Title: The impact of a Medication Review with Follow-up service on hospital admissions in aged polypharmacy patients

Running head: Impact of the Medication Review with Follow-up on hospital admissions

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ABSTRACT

Aims

To assess the impact of a Medication Review with Follow-up (MRF) service provided in community pharmacy to aged polypharmacy patients on the number of medication-related hospital admissions and to estimate the effect on hospital costs.

Methods

This was a sub-analysis of a cluster randomized controlled trial carried out in 178 community pharmacies in Spain. Pharmacies in the intervention group (IG) provided a comprehensive medication review during six months. Pharmacists in the comparison group (CG) delivered usual care. For the purposes of this sub-analysis, an expert panel of three internal medicine specialists screened the hospitalisations occurring during the main study, in order to identify medication-related hospitalisations. Inter-rater reliability was measured using Fleiss´ kappa. Hospital costs were calculated using diagnosis related groups.

Results

1403 patients were included in the main study and they had 83 hospitalisations. 42 hospitalisations (50.6%) were medicine-related, with a substantial level of agreement among the experts (kappa=0.65; 95%CI: 0.52, 0.78; p<0.01). The number of medication-related hospitalisations was significantly lower in patients receiving MRF (IG: 11*;* GC: 31, p=0.042). The probability of being hospitalised was 3.7 times higher in the CG (odds ratio: 3.7; 95%CI: 1.2, 11.3; p=0.021). Costs for a medicine-related hospitalisation were €6,672. Medication-related hospitalisation costs were lower for patients receiving MRF [IG: €94 (SD 917); CG: €301 (SD 2,102); 95% CI: 35.9, 378.0; p=0.018].

Conclusion

MRF 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 aged patients using polypharmacy.

What is known about this subject

- Medication-related hospital admissions are a significant problem in aged polypharmacy patients

- The evidence of the impact of professional pharmacy services on hospital admissions remains uncertain

What this study adds

- The percentage of medication-related hospital admissions was significantly lower in patients receiving Medication Review with Follow-up (26.2% *vs* 73.8%, p<0.05)

- The probability of being hospitalised was 3.7 times higher in the comparison group than in the intervention group (p<0.05).

- Medication-related hospitalisation costs were lower for patients receiving MRF [IG: €94 *vs* CG: €301; p=0.018].

INTRODUCTION

Morbidity associated with the use of medicines represents an important clinical burden [1-6]. A systematic review found that adverse events during hospital admission affect almost one in every ten patients, with 50% of them being preventable [2]. 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 [3, 5-7]. The economic burden arising from healthcare resource consumption associated with drug-related morbidity and mortality in ambulatory care in the U.S. was estimated to be $177.4 billion (2000 year data) [8]. In The Netherlands potentially preventable medication-related hospital admissions cost more than €94 million in 2006 or €5461 for each hospital admission [9].

An ageing population and the use of polypharmacy are risk factors for suffering not only drug related problems (DRPs) [1] but also medication-related hospital admissions [6]. Therefore, aged patients using polypharmacy are bound to benefit from health care interventions aimed at resolving DRPs.

Professional or cognitive pharmacy services are "an action or set of actions undertaken in or organised by a pharmacy, delivered by a pharmacist or other health practitioner, who applies their specialised health knowledge personally or via an intermediary, with a patient/client, population or other health professional, to optimise the process of care, with the aim to improve health outcomes and the value of healthcare" [10]. Professional pharmacy services are an effective strategy to avoid and resolve DRPs as well as negative clinical outcomes related to medicines. However, their effectiveness on reducing hospital admissions has not been clearly established [11].

A nationwide research project called "conSIGUE Program" was undertaken in Spain with the aim of assessing the economic, clinical and humanistic impact of a Medication Review with Follow-up service (MRF), provided in community pharmacies to aged polypharmacy patients [12]. MRF is a professional service aimed at detecting DRP in order to identify, prevent and solve negative clinical outcomes related to medicines [13]. 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 [12]. 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 community pharmacy-led Medication Review with Follow-up provided to aged polypharmacy patients on the number of medication related hospital admissions and estimate the effect on hospital costs.

METHODS

The main study was a cluster randomized controlled trial aimed at assessing the clinical, economic and humanistic impact of the Medication Review with Follow-up 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 occurred 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 1)."

<u>Methods of the main study to assess the clinical, economic and humanistic outcomes of the Medication Review with Follow-up in aged polypharmacy patients</u>

Study design

The conSIGUE project was a cluster randomized controlled trial carried out in 178 community pharmacies in 4 Spanish provinces (Guipuzcoa, Granada, Las Palmas and Tenerife) with 6-month follow-up in each province between 2011 and 2013.

Study population: pharmacies and patients

All the community pharmacies located in the 4 provinces (independent of the urban or rural setting and size of the pharmacy) 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 ten 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 questionnaire. Products registered as medicines in Spain, prescribed and over the counter, were considered medications [14]. Informed consent was obtained from all patients, who were provided with an information sheet prior to the beginning of the study.

Pharmacies were the cluster unit of randomisation in order to minimise contamination bias. After their agreement to participate, pharmacies were randomly allocated by an independent researcher to the intervention group (IG) or comparison group (CG) using a computer-generated list of random numbers (ratio 1:1) and stratified by province. Neither patients nor pharmacists could be blinded due to the characteristics of the intervention.

Sample size was estimated for this main study and not for the sub-analysis; therefore caution is required when interpreting the results.

The study protocol was approved by the Clinical Research Ethics Committee of the Virgen de las Nieves Hospital of Granada, Spain (Ref: 09/123-09/10-06).

MRF and study groups

Pharmacists allocated to the IG provided the MRF service according to national guidelines [13], whereas pharmacists in the CG provided usual care.

The MRF service starts with a comprehensive interview undertaken in a private area of the pharmacy. The pharmacist collects relevant information about the 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. Pharmacists also assess the level of control of health problems by using information referred by patients' and/or clinical and biological parameters, depending on the type of health problem (i.e. pain vs hyperlipidaemia) and classify every health problem as controlled, uncontrolled or unknown. After performing a comprehensive medication review, the pharmacist identifies negative clinical outcomes related to medicines and DRPs. Subsequently, an action plan is agreed upon by the patient and the physician if required. This MRF service is focused on both patients' outcomes and medication use process, and requires a commitment to follow-up.

The usual care in Spanish community pharmacy settings consists of dispensing medicines prescribed by physicians and minor ailments advice [15].

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. The training course was provided by members of the research group. All the lecturers were pharmacists and there was a clinical pharmacist, an expert in MRF methodology and an expert in communication.

Pharmacists in the CG received a brief explanation about the study protocol and instructions to complete the documentation forms. A specifically trained pharmacist called a practice change facilitator [16] helped pharmacists of the IG in the provision of the MRF, identifying barriers specific to each pharmacy and providing solutions. Additionally, the practice change facilitator ensured fidelity to the intervention and supported pharmacists of both study groups on queries about documentation forms.

Study variables including patients' sociodemographic characteristics, health-related quality of life, health problems, medication and use of health resources were collected on a monthly basis. In the CG, this occurred when patients attended the pharmacy to take their chronic medicines and in the IG, during the scheduled visits by the MRF service.

Methods of the sub-analysis to assess the impact on hospital admissions of the Medication Review with Follow-up in aged polypharmacy patients

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.

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 diagnosis related groups (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.

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 suitable expertise in the field since it covers the diagnosis and treatment of a wide array of diseases, including chronic conditions and patients with multimorbidity.

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 DRP contained in the national

guidelines [13] in order to avoid misconceptions between DRP 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 familiarise 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 the Cohen´s kappa for every two raters [17] and the general agreement was assessed using the Fleiss kappa for multiple-raters [18].

Outcome measures

Medication-related hospital admission was the primary outcome of this sub-analysis. Hospital admissions were recorded in patients' visits to the pharmacies, 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 inter-rater reliability (IRR) to measure the agreement among experts.

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

Hospital costs

DRGs of each hospital admission occurred 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 [19]. 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 [20]. Costs were expressed in Euros and updated at 2014 prices using the Spanish consumer price index.

Statistical analysis

Categorical variables were expressed as frequencies and percentages and quantitative variables as means and standard deviations. Student´s t-test was used to analyse the differences between intervention and comparison groups, and Chi Square test or Fisher's exact 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, U.S.), Epidat (Epidat v. 3.1, Galician Health Council and Pan American Health Organisation) and SAS 9.4 (Statistical Analysis Software; SAS Institute, Cary, NC).

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 1). These 83 hospitalisations were distributed over 50 pharmacies. Baseline characteristics of hospitalised patients are shown in table 1. None of the patients died during the 6-month follow-up.

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.

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 2). The cluster effect was inexistent (intracluster correlation coefficient=0).

Table 3 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) [21].

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 usual care [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].

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 professional pharmacy services impacted positively on process indicators associated with the optimization of the patient´s medication management [11]. However, the impact of these services on outcome indicators remains unclear, as reported in a systematic review of systematic reviews published in 2013 [11]. This view has been endorsed in a number of subsequent systematic reviews and meta-analyses, in which the evidence of the impact of professional pharmacy services in hospital admissions is defined as conflicting, insufficient or uncertain or even null [22-28]. 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 professional pharmacy service.

Additionally, different types of professional pharmacy services are compared. However, every service differs on its methodology, complexity, collaboration with other health care providers and level of responsibility assumed by the pharmacist [29]. Therefore it is logical that they are bound to achieve different outcomes. For example, the review carried out by Hatah *et al*. [23] 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 professional pharmacy service may have different characteristics, rates of fidelity and implementation. Zermansky *et al*. [30] 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 methodology and adherence to the guidelines of the MRF leading to the achievement of different outcomes. The study published by Ocampo et al [31] 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 professional pharmacy services and hospitalisation rates. For example, the meta-analysis carried out by Viswanathan *et al*. [28] 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 decreases 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 [12]. 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 which could benefit the most from the MRF.

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 [9] 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 usual care, 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 National Health System by means of reducing the number of hospital admissions rather than reducing the cost per hospitalisation. Several economic evaluations of professional pharmacy services provided in community pharmacy do not include the cost of hospital admissions [32-34]; 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.

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 [21]. 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 [35].

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% [7]. However, percentages around 5.3% [3] and 19.4% [36] are more frequent. The percentage of medication-related hospitalisations in this sub-analysis is high (50.6%, n=42) since this study combines several criteria identified as reporting higher rates of hospitalisations [7]: aged patients, consideration of adverse drug events instead of adverse drug reactions, inclusion of all hospital admissions rather 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 [37] and results must be interpreted with caution. However, the appropriate sample size could be almost unreachable as was the case in a previous study [38]. 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. 25 of the self-reported hospital admissions in the CG and 7 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 to 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 [6] and from considering other possible reasons for non-admission to hospital, such us admission to care homes.

Overall, 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 provides 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.

COMPETING INTERESTS

AUTHORS' CONTRIBUTIONS

SIB, FMM, MAG and VGC acquired funding, designed and coordinated the main study. SIB, EG, BC and AML designed and coordinated the sub-analysis. JMA, PA and JJZ analysed the clinical cases of the sub-analysis. AML and EG analysed the data and interpreted the results of the sub-analysis. AML and VGC drafted the manuscript. All authors participated in the revision of the manuscript.

REFERENCES

[1] Baena MI, Faus MJ, Fajardo PC, Luque FM, Sierra F, Martinez-Olmos J, Cabrera A, Fernandez-Llimos F, Martinez-Martinez F, Jimenez J, Zarzuelo A. Medicine-related problems resulting in emergency department visits. Eur J Clin Pharmacol 2006;62:387-93.

[2] de Vries EN, Ramrattan MA, Smorenburg SM, Gouma DJ, Boermeester MA. The incidence and nature of in-hospital adverse events: a systematic review. Quality & safety in health care 2008;17:216-23.

[3] Kongkaew C, Noyce PR, Ashcroft DM. Hospital admissions associated with adverse drug reactions: a systematic review of prospective observational studies. Ann Pharmacother 2008;42:1017-25.

[4] 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 safety 2009;32:379-89.

[5] McLachlan CY, Yi M, Ling A, Jardine DL. Adverse drug events are a major cause of acute medical admission. Internal medicine journal 2014;44:633-8.

[6] 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;26:951-61.

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

[8] Ernst FR, Grizzle AJ. Drug-related morbidity and mortality: updating the cost-of-illness model. Journal of the American Pharmaceutical Association 2001;41:192-9.

[9] Leendertse AJ, Van Den Bemt PM, Poolman JB, Stoker LJ, Egberts AC, Postma MJ. Preventable hospital admissions related to medication (HARM): cost analysis of the HARM study. Value in health : the journal of the International Society for Pharmacoeconomics and Outcomes Research 2011;14:34-40.

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

[11] 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;42:442-9.

[12] 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 2014. Ed. Spanish General Council of Official Colleges of Pharmacists, Madrid. ISBN: 978-84-87276-83-5.

[13] Pharmaceutical Care Forum. Expert panel. Consensus document. Madrid: General Council of Spanish Pharmacists; 2010 (ISBN: 9788469112434).

[14] Spanish General Council of Official Colleges of Pharmacists. BotPLUS web database. https://botplusweb.portalfarma.com/. Accessed 28 October 2015.

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

[16] Harvey G, Loftus-Hills A, Rycroft-Malone J, Titchen A, Kitson A, McCormack B, Seers K. Getting evidence into practice: the role and function of facilitation. J Adv Nurs 2002;37:577-88.

[17] Cohen J. A coefficient of agreement for nominal scales. Educational and Psychological Measurement 1960;20:37-46.

[18] Fleiss JL. Statistical methods for rates and proportions. New York: John Wiley & Sons; 1973.

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

[20] Ministry of Health, Social Services and Equalty, Spanish Government. Weights and costs of DRGs, Ministry rule APv27.0 (2010).

[21] Landis JR, Koch GG. The measurement of observer agreement for categorical data. Biometrics 1977;33:159-74.

[22] Christensen M, Lundh A. Medication review in hospitalised patients to reduce morbidity and mortality. Cochrane Database Syst Rev 2013;2:CD008986.

[23] 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;77:102-15.

[24] Hohl CM, Wickham ME, Sobolev B, Perry JJ, Sivilotti ML, Garrison S, Lang E, Brasher P, Doyle-Waters MM, Brar B, Rowe BH, Lexchin J, Holland R. The effect of early in-hospital medication review on health outcomes: a systematic review. Br J Clin Pharmacol 2015;80:51-61.

[25] 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;65:303-16.

[26] 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;37:687-97.

[27] Thomas R, Huntley AL, Mann M, Huws D, Elwyn G, Paranjothy S, Purdy S. Pharmacist-led interventions to reduce unplanned admissions for older people: a systematic review and meta-analysis of randomised controlled trials. Age Ageing 2014;43:174-87.

[28] Viswanathan M, Kahwati LC, Golin CE, Blalock SJ, Coker-Schwimmer E, Posey R, Lohr KN. Medication therapy management interventions in outpatient settings: a systematic review and meta-analysis. JAMA Intern Med 2015;175:76-87.

[29] Benrimoj SI, Feletto E, Gastelurrutia MA, Martinez-Martinez F, Faus MJ. A Holistic and Integrated approach to the challenges of implementing Cognitive Pharmaceutical Services in Community Pharmacy. Ars Pharm 2010;51:69-88.

[30] 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.

[31] 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;37:931-40.

[32] 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;50:271-5.

[33] Bosmans JE, Brook OH, van Hout HP, de Bruijne MC, Nieuwenhuyse H, Bouter LM, Stalman WA, van Tulder MW. Cost effectiveness of a pharmacy-based coaching programme to improve adherence to antidepressants. Pharmacoeconomics 2007;25:25-37.

[34] 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;19:113-23.

[35] 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. International journal of clinical pharmacology and therapeutics 2008;46:72-83.

[36] Perez C, Bermejo T, Delgado E, Carretero E. Adverse drug reactions which provoke hospital admission. Farmacia hospitalaria 2011;35:236-43.

[37] Krska J, Cromarty JA, Arris F, Jamieson D, Hansford D, Duffus PR, Downie G, Seymour DG. Pharmacist-led medication review in patients over 65: a randomized, controlled trial in primary care. Age Ageing 2001;30:205-11.

[38] Leendertse AJ, de Koning GH, Goudswaard AN, Belitser SV, Verhoef M, de Gier HJ, Egberts AC, van den Bemt PM. Preventing hospital admissions by reviewing medication (PHARM) in primary care: an open controlled study in an elderly population. J Clin Pharm Ther 2013;38:379-87.
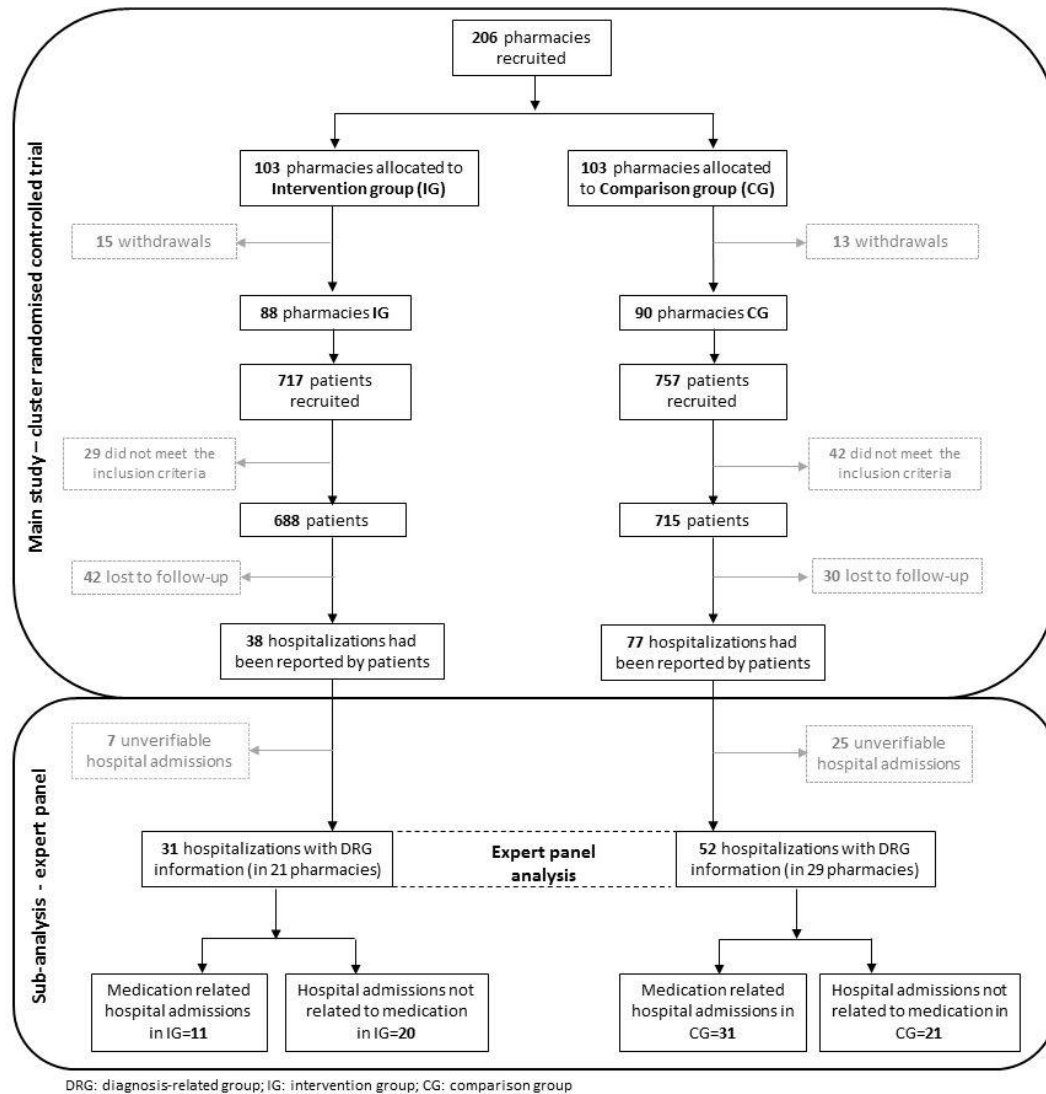
Figure 1: Pharmacy, patient and hospital admission flow diagram in the main cluster randomized controlled trial and in the expert panel sub-analysis.

Table 1: 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)	
Completed primary education	8 (28.60)	14 (40.00)	0.712
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.

Table 2: 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). Adjusted OR (simple logistic regression analysis): 3.7 (95%CI: 1.3-10.8; p=0.015).

Table 3: 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	83.13	0.667 [a]	0.51-0.82
Rater 1 vs Rater 3	81.93	0.639 [a]	0.48-0.80
Rater 2 vs Rater 3	81.93	0.637 [a]	0.47-0.80
Rater 1 vs Rater 2 vs Rater 3	73.49	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 [21].