Original Research Article

Cost-utility analysis of a medication review with follow-up service for older adults with polypharmacy in community pharmacies in Spain: the conSIGUE Program

Short running title: Cost-utility analysis of a medication review with follow-up service

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Abstract

Background

The concept of Pharmaceutical Care is operationalized through pharmaceutical professional services, which are patient-oriented to optimize their pharmacotherapy and to improve clinical outcomes.

Objective

The objective of this study was to estimate the incremental cost-effectiveness ratio (ICER) of a medication review with follow-up (MRF) service for older adults with polypharmacy in Spanish community pharmacies, against the alternative of having their medication dispensed normally.

Methods

The study was designed as a cluster randomized controlled trial, and was carried out over a time horizon of six months. The target population was older adults with polypharmacy, defined as individuals taking five or more medicines per day. The study was conducted in 178 community pharmacies in Spain. Cost-utility analysis adopted a health service perspective. Costs were in euros at 2014 prices and the effectiveness of the intervention was estimated as QALYs. In order to analyze the uncertainty of ICER results, we performed a nonparametric bootstrapping with 5,000 replications.

Results

A total of 1,403 older adults, aged between 65 to 94 years, were enrolled in the study: 688 in the intervention group (IG) and 715 in the control group (CG). By the end of the follow-up, both groups had reduced the mean number of prescribed medications they took, although this reduction was greater in the IG (0.28±1.25 drugs; $p<0.001$) than in the CG (0.07±0.95 drugs; $p=0.063$). Older adults in the IG saw their quality of life improved by 0.0528±0.20 ($p<0.001$). In contrast, the CG experienced a slight reduction in their quality of life: 0.0022±0.24 ($p=0.815$). The mean total cost was €977.57±1.455,88 for the IG and €1,173.44±3,671.65 for the CG. In order to estimate the ICER, we used the costs adjusted for baseline medications and QALYs adjusted for baseline utility score, resulting in a mean incremental total cost of €-250.51±148.61 (95% CI -541.79 to 40.76) and a mean incremental QALY of 0.0156±0.004 (95% CI 0.008 to 0.023). Regarding the results from the cost-utility analysis, the MRF service emerged as the dominant strategy.

Conclusion

MRF service is an effective intervention for optimizing prescribed medication and improving the quality of life in older adults with polypharmacy in community pharmacies. The results from the cost-utility analysis suggest that MRF service is cost effective.

Key points for decision makers

- Polypharmacy is a particular concern in older adult populations, and is associated with negative health outcomes.
- Medication review with follow-up is a service that attempts to optimize pharmacotherapy, not just by focusing on the process of the use of medication, but also by improving clinical outcomes for older adults.
- Medication review with follow-up service is an effective intervention for optimizing prescribed medication and improving the quality of life of older adults with polypharmacy in community pharmacies. Compared with usual dispensing, this service is cost effective.

1 Introduction

In 2013, 18% of the Spanish population was older adults, conventionally defined as aged 65 or over. The percentage was higher among the female (20%) than the male population (16%) [1]. As a result of population aging, this percentage will represent 22% of the Spanish population in the next ten years (20% of males and 24% of females) [2]. Older adults usually present a wider variety of health problems, and therefore make more intensive use of medication than the rest of the population. This often leads to drug-related problems (DRPs) [3] and negative outcomes associated with medication (NOMs) [4].

Polypharmacy is a common phenomenon that increases with age. This increase in medication use is in turn associated with increased morbidity. Although there are a wide range of definitions and different situations associated with this phenomenon [5], the most widespread strategy is to target patients with comorbidities who are using over five drugs or more [6].

Medication is the most widely used healthcare technology for dealing with health problems. In Spain, public expenditure through official prescriptions in the National Health Service (NHS) amounted to €9,183 million in 2013 [7]. Although this figure represents a 6% drop from previous years, such a high level of expenditure requires methods to ensure the rational use of medication, to optimize the results obtained from their use and to ensure that these medications actually do control health problems. Failures in effectiveness and safety have a cost for the health of patients and also in terms of hospital admissions and accident and emergency (A&E) department visits, appointments with general practitioners, and increased pharmacological treatments.

The concept of pharmaceutical care promotes different pharmaceutical professional services, which are patient-oriented in an attempt to optimize their pharmacotherapy [8,9]. Medication review with follow-up (MRF) is a service in which the pharmacist evaluates patients' pharmacotherapies and intervenes in collaboration with the general practitioner and the patients themselves, in order to ensure that therapeutic goals are achieved. One of the main points of the MRF service is that it attempts to optimize pharmacotherapy, not just by focusing on the process of the use of medication, but also by improving clinical results for the patients. When pharmacists play a proactive role in performing medication reviews and in the active education of other healthcare professionals, pharmacotherapy for older patients is improved [10]. However, the evidence of the impact of pharmacists' interventions on health outcomes, quality of life, or cost-effectiveness of care is mixed [11]. Few studies of pharmaceutical care programs for older adults have undertaken a rigorous economic evaluation, and a more standardized approach to data collection is required [12].

Based on this, a national research project, the conSIGUE Program, has been implemented to assess clinical and economic impact of the MRF service for older adults with polypharmacy in Spanish community pharmacies.

The objective of this study was to estimate the incremental cost-effectiveness ratio (ICER) of a MRF service for older adults with polypharmacy in community pharmacies against the alternative of usual dispensing.

2 Methods

2.1 Study design

The study was designed as a cluster randomized controlled trial carried out over six months of follow-up. It was conducted in community pharmacies in Spain from November 2011 to January 2013. The target population comprised older adults, aged 65 or over, with polypharmacy, defined as individuals taking five or more medicines per day. These five medicines are only prescription medication and over-the-counter medicines (officially registered medications).

Sample size was calculated according to the results of a pilot study, conducted in the Spanish province of Cádiz for one month. Taking into account the change in the number of medicines used that resulted from the pilot study, 530 patients were required in each group in order to obtain significant results. However, taking into account the cluster design and the confounding variables, 750 patients were required in each group.

The pharmacists of the participant provinces were informed about the conSIGUE Program through the Official College of Pharmacists, and voluntarily signed up to be included in the research study. Pharmacies were allocated into either the intervention or the control group. Each pharmacy selected ten patients who met the inclusion criteria: age of 65 or over and taking five or more officially registered medicines.

Pharmacists allocated into the intervention group received a three-day off-site training course and on-site visits by a facilitator during the six-month follow-up. The functions of the facilitator were assisting pharmacists in the provision of the service and ensuring the quality and homogeneity of the interventions. Pharmacists and patients had follow-up visits every 1.2 months, and pharmacists were not compensated for providing MRF service in the conSIGUE Program.

The variables recorded to measure the economic and clinical outcomes of the MRF service provided in community pharmacies to older adults with polypharmacy were: the number of used medicines, number of uncontrolled health problems, health-related quality of life, number of visits to A&E departments, number of hospital admissions, and ICER of the MRF service. The secondary objectives were to describe the prevalence of DRPs and NOMs. Variables were recorded during the visits by the patient to the pharmacy where they interacted with a pharmacist.

The study was approved by the Ethics Committee of the Virgen de las Nieves Hospital in Granada in 2009. All patients signed an informed consent before their inclusion in the study.

The study was carried out taking into account the recommendations of the proposed guidelines for economic evaluation of health technologies in Spain [13], which have a high degree of consistency with CHEERS criteria [14], and using data from the NHS. It estimated all identifiable costs to the NHS and health outcomes in quality-adjusted life years (QALYs). The alternatives compared were intervention group (IG), older adults who received MRF service in community pharmacies, and control group (CG), older adults who received usual dispensing in community pharmacies).

2.2 Medication review with follow-up service

The Dader method for MRF service was developed by the Pharmaceutical Care Research Group at the University of Granada, Spain [15]. The aim of the MRF service is to detect DRPs and to prevent and resolve NOMs [16]. In the context of this service it is important to establish the conceptual differences between the terms *medication related problem* and NOM [4]. A NOM is the result affecting the health of the patient, which is or may be associated with the use of medications. Older adults in the IG received the

MRF service as per the methodology agreed upon by a group of pharmaceutical care experts [3]. Table 1 shows the different phases of the MRF service. All sessions were conducted face to face.

Table 1 Phases of the medication review with follow-up service

Stage*	Timing	Description
First interview	First month	Patients took all the medication they were taking to the pharmacy and the pharmacist asked them a series of questions to obtain information about their health problems, clinical information about the control of health problems, and drugs used by patients at the time of the interview. If patients had in their possession any medical report, they brought them to the pharmacist.
Situation assessment	First month	The pharmacist processed the information obtained from patients during the interviews.
Study phase	First month	The pharmacist searched for information in the knowledge database of the General Council of Pharmaceutical Associations of Spain (Bot PLUS) [17], and in other sources of information (clinical practice guides, books, therapy manuals etc.) to enable them to identify DRPs and NOMs.
Evaluation Phase	First month	The pharmacist identified DRPs and NOMs.
Definition of the action plan	First month	The pharmacist agreed with patients on certain therapeutic objectives to be reached regarding their pharmacotherapy, and suggested interventions to patients and/or general practitioners to prevent, resolve, or improve the identified DRPs and NOMs.
Intervention phase	First month	The pharmacist went through with the interventions in the action plan.
Follow-up to ascertain the level of acceptance of the interventions and evaluate their results	Second to sixth month	The pharmacist obtained information about the acceptance or non-acceptance of the proposed interventions by those affected (general practitioners and/or patients). After this, the pharmacist obtained clinical information about patients' health problems, about NOMs, and about the elements of the process of use of the drugs (DRPs), and repeated the process described for the MRF service.
Additional contacts	Second to sixth month	Additional contacts with the patient outside the scheduled contacts.

*Every interview was carried out face to face.

2.3 Control group

Older adults in the CG received usual dispensing in their community pharmacy.

2.4 Community pharmacies

The study was performed in 178 community pharmacies of four Spanish provinces: 64 in Guipúzcoa (34 in IG vs 30 in CG), 42 in Granada (24 in IG vs 18 in CG), 39 in Santa Cruz de Tenerife (16 in IG vs 23 in CG) and 33 in Las Palmas de Gran Canaria (14 in IG vs 19 in CG).

The number of older adults from each province was: 525 in Guipúzcoa (278 in IG vs 247 in CG), 324 in Granada (194 in IG vs 130 in CG), 307 in Santa Cruz de Tenerife (115 in IG vs 192 in CG) and 247 in Las Palmas de Gran Canaria (101 in IG vs 146 in CG).

2.5 Primary outcomes

- Medication prescribed: this information was extracted six times between the beginning and the end of the study from community pharmacy databases, so the measurements were captured every 1.2 months.
- Healthcare resources: we analyzed A&E department visits and hospital admissions. For each older adult, data of healthcare resources during the study was extracted from hospital information system databases for each province [18-20]. In order to analyze the impact of the MRF service, three experts independently evaluated the causes of hospital admissions. They identified hospital admissions related to NOMs that could have been avoided through a MRF service. Names and qualifications of three experts are included in acknowledgments section.
- Health-related quality of life was measured by the Spanish version of the EuroQol-5D-3L questionnaire [21]. This questionnaire was administered in six personal interviews between the beginning and the end of the study, so the measurements were captured every 1.2 months. The EuroQol-5D-3L describes health status in terms of five dimensions (mobility, self-care, usual activities, pain/discomfort, and anxiety/depression), and each of these is defined with three levels of severity. The scores were used to estimate a utility score, a single index on health-related quality of life, which ranges from 1 and 0, where 1 is the best possible state of health and 0 is death. In addition, a Visual Analogue Scale (VAS) was used to measure the subjects' health status with scores at one end of the scale representing the 'worst' (0) and scores at the other end representing the 'best' (100) health state. QALYs were calculated by using an area-under-the-curve analysis, with linear interpolation of utility scores between six interviews (every 1.2 months, between baseline and six months of follow-up) [22].
- Costs: we measured costs of the prescribed medication, of the time employed by the pharmacist, of A&E department visits, of hospital admissions, and of the investment in community pharmacy infrastructure and training. Costs were in euros at 2014 prices. Prices from previous years were updated according to the Spanish consumer price index [23]. The following variables were included in the analysis:
    - Time employed by the pharmacist in the training and in the MRF service was calculated for each patient. Pharmacists recorded the time dedicated in each stage of MRF service. In addition, pharmacists training was estimated taking into account the total time of the training and the total number of customers a pharmacist could supply MRF service in one year (see 3.1 section). The unit cost of the community pharmacist was calculated taking into account the pharmacist' salary in the Spanish community pharmacy agreement [24] and pharmacist's annual working time.
    - Medication cost, excluding additional medication associated with hospitalizations, was calculated from the official list for drug prices [25].
    - A&E department visit cost was calculated using prices from the public system [26].

- Hospital admission cost was calculated using costs from the public system for diagnosis-related groups [27].
- The investment required to commence the MRF service in community pharmacies and its subsequent maintenance over time was estimated taking into account the following premises: a mean of 2,500 customers per community pharmacy [28]; 16% of customers being older adults with polypharmacy [29,30]; 60% of older adults with polypharmacy accepting the MRF service, according to the results of a pilot study.

2.6 Cost-utility analysis

Cost-utility analysis adopted a health service perspective. The effectiveness of the intervention was estimated as QALYs. Results of cost-utility analysis were expressed in terms of the ICER, calculated by dividing the difference in total costs between the IG and the CG by the difference in QALYs between both groups [31]. The total costs included the prescribed medication, A&E department visits, hospital admissions related with NOMs, the pharmacist's intervention and the required investment in the community pharmacy. Moreover, taking into account the differences in the number of medications and in basal utility scores, we used the costs adjusted for baseline medications and QALYs adjusted for baseline utility score.

Because the time horizon of the study did not extend beyond 12 months, discounting of costs and QALYs was not necessary. In order to analyze the uncertainty of ICER results, we performed a nonparametric bootstrapping with 5,000 replications [32]. The resulting 5,000 ICER replicates were plotted on the cost-effectiveness plane and used to construct a cost-effectiveness acceptability curve.

The cost-effectiveness plane is a graphical way of presenting cost-effectiveness results, with the difference in costs on the vertical axis and the difference in health benefits on the horizontal axis [33]. The acceptability curve represents the proportion of simulations in which the intervention is considered cost-effective over a range of values of the threshold cost-per-QALY [34]. Analyses were carried out with the STATA software, version 12.

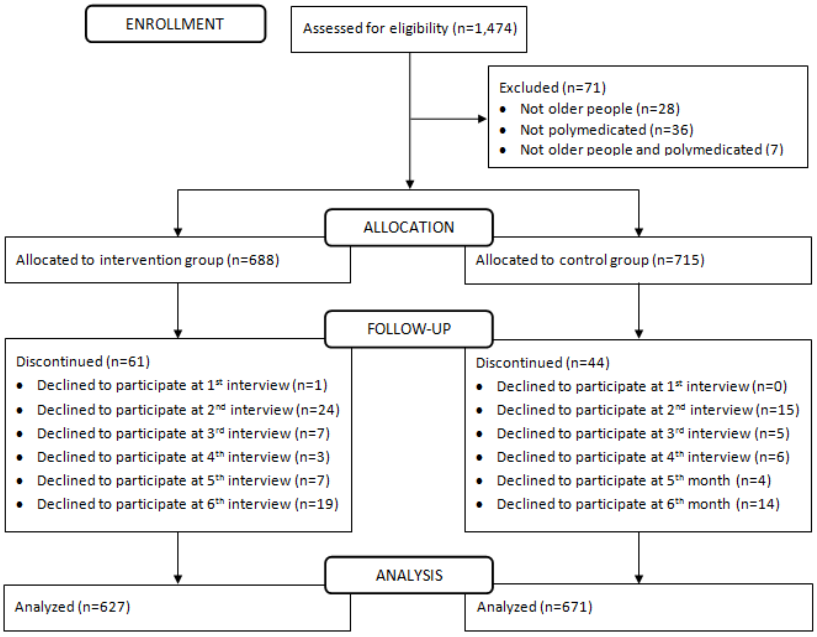
2.7 Statistical analysis

Descriptive analyses of the primary variables included calculating the mean and standard deviation for the quantitative variables and absolute and relative frequencies for the qualitative variables. Bivariate analyses were performed to evaluate the differences between groups in terms of medication prescribed, healthcare resources, health-related quality of life, and costs. Quantitative variables following a normal distribution were analyzed with Student's *t*-test or the Mann-Whitney test for those variables non-normally distributed. The qualitative variables were analyzed with Pearson's $\chi 2$ test or the Fisher test. Significance level was set at $P < 0.05$. Prior to estimating the ICER, we adjusted the main variables of the outcome (cost and QALY) through simple linear regression (Technical appendix).

3 Results

Community pharmacists recruited 1,474 older adults, out of whom 71 were excluded because they did not meet the inclusion criteria: 28 older adults were not old enough, 36 older adults did not take five or more drugs, and seven older adults were not old enough and did not take five or more drugs (Figure 1).

Figure 1 Process of enrollment, allocation, follow-up, and analysis



A total of 1,403 older adults were enrolled, 688 in the IG and 715 in the CG. Table 2 shows the socio-demographic characteristics of participants.

Table 2 Socio-demographic characteristics of participants

	Intervention (n=688)	Control (n=715)	P value
Age; mean ± standard dev.	75.36 ± 6.48	74.91 ± 6.58	0.195
Female; n (%)	409 (60.1)	441 (61.7)	0.535
Living as a couple; n (%)	355 (59.8)	384 (59.3)	0.856
No formal education; n (%)	149 (27.0)	116 (18.6)	0.001
Prescribed medications; mean ± standard dev.	7.74 ± 2.50	7.39 ± 2.37	0.009
A&E department visits[a]; n (%)	193 (28.1)	211 (29.5)	0.547
Hospital admissions[a]; n (%)	44 (6.4)	31 (4.3)	0.086
Mobility problems – EQ-5D; n (%)	1 (0.1)	12 (1.7)	0.003
Self-care problems – EQ-5D; n (%)	11 (1.6)	13 (1.8)	0.754
Usual activities problems – EQ-5D; n (%)	24 (3.5)	25 (3.5)	0.998
Pain/discomfort problems – EQ-5D; n (%)	99 (14.4)	122 (17.1)	0.173
Anxiety/depression problems – EQ-5D; n (%)	36 (5.2)	51 (7.1)	0.142
Visual Analogue Scale; mean ± standard dev.	64.98 ± 18.55	62.95 ± 19.64	0.049

[a]Data from the previous six months.

Both groups of older adults had similar characteristics except for their level of education (27% in the IG and 18.6% in the CG had no formal education; p=0.001) and the mean number of prescribed medications

(7.74 drugs in the IG and 7.39 drugs in the CG; p=0.009). Cost and QALY could not be obtained for 105 participants, who were excluded from the results.

3.1 Intervention times for the medication review with follow-up

The mean time employed by the pharmacist in the stages of the MRF service was 442.74±652.24 minutes: 44.57±29.77 minutes in the first interview; 40.26±34.24 minutes for writing the situation assessment; 75.44±87.26 minutes in the study phase; 39.05±40.60 minutes in the evaluation phase; 29.93±36.76 minutes in the therapeutic plan; 17.83±21.67 minutes in the intervention phase; 162.47±496.03 minutes for follow up; and 33.19±36.34 minutes for additional contacts.

Prior to the intervention, pharmacists were required to complete three-day off-site training course with a total duration of 900 minutes. When the provision of MRF service is on a per annum basis the total time is calculated through doubling follow-up and additional contacts phases. As a result of this assumption, the mean time employed by the pharmacist in the stages of the MRF service would be 638 minutes/year. Dividing the annual working time by total minutes to provide MRF service during a year, a pharmacist could supply MRF service to 156 customers/year. This number of patients was used to estimate the training cost associated with each patient.

3.2 Prescribed medication

Both groups reduced their mean number of prescribed medications (Table 3), although this reduction was greater in the IG (0.28±1.25 drugs; p<0.001) than in the CG (0.07±0.95 drugs; p=0.063). The difference in the observed reduction between the two groups was 0.21±0.06 drugs (95% CI: 0.092 to 0.335).

Table 3 Number of prescribed medications at each study assessment

	Intervention	Control	P value
1st interview	7.76 ± 2.51	7.32 ± 2.32	0.001
2nd interview	7.68 ± 2.45	7.27 ± 2.41	0.002
3rd interview	7.62 ± 2.45	7.26 ± 2.34	0.007
4th interview	7.54 ± 2.45	7.24 ± 2.36	0.025
5th interview	7.50 ± 2.40	7.26 ± 2.36	0.065
6th interview	7.48 ± 2.39	7.25 ± 2.40	0.096
Difference 1st to 6th	-0.28 ± 1.25	-0.07 ± 0.95	0.001

Data are presented as mean ± standard deviation.

3.3 Healthcare resources

Both groups experienced a reduction in the percentage of older adults who at least visited the A&E department once during the six months before and during the six months of the study, although this reduction was greater in the IG (27.9% vs 14.2%; difference 13.7%; p<0.001) than in the CG (29.1% vs 24.9%; difference 4.2%; p=0.044).

The mean number of visits to the A&E department during the six months before and the six months of the study dropped in both groups, although this reduction was larger among older adults in the IG (0.43±0.83 vs 0.19±0.51; difference 0.24; p<0.001) than for older adults in the CG (0.55±1.55 vs 0.42±1.21; difference 0.13; p<0.001).

The percentage of participants with at least one hospital admission during the six months before and the six months of the study dropped among the IG (6.9% vs 4.1%; difference 2.8%; p<0.001), while this percentage increased among the CG (4.3% vs 5.1%; difference 0.8%; p=0.044).

This trend continued with the mean number of hospital admissions during the six months before and the six months of the study dropping among the IG (0.09±0.35 vs 0.05±0.23; difference 0.04; p=0.007) and increasing among the CG (0.05±0.25 vs 0.07±0.36; difference 0.02; p=0.106).

After the group of experts had reviewed the cause behind each hospital admission, the percentage of older adults with at least one hospital admission dropped to 3.2% in the IG and 4.3% in the CG (p=0.285), with a mean of hospital admissions during the six months of the study of 0.03±0.19 in the IG and 0.06±0.31 in the CG. Table 4 shows the mean healthcare resources for the six months before and six months of the study.

3.4 Health-related quality of life

Table 4 shows the mean utility scores and VAS scores obtained from the EuroQol-5D-3L questionnaire at the six interviews. Participants in the IG reported an improvement in their quality of life of 0.0528±0.20 in the utility score (p<0.001) and 4.97±15.29 in the VAS score (p<0.001). In contrast, those in the CG saw a slight reduction in their quality of life of 0.0022±0.24 in the utility score (p=0.815) and 0.90±15.19 in the VAS score (p=0.127). The difference observed between both groups was 0.0550±0.01 in the utility score (95% CI: 0.0306 to 0.0794) and 5.87±0.85 in the VAS score (95% CI: 4.20 to 7.54).

Table 4 Mean utility score and visual analogue scale scores

	Intervention	Control	P value
1st utility score	0.7148 ± 0.28	0.6953 ± 0.31	0.238
2nd utility score	0.7327 ± 0.28	0.7109 ± 0.31	0.184
3rd utility score	0.7425 ± 0.27	0.6969 ± 0.32	0.006
4th utility score	0.7490 ± 0.28	0.7031 ± 0.32	0.006
5th utility score	0.7563 ± 0.27	0.6871 ± 0.34	<0.001
6th utility score	0.7677 ± 0.27	0.6931 ± 0.32	<0.001
Difference 1st to 6th	0.0528 ± 0.20	-0.0022 ± 0.24	<0.001
1st VAS	65.44 ± 18.07	63.22 ± 19.42	0.034
2nd VAS	66.05 ± 17.85	63.25 ± 18.55	0.006
3rd VAS	67.11 ± 17.22	62.72 ± 18.75	<0.001
4th VAS	67.19 ± 17.34	63.07 ± 18.55	<0.001
5th VAS	68.20 ± 17.32	61.86 ± 19.52	<0.001
6th VAS	70.46 ± 17.06	62.29 ± 19.20	<0.001
Difference 1st to 6th	4.97 ± 15.29	-0.90 ± 15.19	<0.001

Data are present as mean ± standard deviation.

The mean QALY scores, corresponding to the six months of the study, were 0.3721±0.12 and 0.3488±0.15 for the IG and CG respectively, resulting in an incremental QALY score of 0.0233

(p=0.002), largely due to the difference in utility scores at baseline (0.7148 vs 0.6953 score for the IG and the CG respectively).

3.5 Costs

A mean cost of €98.35 ± 143.03 was estimated for the time employed in the pharmacists' interventions, including the training previous to the intervention. The mean cost of the prescribed medication for the six months was €655.91±818.53 for the IG and €657.67±600.09 for the CG. The IG saw a reduction in the mean daily cost of prescribed medication, while the CG experienced a slight increase (Table 5). Pharmacists' interventions saved a mean medication cost of €0.17/day (p=0.057) while in the CG there was an increase in the mean cost of €0.02/day (p=0.774). The difference in the reduction observed between both groups was €0.19/day (p=0.079).

Table 5 Evolution of mean prescribed medication cost (€/day)

	Intervention	Control	P value
1st interview	3.72 ± 4.96	3.62 ± 3.29	0.654
2nd interview	3.61 ± 4.52	3.61 ± 3.38	0.996
3rd interview	3.62 ± 4.58	3.63 ± 3.41	0.968
4th interview	3.57 ± 4.52	3.64 ± 3.44	0.752
5th interview	3.61 ± 4.53	3.68 ± 3.47	0.745
6th interview	3.55 ± 4.50	3.64 ± 3.46	0.705
Difference 1st to 6th	-0.17 ± 2.24	0.02 ± 1.58	0.079

Data are presented as mean ± standard deviation.

Participants in the CG reported a greater consumption of healthcare resources, both in terms of visits to the A&E department and of hospital admissions. The mean A&E department visit cost was €33.05±90.98 for the IG and €74.18±213.93 for the CG (difference of €41.12; p<0.001), and the mean hospitalization cost was €215.52±1,263.93 for the IG and €496.79±3,720.07 for the CG (difference of €281.27; p=0.065). After excluding admissions for causes not related to NOMs, the mean hospitalization cost was €173.99±1,184.95 for the IG and €441.60±3,573.71 for the CG (difference of €267.61; p=0.067). The mean healthcare cost was €248.58±1,285.76 for the IG and €570.97±3,765.75 for the CG (difference of €322.40; p=0.037) and, after excluding admissions for causes not related to NOMs, €207.04±1,207.20 for the IG and €515.77±3,621.15 for the CG (difference of €308.73; p=0.037). Finally, the mean cost estimated as the required investment was €4,688.47 for a period of five years and a mean annual maintenance cost of €2,967.02, resulting in a mean cost of €16.27 per person. Table 6 shows each category of total mean cost.

Table 6 Categories of total mean cost (€/person)

	Intervention	Control	Difference
Pharmacists' interventions	98.35 ± 143.03	-	98.35
Prescribed medication	655.91 ± 818.53	657.67 ± 600.09	-1.76
Healthcare resources	207.04 ±1,207.20	515.77 ± 3,621.15	-308.73
A&E department visits	33.05 ± 90.98	74.18 ± 213.93	-41.12
Hospital admissions related to NOMs	173.99 ± 1,184.95	441.60 ± 3,573.71	-267.61
Required investment	16.27 ± 0.00	-	16.27
Total	977.57 ± 1.455,88	1,173.44 ± 3,671.65	-195.88

Data are presented as mean ± standard deviation.

3.6 Cost-utility analysis

The total mean total cost was €977.57±1,455.88 for the IG and €1,173.44±3,671.65 for the CG. To estimate the ICER, we used the costs adjusted for baseline medications and QALYs adjusted for baseline utility score, resulting in a mean incremental total cost of €-250.51±156.82 (95% CI -558.17 to 57.14) and a mean incremental QALY of 0.0156±0.004 (95% CI 0.008 to 0.023). Regarding the results from the cost-utility analysis, the MRF service emerged as the dominant strategy.

Based on 5,000 bootstrap replications, most of the bootstrap simulations are located in the lower-right quadrant (96.8%) and in the upper-right quadrant (3.2%) of the cost-effectiveness plane (Figure 2). The acceptability curve shows that if the willingness to pay is between €30,000/QALY and €45,000/QALY, the probability of the MRF service being cost-effective, compared with usual dispensing, is 100% (Figure 3).

Figure 2 Cost-effectiveness plane

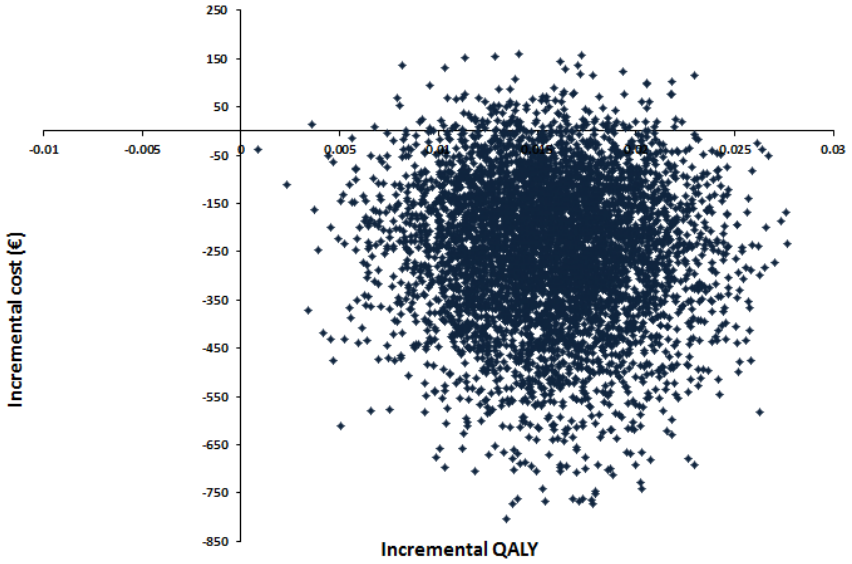
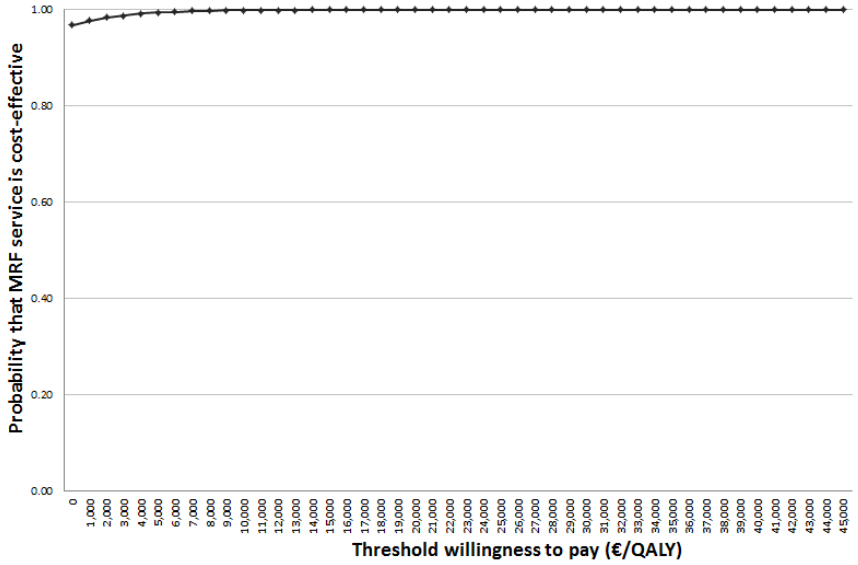


Figure 3 Acceptability curve based on willingness to pay for QALY



4 Discussion

Morbidity and mortality issues related to medication represent an important health and economic problem, which is particularly significant among older adults. This study suggests that a MRF service carried out in pharmacies by pharmacists is an efficient technique for dealing with a health problem that is increasingly prevalent in aging societies.

Pharmacists spent a mean of 443 minutes in the MRF service, which resulted in a cost of €98. If the MRF service was extended to one year, only the follow-up and additional contacts phases would have to be extrapolated to annual values. Pharmacists devoted an average of 199 minutes to the initial phases of the service: interview, situation assessment, study phase, and evaluation phase. These periods of time may indicate that the phases of the MRF service were conducted with rigor. The time employed in the implementation of the interventions was less than that registered in the previous phases, which seems to suggest an appropriate interaction with other health professionals. The aim of the MRF service is not only to reduce the consumption of medication used by the patient, but to improve the clinical results associated with the use of said medication. To achieve this objective, the pharmacist who performs the MRF service suggests interventions, which may or not be drug related. It is logical, therefore, that the number of drugs is reduced only in a few cases.

The effectiveness of services similar to MRF service shows contradictory results in relation to their effect on the number of drugs [35]. In this study, we saw a drop in the number of drugs for both groups, although this tendency was greater among the older adults in the IG (0.28 drugs; $p<0.001$) than for those in the CG (0.07 drugs; $p=0.063$). In a recent study of a MRF service for nursing home residents in Spain [36], pharmacist interventions reduced the mean number of prescribed medications by 0.47 drugs ($p<0.001$), whereas the mean number of prescribed medications increased by 0.94 drugs in the CG ($p<0.001$). Participants were residents aged 65 or over, but their health state was worse than in the case of the participants in the present study, and this may explain why that intervention was more effective in optimizing prescribed medication.

As for the impact of MRF service on the consumption of healthcare resources, in the IG there was a reduction in the percentage of participants who visited A&E departments and who were admitted to hospital compared with the six months before the study. Among the CG there was also a reduction in the number of participants who visited A&E departments, although this was less pronounced than in the IG. There was an increase in the percentage of older adults who were admitted at least once to hospital. However, after reviewing the causes of the hospital admissions and ruling out those that could not have been avoided with this intervention, the percentage of older adults who were admitted at least once to hospital was the same before and during the study. Differences in A&E and hospitalizations between groups are very small but significant differences were found primarily due to large sample size.

The results of this study point to a positive effect of MRF service on health-related quality of life. Older adults who received the MRF service benefited from a significant increase in their quality of life as measured through the EuroQol-5D-3L questionnaire. One possible explanation for this could be linked to the high degree of personal contact between participants and pharmacists during the implementation of the MRF service. This was higher than the usual contact and may have had a great impact on the quality of life as perceived by the older adults in the study. Furthermore, it is only logical that better control of health problems is going to be reflected in an improvement in quality of life. In contrast, this improvement was not mirrored in the CG, where there was a decrease in their health-related quality of life. Moreover, CG had significantly more mobility problems than IG and it could perhaps have contributed to the lack of quality of life improvements across the CG because mobility is a strong predictor of quality of life. The utility decrements in the CG were unexpected because we applied a random methodology for the selection of pharmacies. The difference in the utility scores between the two groups might be consequence of the greater mobility problems in CG and the improving quality of life in the IG. We believe that higher control of IG due to the MRF service and greater personal interrelation between pharmacists and patients might have influence this results. Likewise, this can lead to improvements in perceived health higher than those strictly derived from the MRF service. These emotional improvements for the MRF service should be analyzed in future research.

In Spain there is no official threshold of cost/QALY. With €30,000/QALY [37] or €30,000/QALY-€45,000/QALY [38] being the threshold for determining whether a health technology is cost-effective, we have determined that MRF service for older adults with polypharmacy in community pharmacies is cost-effective compared with usual dispensing. We estimated that MRF service was a dominant intervention (less costly and more effective than usual dispensing) and the acceptability curve showed that there was little uncertainty, due to the fact that 100% of the bootstrap simulations were below €30,000/QALY and €45,000/QALY.

Jódar-Sánchez et al. [36] evaluated the cost-effectiveness of a MRF service for older adult residents in nursing homes in Spain, obtaining an adjusted ICER of €6,574/QALY (in the more realistic scenario). The decreased results obtained in this study may be due to the fact that, rather than adopting the perspective of the NHS, it considered a more restrictive perspective, focusing on the variation in direct costs of medication and pharmacists' time.

This study presents some limitations. First, although cluster randomized trial is a recommended design [39], the main limitation of this study was the non-random selection of the sample of older adults.

Randomizing the pharmacies instead of the participants was intended to ensure that the same pharmacist did not deliver the service to participants from both groups, which could have led to problems of selection bias, ethical conflicts, and potential problems of contamination between groups. Second, the cost of outpatient physician visits was not included, as this information was not available.

Despite these limitations, the study is important for several reasons. It strengthens the limited international evidence on the cost-effectiveness of MRF service (or pharmaceutical care, in general) for improving the effectiveness and security of polypharmacy care for older adults in community pharmacies. In Spain this type of service is not offered by the NHS or by any regional health service in the autonomous regions, yet the results of the study suggest high social benefits, particularly in relation to the number of potentially avoided A&E department visits and hospital admissions. The incorporation of this technique into the portfolio of services offered by the NHS, or by other health services committed to a universal system open to all citizens, provides options for policy decision makers. Adopting this strategy would be beneficial due to its potential to improve the efficiency of the treatment of older adults with polypharmacy, specifically as this population will inevitably grow in importance when population aging increases in most developed countries.

5 Conclusion

MRF service is an effective intervention for optimizing prescribed medication and improving the quality of life of older adults with polypharmacy in community pharmacies. The results from the cost-utility analysis suggest that MRF service is cost-effective.

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Disclosures

The authors have no conflicts of interest.

Author contributions

FMM and SIB acquired funding and coordinated the study. AML, FMM, MAGG, VGC, DSH, LSB, and SIB designed the study and database. AML registered the data. FJS, JJM, LG, and MPLA analyzed the data and interpreted the results. All authors participated in the preparation of the manuscript. JJM guarantee the overall content in the author contributions section.

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