-benefit ratios of the studies included in the reviews are similar to our cost-benefit ratio, endorsing our findings ($1:4.1, $1:4.68 and $1:4.81[32]).

The main purpose of EE is for policymakers to make decisions. If policymakers and their political advisors do not have strong technical knowledge in health economics, the presentation of clear EE to inform the process of decision making is required. In the consultations with Spanish policymakers, it was evident that the "cost per QALY" concept generated in the previous economic evaluation of the conSIGUE Program[68] was difficult to understand. In this analysis we translated this abstract concept to a more easily interpretable cost-benefit ratio. Furthermore, in this analysis we included more accurate costs and estimations of the economic impact that could be expected when implementing the MRF in the real practice.

The monetary value of health gain used in this analysis was obtained through empirical research rather than cost-effectiveness thresholds based on literature reviews[106] with lack of explicit scientific evidence[107]. The assignment of a monetary value to the QALY has been the objective of several

[106] Sacristan JA, Oliva J, Del Llano J, Prieto L, Pinto JL. [What is an efficient health technology in Spain?]. Gac Sanit. 2002;16(4):334-43.
[107] Shiroiwa T, Sung YK, Fukuda T, Lang HC, Bae SC, Tsutani K. International survey on willingness-to-pay (WTP) for one additional QALY gained: what is the threshold of cost effectiveness? Health econ. 2010;19(4):422-37.

studies[108,109,110]. However these studies performed their estimations with a high level of variability. One of the most recent studies is the one developed by Robinson *et al.*[96] whose estimations have been used in the present study, and where the monetary value of QALY was estimated by the "chained" approach through data from 9 European countries, including Spain. Robinson *et al.* suggested that the WTP per QALY ranged from $18,247 to $34,097 (US dollars, 2013). In a previous study King *et al.*[109] found that the mean WTP per QALY ranged from $12,500 to $32,200 (2003 $US). These data obtained by contingent valuation are lower than the currently used cost-effectiveness thresholds, so the willingness of society to pay might have been overestimated when accepting cost-effectiveness thresholds. Alternatively, it is known that the WTP per QALY is higher for worse health status than for better ones[111]. In our study, patients´ health status was better than in Robinson's study and therefore, the cost-benefit ratio obtained using the lower limit of the monetary value of QALY (3.3:1) would be more likely to happen than 6.2:1.

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[108] Hirth RA, Chernew ME, Miller E, Fendrick AM, Weissert WG. Willingness to pay for a quality-adjusted life year: in search of a standard. Med Decis Making. 2000;20(3):332-42.
[109] King JT Jr, Tsevat J, Lave JR, Roberts MS. Willingness to pay for a quality-adjusted life year: implications for societal health care resource allocation. Med Decis Making. 2005;25(6):667-77.
[110] Pinto-Prades JL, Loomes G, Brey R. Trying to estimate a monetary value for the QALY. J Health Econ. 2009;28(3):553-62.
[111] Shiroiwa T, Igarashi A, Fukuda T, Ikeda S. WTP for a QALY and health states: More money for severer health states? Cost Eff Resour Alloc. 2013;11:22.

The main limitation of the study could be that some direct medical costs such as visits to the physician, visits to specialist doctors and laboratory costs were not assessed in the conSIGUE Program, and therefore could not be included in this analysis. The number of visits to the physician is the indicator most likely to be affected by MRF service provision. However, several studies assessing similar services to MRF concluded that there are not significant differences in number of visits[64], cost [112] or both[113] of physician visits between IG and CG.

[112] Cowper PA, Weinberger M, Hanlon JT, Landsman PB, Samsa GP, Uttech KM, et al. The cost-effectiveness of a clinical pharmacist intervention among elderly outpatients. Pharmacotherapy. 1998;18(2):327-32.
[113] Touchette DR, Masica AL, Dolor RJ, Schumock GT, Choi YK, Kim Y, et al. Safety-focused medication therapy management: a randomized controlled trial. J Am Pharm Assoc (2003). 2012;52(5):603-12.

2.5 Conclusions

In the context of the economic pressure on the healthcare system, the identification and implementation of alternatives to increase the efficiency of health services and ensure the sustainability of the health system are required. Our study showed that MRF provided by community pharmacists, targeted to aged polypharmacy patients and compared to the UC, avoids substantial costs to the NHS besides providing health benefits to patients. Investment in the implementation of this service would represent an efficient use of healthcare resources, and a payment from the NHS to pharmacies for delivering MRF should be considered.

2.6 Reference

Malet-Larrea A, Goyenechea E, Gastelurrutia MA, Calvo B, García-Cárdenas V, Cabases JM , Noain A, Martínez-Martínez F, Sabater-Hernández D, Benrimoj SI. Cost analysis and cost-benefit analysis of a Medication Review with Follow-up service in aged polypharmacy patients. Accepted for publication in The European Journal of Health Economics.

3. Chapter 3:

The impact of a medication review with follow-up service on hospital admissions in aged polypharmacy patients

3.1 Introduction

Morbidity associated with the use of medicines represents an important clinical burden[15,16,18,20,114,115]. A systematic review found that adverse events during hospital admission affect almost one in every 10 patients, with 50% of them being preventable[16]. Between 0.1% and 54% of hospital admissions are medication-related with 20% being most common. Of these admissions 50% are preventable and most of them involve the elderly population[15,20,115,116]. The economic burden arising from healthcare resource consumption associated with drug related morbidity and mortality in ambulatory care in the US was estimated to be $177.4 billion (2000 year data)[24]. In the Netherlands potentially preventable medication-related hospital admissions cost more than €94 million in 2006 or €5461 for each hospital admission[26].

An ageing population and the use of polypharmacy are risk factors for suffering not only DRPs[18] but also medication-related hospital admissions[20]. Therefore, aged patients using polypharmacy are bound to benefit from healthcare interventions aimed at resolving DRPs.

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[114] Lewis PJ, Dornan T, Taylor D, Tully MP, Wass V, Ashcroft DM. Prevalence, incidence and nature of prescribing errors in hospital inpatients: a systematic review. Drug Saf. 2009;32(5):379-89.

[115] McLachlan CY, Yi M, Ling A, Jardine DL. Adverse drug events are a major cause of acute medical admission. Intern Med J. 2014;44(7):633-8.

[116] Leendertse AJ, Visser D, Egberts AC, Bemt PM. The relationship between study characteristics and the prevalence of medication-related hospitalizations: a literature review and novel analysis. Drug Saf. 2010;33(3):233–44.

Professional or cognitive pharmacy services are 'an action or set of actions undertaken in or organized by a pharmacy, delivered by a pharmacist or other health practitioner, who applies their specialized health knowledge personally or via an intermediary, with a patient/client, population or other health professional, to optimize the process of care, with the aim to improve health outcomes and the value of healthcare'[117]. PPSs are an effective strategy to avoid and resolve drug related problems as well as negative clinical outcomes related to medicines. However, their effectiveness on reducing hospital admissions has not been clearly established[34].

A nationwide research project called 'conSIGUE Program' was undertaken in Spain with the aim of assessing the economic, clinical and humanistic impact of a MRF service, provided in community pharmacies to aged polypharmacy patients[46]. The conSIGUE Program obtained promising results in terms of hospital admission rates, as shown in the non-peer reviewed report published by the Spanish General Council of Official Colleges of Pharmacists[46]. However, a more in-depth analysis was needed to analyse the cause and effect relationship between medication use and hospitalisations. The aims of the present study were to assess the impact of

[117] Moullin JC, Sabater-Hernandez D, Fernandez-Llimos F, Benrimoj SI. Defining professional pharmacy services in community pharmacy. Res Social Adm Pharm. 2013;9(6):989-95.

community pharmacy-led MRF provided to aged polypharmacy patients on the number of medication related hospital admissions and estimate the effect on hospital costs.

3.2 Methods

The main study was the conSIGUE Program, the previously described cluster randomized controlled trial aimed at assessing the clinical, economic and humanistic impact of the MRF performed in community pharmacy on aged polypharmacy patients. The aim of the retrospective sub-analysis reported in this manuscript was to analyse the impact of the MRF on hospital admissions. Therefore, hospital admissions occurring during the main study were retrieved and an expert panel was convened in order to separate those hospital admissions related to medicines from hospital admissions not related to medicines (see Figure 6).

3.2.1 Study design

This retrospective sub-analysis consisted of an expert panel that analysed the clinical cases of patients hospitalised during the 6 month follow-up period of the previously described cluster randomized controlled trial, in order to identify medication-related hospital admissions.

3.2.2 Study population: clinical cases of hospital admissions

Clinical cases of those patients hospitalised during the 6 months of follow-up of the conSIGUE Program were retrieved. Patient's self-reported information on hospitalisations was verified with the official records of the Spanish public health network. The list of DRGs was requested from the regional health directorates and public hospitals of the provinces participating in the main study. When the information reported by the patient and the information provided by regional health directorates or hospitals was discordant, the latter was accepted.

3.2.3 Expert panel

The expert panel consisted of three internal medicine specialists of the Donostia Hospital who had extensive professional experience. Internal medicine was considered to be a suitable expertise in the field since it covers the diagnosis and treatment of a wide array of diseases, including chronic conditions and patients with multi-morbidity.

The expert panel was informed of the following concepts in a face to face meeting: the conceptual and methodological basis of the conSIGUE Program, the MRF service, the aim and methodology of this sub-analysis and

patient clinical cases. Furthermore, the concept of DRP was clarified and experts were provided with the list of DRPs contained in the national guidelines[31] in order to avoid misconceptions between DRPs and another terms like adverse drug reactions.

The experts were provided with the following information about each clinical case: age, gender, health problems, level of control of the health problems, daily dose and frequency of the medicines used and the description of the DRG. Experts were blinded to the patient group allocation. Records were provided in paper and electronic format.

Initially a pilot study was undertaken to familiarize experts with the rating process. Data of five patients of the main study were slightly modified in order to maintain the relevant characteristics and avoid the double assessment of these cases. All the experts rated the five cases independently, and sent the feedback to the research group.

In the sub-analysis all hospital admission cases were assessed independently by each expert. The question posed to the experts was 'Do you think that in this case the hospital admission can be associated with a DRP?' The possible answers were 'yes' or 'no'. Each hospital admission was

considered to be associated with a DRP when at least two out of the three experts stated so.

The experts were requested to answer individually for each case and the degree of agreement between them was later established. The inter-rater reliability (IRR) was measured using Cohen's kappa for every two raters[118] and the general agreement was assessed using the Fleiss kappa for multiple raters[119].

3.2.4 Outcome measures

Medication-related hospital admission was the primary outcome of this sub-analysis. Hospital admissions were recorded in patients' visits to the pharmacies during the conSIGUE Program and the medication related ones were identified through the expert panel after the fieldwork. Kappa values ranging from 0.61 to 1 were considered as an acceptable IRR to measure the agreement among experts.

[118] Cohen J. A coefficient of agreement for nominal scales. Educ Psychol Meas. 1960; 20(1):37-46.
[119] Fleiss JL. Statistical methods for rates and proportions. New York: John Wiley & Sons, 1973.

The cost of hospital admissions estimated by DRG was a secondary outcome and the DRGs were recorded after the fieldwork. Demographic variables were recorded at baseline.

3.2.5 Hospital costs

DRGs of each hospital admission occurring during the 6 months of the main study were gathered from regional health directorates and public hospitals. DRGs are the system used in several countries for hospital reimbursement and in-hospital budgeting management[120]. For each hospital admission the description of the clinical problem led to the identification of the DRG and its designated costs by the Spanish government[91]. Costs were expressed in euros and updated at 2014 prices using the Spanish consumer price index.

3.2.6 Statistical analysis

Categorical variables were expressed as frequencies and percentages and quantitative variables as means and SDs. Student's t-test was used to analyse the differences between the IG and CG and chi square test or Fisher's exact

[120] Vogl M. Assessing DRG cost accounting with respect to resource allocation and tariff calculation: the case of Germany. Health Econ Rev. 2012;2:15.

test was used to assess the differences in frequency distribution. The risk of hospitalisation was calculated through a multivariate logistic regression model using the SAS GLIMMIX procedure. This analysis included a random intercept for pharmacy-nested within group to account for clustering of patients within pharmacies and was adjusted by covariates that could affect hospital admissions (age, gender and number of health problems). Differences between groups in hospital costs were analysed by hospital admission and by patient, and the latter ones adjusted by ANCOVA for the number of health problems. Statistical significance was set at $P < 0.05$. Analyses were conducted using SPSS (Statistical Package for the Social Sciences v. 18.0 for Windows XP, Microsoft, USA), Epidat (Epidat v. 3.1, Galician Health Council and Pan American Health Organization) and SAS 9.4 (Statistical Analysis Software; SAS Institute, Cary, NC, USA).

3.3 Results

A total of 1403 patients (IG, n = 688; CG, n = 715) were included in the main study from 178 pharmacies, with a mean of 7.9 (SD 2.4) patients per pharmacy. These patients reported 115 hospital admissions, 83 of them were verifiable with official records and their DRGs were retrieved (Figure 6). These 83 hospitalisations were distributed over 50 pharmacies. Baseline characteristics of hospitalised patients are shown in Table 8. None of the patients died during the 6 month follow-up.

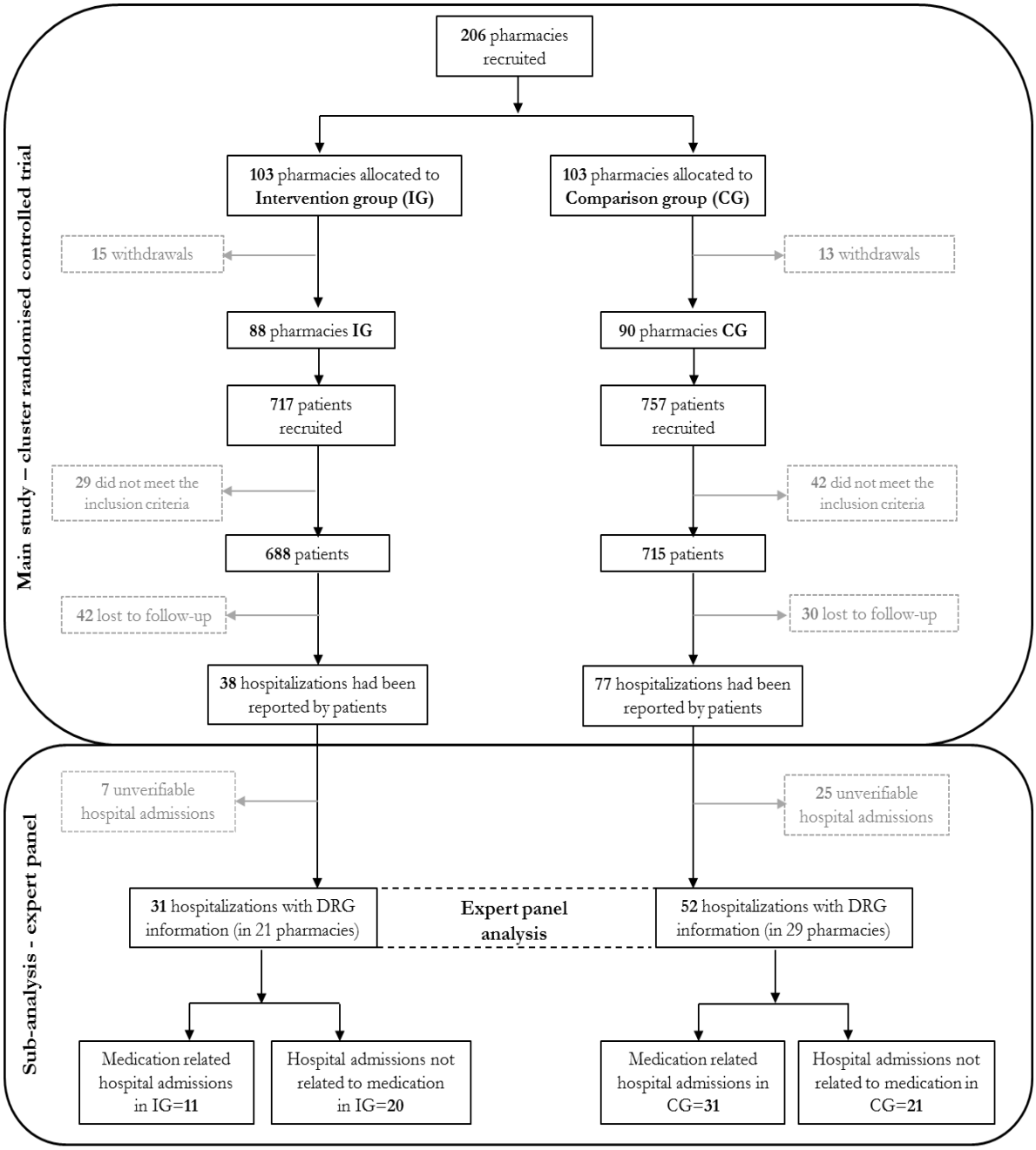

Figure 6: Pharmacy, patient and hospital admission flow diagram in the main cluster randomized controlled trial and in the expert panel sub-analysis

According to the expert panel 42 (50.6%) of the hospital admissions were medication-related, with a kappa of 0.65 (95% CI 0.52, 0.78; p<0.01). Significant differences for medication-related hospital admissions were identified between study groups (p=0.042); 31 (73.8%) of the medication-related hospital admissions occurred in patients in the CG and 11 (26.2%) in the IG.

Table 8: Baseline characteristics of hospitalised patients

	IG	CG	P value
Age (years, mean (SD))	76.07 (6.62)	74.17 (6.07)	0.240
Gender (female); n (%)	17 (60.71)	14 (40.00)	0.102
Partner status (with partner); n (%)*	8 (28.60)	20 (57.10)	0.053
Education; n (%)**			
No formal education	6 (21.40)	5 (14.30)	0.712
Completed primary education	8 (28.60)	14 (40.00)	
Completed secondary education	4 (14.3)	7 (20.00)	
Completed university education	2 (7.10)	1 (2.9)	
Number of medicines used (mean (SD))	8.32 (2.40)	7.74 (3.42)	0.450
Number of health problems (mean (SD))	6.57 (2.20)	5.23 (1.91)	0.012

IG: intervention group (n=28); CG: comparison group (n=35).*Missing values: IG =5; CG=2. **Missing values: IG=8; CG=8.

The probability of being hospitalised was significantly higher in the CG compared with the IG. The unadjusted model showed an odds ratio (OR) of 2.7 (95% CI 1.1, 6.7; p=0.036). When adjusting for other covariates (age,

gender and number of health problems), the OR increased to 3.7 (95% CI 1.2, 11.3; p=0.021) (Table 9). The cluster effect was non-existent (intracluster correlation coefficient (ICC)=0).

Table 9: Multivariate logistic regression analysis to assess the effect of medication review with follow-up on medication-related hospital admissions

	Adjusted OR	95% CI	P value
Group (IG → CG)	3.747	1.241-11.319	0.021
Age	1.004	0.933-1.080	0.915
Gender	0.762	0.290-2.006	0.571
Number of health problems	1.180	0.900-1.548	0.222

IG: intervention group; CG: comparison group; OR: odds ratio; CI: Confidence Interval. Raw OR (simple logistic regression analysis): 2.7 (95%CI: 1.1-6.7; p=0.036).

Table 10 shows the level of agreement between the three experts in regards to whether hospital admissions could be associated with a DRP or not. The multi-rater kappa revealed a substantial agreement degree (kappa = 0.646; 95% CI 0.52, 0.78, p<0.01)[121].

[121] Landis JR, Koch GG. The measurement of observer agreement for categorical data. Biometrics.1977;33(1):159–74.

Table 10: Inter-rater reliability between each pair of rater and overall agreement by answering whether hospital admission could be associated with drug related problems or not

Raters	Agreement (%)	Kappa statistic	95%CI
Rater 1 vs. Rater 2	83.1	0.667 [a]	0.51-0.82
Rater 1 vs. Rater 3	81.9	0.639 [a]	0.48-0.80
Rater 2 vs. Rater 3	81.9	0.637 [a]	0.47-0.80
Rater 1 vs. Rater 2 vs. Rater 3	73.5	0.646 [b]	0.52-0.78

CI=confidence interval. [a]Cohen´s kappa; [b]Fleiss´ kappa. Kappa <0.0 Poor agreement, kappa 0.0-0.20 Slight agreement, kappa 0.21-0.40 Fair agreement, kappa 0.41-0.60 Moderate agreement, kappa 0.61-0.80 Substantial agreement, 0.81-1.0 Almost perfect agreement[121].

The total cost of the hospital admissions (n=83) was found to be €516,365. Medication-related hospital admissions (n=42) amounted to €280,229 (IG: €64,846; CG: €215,383) and the mean cost per medication-related hospital admission was €6,672 (SD 5,298) [IG: €5,895 (SD 4,496); CG: €6,948 (SD 5,597), p=0.578]. When the costs per group of the medication-related hospital admissions were divided by the number of patients per group in the main study (IG: 688; CG: 715), medication-related hospital admission cost per patient receiving MRF was significantly lower than patients receiving UC [IG: €94 (SD 917); CG: €301 (SD 2,102); 95% CI 35.9, 378.0; p=0.018]. When adjusted by number of health problems similar results were found [IG: 99 (SE 62), CG: 296 (SE 61); p=0.026].

3.4 Discussion

More than half of the hospitalisations (42 out of 83) of this sub-analysis were medication-related. MRF seems to be an effective strategy to address medication-related hospital admissions, since the probability of being hospitalised in our study sample was 3.7 times higher in the CG compared with the IG ($p<0.05$). Medication-related hospital costs were significantly lower in patients receiving MRF.

Several PPSs impacted positively on process indicators associated with the optimization of the patient's medication management[34]. However, the impact of these services on outcome indicators remains unclear, as reported in a systematic review of systematic reviews published in 2013[34]. This view has been endorsed in a number of subsequent systematic reviews and meta-analyses, in which the evidence of the impact of PPSs on hospital admissions is defined as conflicting, insufficient, uncertain or even null[122,123,124,36,125,37,126].

[122] Christensen M, Lundh A. Medication review in hospitalised patients to reduce morbidity and mortality. Cochrane Database Syst Rev. 2013;2:CD008986.
[123] Hatah E, Braund R, Tordoff J, Duffull SB. A systematic review and meta-analysis of pharmacist-led fee-for-services medication review. Br J Clin Pharmacol. 2014;77(1):102–15.
[124] Hohl CM, Wickham ME, Sobolev B, Perry JJ, Sivilotti ML, Garrison S, et al. The effect of early in-hospital medication review on health outcomes: a systematic review. Br J Clin Pharmacol. 2015;80(1):51–61.
[125] Rotta I, Salgado TM, Silva ML, Correr CJ, Fernandez-Llimos F. Effectiveness of clinical pharmacy services: an overview of systematic reviews (2000-2010). Int J Clin Pharm. 2015;37(5):687-97.

However, a large number of studies included in those reviews did not evaluate the association of hospital admissions with medicines. This fact may have biased the results obtained, since not all hospitalisations may have been associated with medications and therefore may not have been avoided through the provision of any PPS.

Additionally, different types of PPSs are compared. However, every service differs in its methodology, complexity, collaboration with other healthcare providers and level of responsibility assumed by the pharmacist[33]. Therefore it is logical that they are bound to achieve different outcomes. For example, the review carried out by Hatah *et al.*[123] performed a subgroup analysis showing that a medication review service had significant impact on reducing hospitalisations (OR: 0.46; 95% CI 0.26, 0.83), whereas interventions focused on adherence did not demonstrate the same trend (OR: 0.88; 95% CI 0.59, 1.32). Even the same type of PPS may have different characteristics, rates of fidelity and implementation. Zermansky *et al.*[127] assessed a pharmacist-led medication review similar to this MRF. However, the practice change facilitator of this study could have increased pharmacists' fidelity to the

[126] Viswanathan M, Kahwati LC, Golin CE, Blalock SJ, Coker-Schwimmer E, Posey R, et al. Medication therapy management interventions in outpatient settings: a systematic review and meta-analysis. JAMA Intern Med. 2015;175(1):76–87.
[127] Zermansky AG, Petty DR, Raynor DK, Freemantle N, Vail A, Lowe CJ. Randomised controlled trial of clinical medication review by a pharmacist of elderly patients receiving repeat prescriptions in general practice. BMJ. 2001;323:1340–3.

methodology and adherence to the guidelines of the MRF leading to the achievement of different outcomes. The case study published by Ocampo *et al.*[128] in which the service provided was exactly the same as in our study also found significant differences in hospital admissions.

The assessment of patients with different baseline characteristics can also be a confounder when analysing the association between the provision of PPSs and hospitalisation rates. For example, the meta-analysis carried out by Viswanathan *et al.*[126] suggests that the evidence of the impact of medication therapy management (MTM) on the outcomes of morbidity and mortality is insufficient. Nevertheless, they undertook a sub-analysis on a sample of patients suffering from diabetes mellitus or heart failure and it showed that MTM decreased the risk of being hospitalised and therefore hospitalisation costs. Interestingly, we observed that the baseline number of health problems and medicines used by patients in the sub-analysis was much higher than in the whole sample of the main study[46]. It could be said that a MRF service might reduce hospitalisations in a more complex type of patient, with specific chronic illnesses or treatments. In the future, it would be interesting to identify the group of patients who could benefit the most from the MRF.

[128] Ocampo CC, Garcia-Cardenas V, Martinez-Martinez F, Benrimoj SI, Amariles P, Gastelurrutia MA. Implementation of medication review with follow-up in a Spanish community pharmacy and its achieved outcomes. Int J Clin Pharm. 2015;37(5):931-40.

In this study, total costs of all the medication-related hospitalisations amounted to €280,229 and the cost of a medication-related hospital admission was €6,672. Another recent study from the Netherlands estimated this cost as €5,461[26] indicating some consistency across studies. The mean cost per hospital admission was similar in both study groups [IG: €5,895 (SD 4,496), CG: €6,948 (SD 5,597); p=0.578]. However, when distributing medication-related hospitalisation costs among all the patients who had been allocated to receive the MRF or UC, costs were significantly lower in patients receiving MRF [IG: €94 (SD 917), CG: €301 (SD 2,102); p=0.018]. It can be concluded that the MRF avoids costs to the NHS by means of reducing the number of hospital admissions rather than reducing the cost per hospitalisation. Several economic evaluations of PPSs provided in community pharmacy do not include the cost of hospital admissions[66,129,130]. It could be due to the difficulty of accessing these data from the community pharmacy. However, the measurement of this variable is encouraged as it could lead to the cost-effectiveness of the service.

[129] Bond C, Matheson C, Williams S, Williams P, Donnan P. Repeat prescribing: a role for community pharmacists in controlling and monitoring repeat prescriptions. Br J Gen Pract. 2000;50(453):271-5.

[130] Munroe WP, Kunz K, Dalmady-Israel C, Potter L, Schonfeld WH. Economic evaluation of pharmacist involvement in disease management in a community pharmacy setting. Clin Ther. 1997;19(1):113-23.

In the hospitalisation screening, the experts' independency and blindness to the study group were essential to assure the quality of the results and minimize possible bias. IRR (kappa = 0.646; 95% CI 0.52, 0.78) reached the 'substantial agreement' level in the scale proposed by Landis & Koch[121]. It is highly likely that a higher IRR could have been reached if full diagnosis had been available for the experts, instead of just DRG description. However, this kappa value can be considered acceptable. For instance, the STOPP/START criteria, which have been widely accepted and implemented in real practice, reached the same level of agreement[131].

A large number of studies reporting the prevalence of medication-related hospitalisations have been published, although hospitalisation rates vary widely. A recently published literature review which sifted through 95 studies, found that they ranged from 0.1% to 54%[116]. However, percentages around 5.3%[15] and 19.4%[132] are more frequent. The percentage of medication-related hospitalisations in this sub-analysis was high (50.6%, n = 42) since this study combined several criteria identified as reporting higher rates of hospitalisations[116]: aged patients, consideration of adverse drug events instead of adverse drug reactions, inclusion of all hospital admissions rather

131 Gallagher P, Ryan C, Byrne S, Kennedy J, O'Mahony D. STOPP (Screening Tool of Older Person's Prescriptions) and START (Screening Tool to Alert doctors to Right Treatment). Consensus validation. Int J Clin Pharmacol Ther. 2008;46(2):72–83.
132 Perez C, Bermejo T, Delgado E, Carretero E. Adverse drug reactions which provoke hospital admission. Farm Hosp. 2011;35(5):236-43.

than only acute ones and screening of the hospital admissions through a medical chart. Additionally, polypharmacy could be another factor leading to more medication related-hospital admissions.

The small number of hospital admissions may be the main limitation of this study. Due to the low frequency of the final outcome, this is a common limitation in studies analysing hospitalised patients after receiving a pharmacist-led intervention[133] and results must be interpreted with caution. However, the appropriate sample size could be almost unreachable as was the case in a previous study[134]. Even with few medication-related hospitalisations we found significant differences in both number and costs of admissions between groups, although confidence intervals were wide.

There was a lack of concordance between some of the hospital admissions self-reported by patients and those recovered from health regional directorates and official hospital registrations. Twenty-five of the self-reported hospital admissions in the CG and seven in the IG were unverifiable. Causes of this discordance could include an error in patients' perception, hospital admissions in private hospitals or in different provinces

[133] Krska J, Cromarty JA, Arris F, Jamieson D, Hansford D, Duffus PR, et al. Pharmacist-led medication review in patients over 65: a randomized, controlled trial in primary care. Age Ageing. 2001;30(3):205–11.
[134] Leendertse AJ, Koning GH, Goudswaard AN, Belitser SV, Verhoef M, Gier HJ, et al. Preventing hospital admissions by reviewing medication (PHARM) in primary care: an open controlled study in an elderly population. J Clin Pharm Ther. 2013;38(5):379-87.

from the ones where the study was undertaken. We verified patients' self-reported data with official sources, but other systems are needed in future studies to ensure the recovery of a greater number of hospital admissions. Furthermore, the retrospective design of the study limited the information available and it prevented us from comprehensively assessing the preventability of the medication-related hospital admissions[20] and from considering other possible reasons for non-admission to hospital, such us admission to care homes.

3.5 Conclusions

Medicines are the most widely used technology to resolve and control health problems and they consume a substantial part of the healthcare budget. However, this study endorses that patients are suffering a high number of hospital admissions due to the ineffective and unsafe use of medicines. Policy decision makers should consider the implementation of strategies proven to avoid such events in order to optimize population health as well as healthcare resource allocation. A MRF service provided by community pharmacists might be an effective strategy to balance the assurance of the benefit from medications and the avoidance of medication-related hospitalisations in older people using polypharmacy. This study provided novel evidence on the positive impact of a MRF service on hospital admissions, increasing the well-being of the elderly and enhancing the allocation of healthcare resources.

3.6 Reference

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Discussion

This thesis has provided evidence on health and economic outcomes of professional pharmacy services, and specifically for MRF, in the community pharmacy setting. The MRF is a dominant alternative improving patients´ health while saving costs to the health system, especially due to its positive effect on hospital admissions.

The cost-effectiveness results of the systematic review showed that PPSs can improve patients' health with low financial investment, and/or even saving costs to the healthcare system. Decision makers should consider funding services that improve populations' health outcomes in a cost-effective way to ensure their sustainability. Several services are being remunerated in some countries[135]. Funding of PPSs across countries could facilitate community pharmacy to successfully make the transition started some decades ago from product oriented to patient oriented practice[136].

Most of the economic evaluations (7 out of 13) found that PPSs were more effective and more costly than the UC, which is the most frequent outcome when assessing new healthcare technologies. However, taking into

[135] Houle SK, Grindrod KA, Chatterley T, Tsuyuki RT. Paying pharmacists for patient care: A systematic review of remunerated pharmacy clinical care services. Can Pharm J (Ott). 2014;147(4):209-32.
[136] van Mil JWF, Schulz M, Tromp TF. Pharmaceutical care, European developments in concepts, implementation, teaching, and research: a review. Pharm World Sci. 2004;26(6):303-11.

account the amount of money needed to improve one QALY or any other effectiveness unit, the investment needed was low. The interesting point is that in four economic evaluations, PPSs turned out to be more effective and less costly than the UC, which is the optimal outcome when assessing a healthcare technology. Furthermore, the results provided by two of these studies were highly reliable since they were high quality studies. One of the PPSs was an adherence service for patients with chronic obstructive pulmonary disease[77] whereas the other one was the first EE performed on the MRF of the conSIGUE Program[68].

Initially a CUA was proposed when developing the economic evaluation of the conSIGUE Program. However, when negotiating with local and national Spanish decision makers we realized that this analysis was insufficient for them to consider a payment for the service. The cost per QALY concept was difficult to understand and they were interested in the cost-savings generated by the MRF. Thus, we calculated the cost-savings and transformed the cost per QALY to a more easily interpretable cost-benefit ratio.

In the conSIGUE Program, the MRF saved €97 per patient during the 6-month follow-up for the health system. It was estimated that even if health administration paid €22 per patient-month, MRF would save €273 per

patient-year. In order to transform the cost per QALY to a cost-benefit ratio, a monetary value ranging from €13,863 to €25,905 obtained through contingent valuation in nine European countries was allocated to the QALY. Recently, a cost-effectiveness threshold ranging from €20,000 and €25,000 per QALY by estimating the relation between the health expenditure and health has been suggested for Spain[137]. If one used this threshold as the monetary value of QALY in the cost-benefit analysis, the results would be very similar with the lower limit slightly higher.

The MRF showed a cost-benefit ratio between €3.3:1 and €6.2:1, which indicates that for every €1 invested in MRF, a benefit of €3.3 to €6.2 can be expected. This cost-benefit ratio was similar to the median values of cost-benefit ratios found in different systematic reviews[32]. The "benefit" concept includes both the improvements in health outcomes by allocating a monetary value to these improvements and the cost-savings generated by the service. The reason for the service generating net savings was that the extra costs of the service (the investment of the pharmacy, time of the practice change facilitator and the time of the pharmacists) were compensated with savings in medication, ED visits and especially the decrease in hospital admission costs.

[137] El Global. [Spain has a cost-effectiveness threshold: between 20.000 and 25.000 € per QALY]. Madrid, June 2016. Available from: http://www.elglobal.net/noticias-medicamento/2016-06-17/politica-sanitaria/el-coste-efectividad-ya-tiene-umbral-en-espana-entre-20-000-y-25-000-%E2%82%ACavac/pagina.aspx?idart=988203. [Accessed August 5, 2016].

Hospital admissions are the most costly resource analysed in this research project. When we firstly analysed the hospital costs to calculate the cost-benefit ratio by allocating a mean cost to patient-reported hospital admissions, we realised that it was not a reliable method. We needed a more accurate strategy, thus DRG were used. Through this strategy we confirmed patient-reported information with official sources; we had more specific cost estimation for each hospital admission and the clinical description of the hospitalisations. This information was used to assess whether hospitalisations were related to medicines and to include in the analysis only those admissions related to medicines, lessening the variability in both clinical and economic analyses.

The reporting of this process plus the necessity of generating evidence on the effectiveness of PPSs on health outcomes led to the third chapter of the thesis. This study evidenced the high prevalence of medication-related hospital admissions in elderly population using polypharmacy and the significant impact of the MRF on avoiding medication-related hospital admissions. Additionally, it showed that the MRF decreases hospital costs to the health system by means of reducing the number of hospitalisations.

Our findings contrast with other studies in which the impact of PPSs on hospital admissions is uncertain. This uncertainty could be due to the

assessment of a different type of PPSs; different characteristics, rates of fidelity and implementation of the service; different patients´ baseline characteristics or not evaluating the association of hospital admissions with medicines. We found a significant impact of the MRF on the number and costs of medication-related hospital admissions in the polymedicated elderly, although confidence intervals were wide. The variability could be due to the small number of hospitalisations, a common limitation in studies analysing hospitalised patients after receiving a pharmacist-led intervention[133,134]. Hospital admissions are infrequent events and at the same time, the impact on patients´ health outcomes and healthcare resources is high. Thus, hospital admissions must be recorded accurately. In future studies a system that goes beyond patients´ self-reporting and that standardises public and private health systems´ registries is needed to ensure the correct recording of all the hospital admissions.

The final aim of EE is to provide policy makers with information to facilitate the process of decision making in rational choice among alternative technologies. Therefore the generation of accurate, reliable and easily understandable results is needed. The method used to report the results was specifically one of the objectives in two of the three papers released in the context of the present thesis, since in the beginning of the process we realised

that the most frequent tools used to report the results of the EE were not the most appropriate to communicate with decision makers. It seems important to diminish the gap between non-health economist decision makers and the complex concepts, methodology and interpretation of health economic results, in order to foster the process of accepting new technologies that will promote the efficiency of the health system.

Health innovation relies on demonstrating that the technology is safe, effective, cost-effective, affordable and how will the technology be adopted and disseminated in the practice[138]. Overall, PPSs provided in community pharmacy have demonstrated to be effective and cost-effective (see chapter 1). Particularly the MRF is a dominant strategy for the Spanish health system. Since the MRF improves health outcomes while saving money to the health system, decision makers should consider including the MRF in the primary care service portfolio.

However the affordability of MRF for the NHS should be analysed as well, considering what the likely population to receive the service is and what the overall costs would be. To address this issue, a budget impact analysis should be undertaken. This budget impact analysis would most likely be

[138] National Information Center on Health Services Research and Health Care Technology (NICHSR). Chapter II: Fundamental concepts. U.S. National Library of Medicine. Available from: https://www.nlm.nih.gov/nichsr/hta101/ta10104.html. [Accessed July 27, 2016].

positive since the MRF is less costly than the UC. The health system should generate a new budget line for the payment of the service, taking into account not the incremental differences between the MRF and the UC but the total costs, savings and budget constraints. Finally, the adoption and dissemination of the technology in the practice should be discussed, taking into account the funding, availability and equity of access to the service. Once implemented, the adoption and the use of the service in routine delivery should be monitored[138].

Health promotion strategies provided in primary care are one of the strategies suggested to promote the sustainability of health systems in some core reports released by the World Health Organization[4-6]. The MRF service is an intervention provided in primary care setting, targeted at polymedicated elderly and focused on the prevention and solution of DRPs and NCOMs and improving the control of chronic diseases. One of the key ideas suggested in these reports is that "by expanding the scope of what primary care settings can provide, if more (healthcare) can be provided within primary care, less needs to be provided in more resource intensive settings"[6]. Spanish community pharmacists currently provide basic services such as dispensing and minor ailments advice[47]. Providing services with the complexity and responsibility level required by the MRF would suppose an expansion of the

role of the pharmacists. Additionally, these reports released by the WHO state that given the long-term implications, the strategies to meet the needs of ageing populations must be introduced in health systems even in the current economic crisis[4]. Therefore the current investment in the implementation of the MRF would be justified since the later these interventions are implemented, the higher will be the financial impact of using secondary care resource-intensive settings.

Conclusions

1. The systematic review of economic evaluations based on randomized controlled trials concluded that professional pharmacy services, i.e. those activities in which the pharmacists would use their professional knowledge and abilities to improve pharmacotherapy and disease management by means of interacting with the patient or with other health professional, are overall cost-effective compared with the usual care provided in the community pharmacy. Four studies concluded that professional pharmacy services were dominant, since they improved patients' clinical outcomes and health-related quality of life while saved costs to the healthcare system. The majority of the studies concluded that professional pharmacy services could improve patients' outcomes with a financial investment far below the cost-effectiveness threshold.

2. The existing evidence on the cost-effectiveness of professional pharmacy services provided in community pharmacy should be complemented with more high quality studies assessing each individual service, due to the low number of studies published, limited comparability and the uncertainty related to some incremental cost-effectiveness ratios. Those professional pharmacy services that have already been assessed through high quality studies and obtained

positive and robust cost-effectiveness results, could be considered by policy makers to be implemented within specific health systems of different countries.

3. Medication review with follow-up, a professional pharmacy service aimed at resolving both drug related problems and their negative clinical outcomes through an optimisation of the medication, provided by community pharmacists and targeted to aged polypharmacy patients, was the dominant alternative in the conSIGUE Program, since it avoided €97 per patient in 6 months to the health system besides providing health benefits to patients. Investment in the implementation of this service would represent an efficient use of healthcare resources since for every €1 invested, a benefit of €3.3 to €6.2 can be expected.

4. In the conSIGUE Program, 50% of the hospital admissions in elderly patients using polypharmacy were associated with the ineffective and unsafe use of medicines. Medication review with follow-up provided by community pharmacists has a positive impact on medication-related hospital admissions, since the probability of being hospitalised

was 3.7 times higher in the comparison group compared with the intervention group.

5. The impact of the medication review with follow-up service provided by community pharmacists on medication-related hospital admissions led to a decrease in hospital costs. The mean hospital cost per elderly patient using polypharmacy in the intervention group of the conSIGUE Program was three times lower than for patients in the comparison group.

6. Community pharmacist-led medication review with follow-up is a cost-effective strategy to meet ageing population´s health needs, decrease the preventable clinical and economic burden caused by drug related problems and in long-term, promote the sustainability of the Spanish health system.

Conclusiones

1. La revisión sistemática de evaluaciones económicas basadas en ensayos controlados aleatorizados permite concluir que los servicios profesionales farmacéuticos, entendidos como las actividades en las que el farmacéutico utiliza su conocimiento y habilidades profesionales para mejorar la farmacoterapia y el manejo de las enfermedades interactuando con el propio paciente o con otros profesionales sanitarios son, en general, coste-efectivos en comparación con la atención habitual realizada en la farmacia comunitaria. Cuatro estudios concluyeron que los servicios profesionales farmacéuticos evaluados eran dominantes, ya que mejoraban los resultados en salud de los pacientes a la vez que generaban un ahorro para el sistema sanitario. La mayoría de los estudios concluyeron que los servicios profesionales farmacéuticos pueden mejorar los resultados en salud de los pacientes con una inversión económica muy por debajo del umbral de coste-efectividad.

2. La evidencia disponible sobre el coste-efectividad de los servicios profesionales farmacéuticos realizados en farmacia comunitaria debería ser complementada con estudios adicionales de calidad que

evalúen individualmente cada servicio, debido al bajo número de estudios publicados, limitada comparabilidad y la incertidumbre relacionada con algunos de los ratios de coste-efectividad incremental. En el caso de los servicios que ya han sido evaluados mediante estudios de calidad y han obtenido resultados de coste-efectividad positivos y robustos, son susceptibles de ser valorados por los decisores sanitarios para ser implantados en los sistemas sanitarios específicos de diferentes países.

3. El seguimiento farmacoterapéutico, servicio profesional farmacéutico dirigido a resolver tanto los problemas relacionados con la medicación como los resultados clínicos negativos de los mismos a través de la optimización de la medicación, realizado por farmacéuticos comunitarios y dirigido a pacientes mayores polimedicados, demostró en el Programa conSIGUE ser la alternativa dominante en comparación con la atención habitual, ya que ahorró 97€ al sistema sanitario por paciente en 6 meses, además de proporcionar beneficios en salud a los pacientes. La inversión en la implantación de este servicio representaría un uso eficiente de los recursos sanitarios, ya que por cada 1€ invertido, el servicio proporcionaría un beneficio de entre 3,3€ y 6,2€.

4. La mitad de los ingresos hospitalarios sufridos por los pacientes mayores polimedicados participantes en el Programa conSIGUE estaban asociados al uso inefectivo e inseguro de los medicamentos. El seguimiento farmacoterapéutico realizado por farmacéuticos comunitarios ejerció un impacto positivo en el número de ingresos hospitalarios relacionados con la medicación, en tanto que la probabilidad de ser ingresado fue 3,7 veces mayor en el grupo comparación respecto al grupo intervención.

5. El impacto del servicio de seguimiento farmacoterapéutico realizado por farmacéuticos comunitarios en los ingresos hospitalarios relacionados con la medicación se tradujo en una disminución de los costes hospitalarios, siendo el valor medio de este coste por cada paciente mayor polimedicado en el grupo intervención del Programa conSIGUE tres veces menor que en los pacientes del grupo comparación.

6. El seguimiento farmacoterapéutico realizado por farmacéuticos comunitarios resulta ser una estrategia coste-efectiva para responder a las necesidades sanitarias de la población mayor, reducir la carga

clínica y económica prevenible causada por los problemas relacionados con los medicamentos y a largo plazo, promover la sostenibilidad del sistema sanitario en España.

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