



PROTOCOL

Bilingual edition English/Spanish

**Pharmacist-led intervention on potentially inappropriate prescription in patients with polypharmacy: PHARM-PC clinical trial protocol**

**Intervención del farmacéutico en la prescripción potencialmente inapropiada en pacientes polimedicados: Protocolo ensayo clínico PHARM-PC**

Jesús Martínez-Sotelo<sup>1</sup>, Manel Pinteño-Blanco<sup>1</sup>, Rosario García-Ramos<sup>2</sup>, Joan Llobera-Cànaves<sup>3</sup>, María Isabel Cadavid-Torres<sup>4</sup>

<sup>1</sup>Department of Pharmacy, Hospital Comarcal de Inca, Inca (Balears). Spain. <sup>2</sup>Department of Pharmacy, Hospital Universitario de Santiago de Compostela, Santiago de Compostela (A Coruña). Spain. <sup>3</sup>Primary Care Research Unit, Mallorca, Servicio de Salud de las Islas Baleares. Instituto de Investigación Sanitaria Islas Baleares (IdISBa). RedIAPP. Spain. <sup>4</sup>Department of Pharmacology, Pharmacy and Pharmaceutical technology, Universidade de Santiago de Compostela, Santiago de Compostela (A Coruña). Spain.

**Author of correspondence**

Jesús Martínez Sotelo  
Carretera Vella de Llubí, s/n  
07300 Inca (Balears). Spain.

Email:  
jesus.martinezs@hcin.es

Received 22 October 2020;  
Accepted 23 February 2021.  
DOI: 10.7399/fh.11575

**How to cite this paper**

Martínez-Sotelo J, Pinteño-Blanco M, García-Ramos R, Llobera-Cànaves J, Cadavid-Torres MI. Pharmacist-led intervention on potentially inappropriate prescription in patients with polypharmacy: PHARM-PC clinical trial protocol. *Farm Hosp.* 2021;45(4):210-5.

**Abstract**

**Objective:** Polypharmacy and potentially inappropriate medications (that is, those associated with an unfavorable risk-benefit ratio) are common concerns in the context of elderly patients treated in primary care as they may increase the risk of morbidity and mortality, as well as health-care costs. Several studies have assessed the impact of pharmacist-led systematic reviews with respect to prescription appropriateness, health outcomes and/or costs. However, no cluster-randomized controlled trial has been identified that provides an overall assessment of these variables. The objective is to determine the effectiveness of a pharmacist-led systematic medication review in reducing the mean number and proportion of patients on potentially inappropriate medications (primary goal); as well as in decreasing morbidity and mortality and the cost of medications and the use of healthcare resources (secondary goals).

**Method:** An open-label, cluster-randomized controlled trial will be conducted; where primary care physicians will be randomized either to receive (intervention group) or not to receive pharmacist recommendations to withdraw potentially inappropriate medications detected through the combined use of explicit and implicit criteria (control group). Primary end-

**Resumen**

**Objetivo:** La polimedicación y la medicación potencialmente inapropiada (que presenta balance beneficio-riesgo desfavorable) son importantes preocupaciones respecto a los pacientes mayores en atención primaria, ya que pueden incrementar el riesgo de morbimortalidad y los costes sanitarios. Diversos estudios han evaluado el impacto de la revisión sistemática de la medicación conducida por el farmacéutico sobre variables de adecuación, recursos sanitarios y/o costes. Sin embargo, no se han encontrado ensayos controlados aleatorizados por clúster que evalúen globalmente todas estas variables. El objetivo de este estudio es determinar el impacto de una revisión sistemática de medicación conducida por el farmacéutico para reducir el número medio y la proporción de pacientes con medicación potencialmente inapropiada (objetivo principal), así como para reducir la morbimortalidad y los costes (objetivos secundarios).

**Método:** Se realizará un ensayo clínico abierto, controlado y aleatorizado por clústeres, donde los médicos de atención primaria, en representación de sus respectivos cupos de pacientes, serán aleatorizados a recibir recomendaciones del farmacéutico para retirar medicaciones potencialmente inapropiadas detectadas mediante combinación de méto-

**KEYWORDS**

Pharmaceutical care; Inappropriate prescribing; Elderly; Polypharmacy; Primary care.

**PALABRAS CLAVE**

Atención farmacéutica; Prescripción inapropiada; Ancianos; Polimedicación; Atención primaria.



Los artículos publicados en esta revista se distribuyen con la licencia  
Articles published in this journal are licensed with a  
Creative Commons Attribution-NonCommercial-ShareAlike 4.0 International License.  
<http://creativecommons.org/licenses/by-nc-sa/4.0/>  
La revista Farmacia no cobra tasas por el envío de trabajos,  
ni tampoco por la publicación de sus artículos.

points will be the proportion of patients on potentially inappropriate medications and the mean number of such medications per patient. Secondary endpoints will be healthcare resources used, the proportion of patients who die and the mean number of days survived, as well as the cost of medications and cost of healthcare resources used.

**Conclusions:** In line with similar reports and based on our study's design, we hope to obtain statistically significant reductions in the use of potentially inappropriate medications and in medication costs overall. We do not however expect to obtain significant reductions in morbimortality or the cost of health resources employed.

## Introduction

Prescription of potentially inappropriate medications (PIMs) is a major concern, especially in the context of elderly and/or polymedicated patients, given its high prevalence<sup>1,2</sup> and its negative impact, demonstrated through a high morbimortality risk and elevated healthcare costs<sup>3,4</sup>.

A medication is considered potentially inappropriate if it is associated with an unfavorable risk/benefit and/or cost/effectiveness ratio<sup>5</sup>. Several tools are available for identifying PIMs. On the one hand, there are several implicit methods (e.g., the medication appropriateness index<sup>6</sup>), based on clinical judgement and specific patient- and treatment-related circumstances. On the other, explicit methods have been developed, which consider predefined evidence and expert consensus-based PIM scenarios. These include the widely used Beers Criteria and the STOPP/START tool (Screening Tool of Older Persons' Prescriptions/Screening Tool to Alert Doctors to Right Treatment)<sup>7,8</sup>. There are also the so-called prescribing quality indicators (PQIs), which comprise a series of management tools developed by healthcare institutions to detect drugs or drug groups for which more cost-effective alternatives exist<sup>9</sup>.

No single ideal method exists to evaluate the appropriacy of the medication prescribed to multimorbid and/or polymedicated (treated with  $\geq 5$  drugs) and hyperpolymedicated ( $\geq 10$  drugs) patients<sup>10</sup>. For that reason, Alfaro-Lara *et al.* consider it necessary to develop strategies based on a combination of different methods<sup>11</sup>.

The involvement of pharmacists in the optimization of geriatric patients' treatments has yielded positive results as it has decreased the use of PIMs and the overall drug therapy costs<sup>12-14</sup>. Results have nonetheless been less encouraging with respect to health outcomes<sup>15</sup>.

Although significant efforts have been made in this area, no cluster-randomized trials have to the best of our knowledge been carried out on the use of PIMs primary care, to prevent contamination across patients belonging to IG and CG treated by the same physician, which provide a comprehensive evaluation of the effectiveness of a pharmacist-led systematic medication review (PL-SMR) based on a combination of different PIM detection tools in analyzing appropriateness variables, health outcomes and healthcare costs in polymedicated elderly patients.

On the basis of the hypothesis that an (PL-SMR) could reduce the prevalence of PIMs in polymedicated elderly patients in the primary care setting, a prospective multicenter open-label cluster-randomized controlled clinical trial will be performed in order to evaluate the potential reduction that could be achieved in (i) the proportion of patients on  $\geq 1$  PIMs and in the mean number of PIMs/patient (main goals); and (ii) in the incidence of morbimortality and the cost of drugs and healthcare resources (secondary goals).

## Methods

The methodology to be followed in this study will be based on the Standard Protocol Items: Recommendations for Intervention Trials (SPIRIT)<sup>16</sup> guidelines.

## Scope

The study will be conducted in six primary care health centers of the Tramuntana area (Balearic Islands), which cater for a population of around 128,000 inhabitants, approximately 15% of them over 65 years of age.

dos implícitos y explícitos (grupo intervención) o no recibirlas (grupo control). Las variables primarias serán la proporción de pacientes y el número medio de medicaciones potencialmente inapropiadas por paciente. Las variables secundarias serán los recursos asistenciales frecuentados, proporción de pacientes fallecidos y días de supervivencia; y costes de medicamentos y de recursos asistenciales.

**Conclusiones:** Análogamente a estudios similares, y en base al diseño de nuestro estudio, esperamos obtener reducción estadísticamente significativa para medicaciones potencialmente inapropiadas y costes de medicamentos. Sin embargo, no esperamos diferencias significativas en morbimortalidad ni en costes de recursos asistenciales.

## Selection criteria

Each cluster will comprise all the patients assigned to a primary care physician, who will be required to sign the relevant informed consent form. Only patients  $\geq 65$  years and on  $\geq 5$  chronic drugs will be eligible. In addition, patients who meet at least one of the following criteria will be excluded: regular use of private healthcare, being displaced, institutionalized, or on the home care program (Figure 1).

## Intervention

Interventions will be carried out at cluster level and will consist in the performance of (PL-SMR) to detect instances where PIMs are used and provide recommendations to the prescribing physician about appropriate therapeutic alternatives, as explained below:

- At the outset, the required baseline data will be obtained from the electronic medical record (EMR) of patients in both the IG and the CG.
  - Demographic data: age, sex.
  - Clinical data: chronic conditions.
  - Pharmacotherapeutic data: chronic medications.
- Detection of PIMs: To be carried out, both in the IG and the CG by means of a combination of explicit and implicit methods (STOPP/START criteria<sup>8</sup>, data from the medication labels [<https://cima.aemps.es/cima/publico/home.html>]), "Do not do" recommendations for complex chronic patients<sup>7</sup>, using CheckTheMeds<sup>®</sup> software (<https://www.checkthemed.com>); and a battery of PQIs developed by the Balearic Islands Health System.
- For patients in the IG, prescribing physicians will be informed, through the patients' EMR and/or verbally if necessary, about the most appropriate strategy for managing each instance of PIM, taking the patients' individual circumstances into consideration, e.g., whether they were treated previously with the proposed alternative, their potential comorbidities and/or other treatments). Such strategies may involve discontinuation of treatment; dose adjustments, replacement of the medication, addition of a new drug, and include specific management recommendations such as gradual withdrawal or onset of drugs when necessary. If use of a PIM is detected in the CG, prescribing physicians will be informed but no recommendations will be issued.

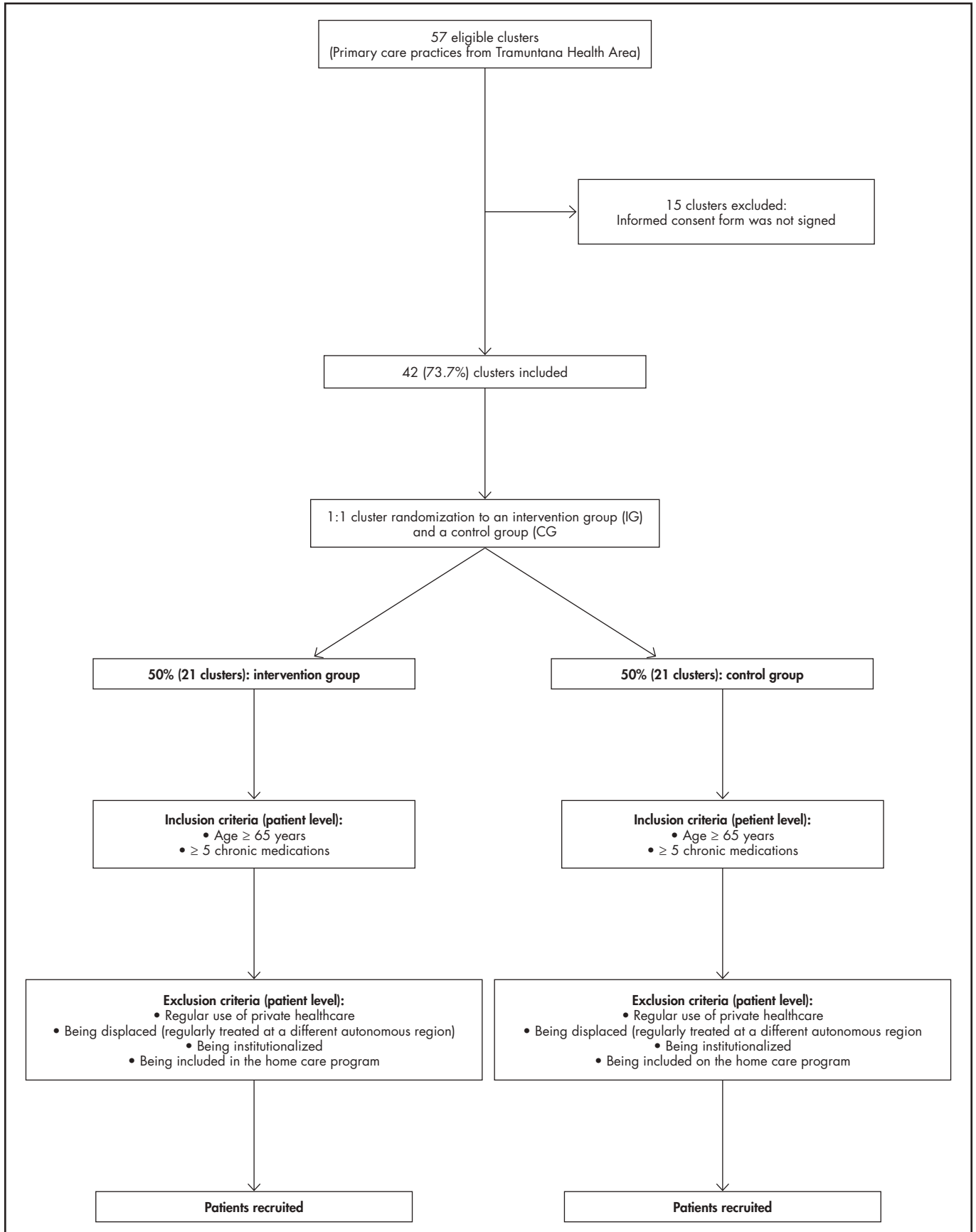
## Variables

Given the purpose of the study, the following variables will be evaluated across all participating subjects:

- Independent variables:
- Demographic: age, sex.
  - Clinical: Charlson Comorbidity Index (CCI), percentage of patients with  $\geq 2$  chronic conditions.
  - Pharmacotherapeutic: number of chronic medications, proportion of polymedicated and hyperpolymedicated patients.

Primary variables: Difference between the proportion of patients on PIMs and the mean PIM/patient ratio over the period running from the time of intervention and 6 months post-intervention. To be considered a PIM, drug regimens must meet at least one of the following criteria: not evidence-based indication, prescribed dose higher and lower than recommended; duplication, contraindication, interaction, absence of a potentially beneficial drug. Moreover, all drugs marketed in the five years prior to the intervention that failed to demonstrate any significant

Figure 1. Patient selection process. Criteria used to select participants both at cluster and at individual level.



therapeutic effect as compared with already available alternatives (e.g., saxagliptin, silodosin, rosuvastatin) as well as drugs other than those regarded as first-choice for the treatment of the most prevalent conditions in the outpatient setting (e.g., antiulcer agents-omeprazole, oral antidiabetics-metformin, statins-simvastatin) will also be considered PIMs, on the basis of the prescription quality criteria established by the Balearic Islands Health System.

Secondary variables:

- Morbidity: Difference between the mean number of (in- and outpatient) healthcare facilities visited in the 12 months prior and subsequent to the intervention. The INPATIENT variable comprises the number of hospital days (NHDs) spent (a stay of  $\geq 13$  hours in a hospitalization or emergency unit to receive specialized care was required<sup>18</sup>) and of visits made to the hospital's emergency department (ED). The OUTPATIENT variable comprises visits to the primary care emergency unit, the specialist care outpatient unit, and the primary care clinic<sup>19</sup>.
- Mortality: Proportion of patients who died within the first 12 months following the intervention, and the number of days survived within the first 12 months following the intervention.
- Cost of the medication: Difference in the estimated mean per-patient annual cost of the drugs considered PIMs (AC-PIM) at the time of intervention as compared with 6 months post-intervention (same time period as that used for the primary variable), according to the prices stated in the Balearic Islands' formulary drugs price list.
- Cost of healthcare resources: Difference in the mean per-patient cost of the health resources (INPATIENT + OUTPATIENT) used during the 12 months prior to the intervention as compared with 12 months post-intervention, according to the official rates published in the Balearic Islands' Official Gazette<sup>18</sup>.

## Time span

The time periods corresponding to the different stages of the study were as follows:

- Cluster recruitment: April-May 2014.
- Cluster allocation: January 2015.
- Patient recruitment: January-May 2015.
- Intervention: January-May 2015.
- Assessment of baseline characteristics: January-May 2015.
- Assessment of primary variables: July-November 2015.
- Evaluation of the cost of medications: July-November 2015.
- Morbimortality evaluation: January-May 2016.
- Evaluation of the cost of healthcare resources: January-May 2016.
- Analysis and dissemination of results: June 2016-present.

## Sample size

The sample size will be calculated using proportion testing for a difference of 15% in the proportion of patients on PIMs in the IG (80%) and the CG (65%), based on the results of an unpublished pilot study. For a statistical power of 80% and assuming a loss rate of around 10%, the sample size required was set at 153. Dividing the sample size by the 21 clusters included it was established that each group should contain a mean of 8 patients. Application of an intra-cluster correlation coefficient of 0.05<sup>20</sup> yielded an inflation factor of 1.35, which resulted in a final sample size of 207 patients per group.

## Recruitment

- Cluster level: All primary care physicians of the Tramuntana health area will be required to sign the relevant informed consent form on behalf of their respective patient practices. Subsequently, they will be recruited and randomly allocated to a GI or GC by the Balearic Islands Healthcare Research Institute (IdISBa).
- Patient level: Pharmacists in charge of the PL-SMR will, on a daily basis and in consecutive order, select one IG and one CG cluster from the list resulting from the randomization process; of which, all patients with an appointment for the next day who meet eligibility criteria will be recruited. This routine will be followed until the target sample size is reached.

## Allocation

To prevent contamination across patients treated by the same physician, IdISBa will randomize clusters to the IG or the CG in a 1:1 ratio in four cluster blocks using a balanced randomization scheme. This will be done using the WINPEPI Computer Program for Epidemiologists (<http://www.brixtonhealth.com/pepi4windows.html>) ensuring that the confidentiality of the result of the randomization process is preserved to ensure proper data masking.

## Blinding (masking)

Blinding of participants (clusters) will not be feasible given that the PIM management strategies will be shared with the physicians allocated to the IG.

## Data collection and processing

The data will be collected by the pharmacist in charge of the PL-SMR in an electronic spreadsheet, which will be duly encrypted and stored on a secure server guarded by the IT Department of the Inca County Hospital.

## Statistical analysis

### Variables

Study variables will be analyzed at patient level following the intention-to-treat principle, each patient being considered according to the group they were initially randomized to.

Baseline characteristics will be subjected to:

- A descriptive analysis: Frequency and percentage measures will be used for qualitative variables and mean $\pm$ standard deviation or median (interquartile range) for quantitative variables, depending on whether the distribution is normal or not, respectively. Normality of distribution of quantitative variables and variance homogeneity will be verified by means of the Kolmogorov-Smirnov and Levene tests, respectively.
- A comparative analysis: Homogeneity between the IG and CG will be evaluated using the Chi-Squared Test or Fisher's Exact Test for qualitative variables if at least 25% of expected frequencies is  $< 5$ . Student's *t* test and the Mann Whitney U test were used for quantitative variables, depending on whether distribution is parametric or not, respectively.

The magnitude of effect, expressed as difference in means (quantitative variables) or difference in proportions (qualitative variables), will be calculated for the primary and secondary variables. The corresponding 95% confidence intervals (95% CIs) will be calculated using the following statistical tests:

- Primary variables:
  - Patients on PIM: Difference in proportions (95% CI). Chi-Squared Test.
  - PIMs/patient: Difference in means (95% CI). Student's *t* test / Mann Whitney U test.

The kappa correlation coefficient will be calculated for primary variables to take into account the cluster effect.

- Secondary variables:
  - Morbidity: Difference in means of clinical episodes (both INPATIENT and OUTPATIENT) (95% CI). Student's *t* test/Mann Whitney U test.
  - Mortality:
    - Difference in proportions of deceased patients (95% CI). Chi-Squared Test.
    - Difference in days survived (95% CI). Kaplan-Meier log-rank test.
  - Cost (of drugs and healthcare resources): difference in means (95% CI). Student's *t* test / Mann Whitney U test.

The *p* value will be considered statistically significant if  $< 0.05$ .

The statistical analysis will be performed using the Statistical Package for Social Sciences for Windows" (SPSS®) v22.0 software.

## Additional analyses

Although not specified in the protocol, an evaluation will be made of the effect of the intervention on hospital admissions in the different subgroups resulting from the combination of the following criteria: sex (males/females); age (below/over 85 years); number of drugs (5-9/10 or more).

## Monitoring

It is not considered necessary to set up a formal external data monitoring committee or to conduct a preliminary analysis as no intervention-related damage is expected. Furthermore, in the event of recurrence of symptoms associated to the withdrawal of inappropriate medication, the intervention can be resumed at any time subject to clinical judgement.

## Ethics and dissemination

### Approval by Ethics Committee

The study protocol was evaluated and approved by the Balearic Islands' Primary Care Research Ethics Committee and Research Ethics Committee (approval number IB2360/14) on 30 June 2014.

### Amendments to the protocol

The protocol has undergone several alterations since its initial version. Such changes can be reviewed via the following link: <https://clinicaltrials.gov/ct2/history/NCT02224833>.

### Informed consent

The Research Ethics Committee of the Balearic Islands agreed to ask physicians rather than patients to complete the informed consent form relative to the study. This was due to the fact that the PL-SMR is addressed to physician, who are the ones that must eventually decide whether the patient's treatment must be altered or not on the basis of the recommendations made by the pharmacist. Moreover, given that patients will be recruited the day before the medical appointment without any pre-screening being performed, and that the participating centers are widely dispersed across the Tramuntana health area, signature of the consent forms by the patients would be virtually unfeasible.

### Confidentiality

To ensure the confidentiality of information, patients will be identified by a 3-digit alphanumeric code followed by a letter.

### Data access

This study is part of the PhD thesis of the principal investigator. For that reason, neither the data nor the materials will be made available to the public. They can only be transferred to third parties with the written consent of the University of Santiago de Compostela ([http://www.usc.es/export9/sites/webinstitucional/gl/centros/cptf/edi/descargas\\_EDI/CDS\\_cas\\_06\\_10\\_16.pdf](http://www.usc.es/export9/sites/webinstitucional/gl/centros/cptf/edi/descargas_EDI/CDS_cas_06_10_16.pdf)).

### Dissemination policy

The results of this study will be published in peer-reviewed journals and presented at geriatrics, clinical pharmacy, and general medicine conferences, as well as in the PhD thesis of the principal investigator. The relevant author selection guidelines will be followed and no professional writers will be engaged.

## Discussion

Given the proposed design of the study, we hope to achieve a statistically significant reduction in the proportion of patients on PIMs, in the mean number of PIMs per patient, and in the cost of the drugs themselves, in line with the other reports in the literature<sup>3,14</sup>. However, although we expect to observe a reduction in morbimortality and in the costs of healthcare resources, the differences obtained may not reach statistical significance given that our sample size was not calculated with that purpose in mind but rather to demonstrate a significant reduction in the number of patients on PIMs.

The strengths of this study include its cluster randomization design, which may reduce the occurrence of biases in the results by preventing contamination across patients in the IG and CG treated by the same physician; and

the applicability of the results obtained both to other areas of primary care and to clinical units with a high prevalence of these types of patients such as internal medicine and geriatrics, as well as to extended care facilities, nursing homes, etc. Its pragmatic nature and the flexible selection criteria employed are also unquestionable assets. In addition, the combined use of multiple tools (including efficiency criteria) will make it possible to detect a greater number of PIMs and propose a wider range of scenarios where prescription may be optimized.

However, the study is not without limitations. Firstly, its open-label design could result in a certain bias given that physicians in the IG will be aware that they have been allotted to that group when they receive the pharmacists' recommendations. This bias could be minimized by entrusting the cluster randomization process to personnel external to the study. Another limitation could result from regarding the EMR as the only valid source of information and the main channel of communication. This could lead to underdetection or overdetection of PIMs, as non-reimbursable drugs or conditions not recorded on the EMR would not be taken into consideration. However, given that the study's randomized design will ensure that the groups are well-balanced, it is to be expected that underdetection and overdetection will affect both groups in a similar way without excessively impacting the result of the intervention. Moreover, some authors consider that direct communication with the pharmacist makes physicians particularly prone to accepting the former's recommendations about prescription appropriateness<sup>13</sup>. This will unfortunately not be possible in our study given that patient recruitment and performance of the PL-SMR will take place the day before the medical appointment, and because of the wide geographical dispersion of participating centers.

In a nutshell, this cluster-randomized controlled study will provide evidence on the effectiveness of an PL-SMR in detecting the use of PIMs through a combination of different tools (including efficiency criteria) and suggesting the most appropriate individualized strategies to address cases of PIM use by polymedicated elderly patients: not only with respect to intermediate appropriateness variables but also regarding such significant variables as morbimortality and healthcare costs.

## Funding

No funding.

## Acknowledgements

The authors would like to thank Aina María Yañez Juan and the Balearic Islands' Healthcare Research Institute for their contribution with the cluster randomization process. Special thanks also go to Alfonso Leiva Rus for his support with the statistical analysis and to Pilar Gayoso Diz for agreeing to review the data collection form.

## Presentation at congresses

Research project presented at VII Congreso Atención Sanitaria al Paciente Crónico. Centro Cultural Miguel Delibes (Valladolid, Spain); 5-7 March 2015.

## Conflict of interests

No conflict of interest.

## Contribution to the scientific literature

The present study will provide evidence of the clinical and economic impact of pharmacist-led interventions on the optimization of the treatment regimens used in geriatric patients.

The results obtained may be applied not only to other areas of primary care but also to units with a high prevalence of elderly patients, such as internal medicine and geriatrics, as well as to extended care facilities, nursing homes, etc.

## Bibliography

1. Filomena-Paci J, García-Alfaro M, Redondo-Alonso EJ, Fernández-San-Martín MI, Grupo Polimedición Litoral. Prescripción inadecuada en pacientes polimeditados mayores de 64 años en atención primaria. *Aten Primaria*. 2015;47(1):38-47. DOI: 10.1016/j.aprim.2014.03.013
2. Galván-Banqueri M, González-Méndez AI, Alfaro-Lara ER, Nieto-Martín MD, Pérez-Guerrero C, Santos-Ramos B. Evaluación de la adecuación del tratamiento farmacológico en pacientes pluripatológicos. *Aten Primaria*. 2013;45(5):235-43. DOI: 10.1016/j.aprim.2012.11.010
3. Liew TM, Lee CS, Goh Shawn KL, Chang ZY. Potentially Inappropriate Prescribing Among Older Persons: A Meta-Analysis of Observational Studies. *Ann Fam Med*. 2019;17(3):257-66. DOI: 10.1370/afm.2373
4. Heider D, Matschinger H, Meid AD, Quinzler R, Adler JB, Günster C, et al. The impact of potentially inappropriate medication on the development of health care costs and its moderation by the number of prescribed substances. Results of a retrospective matched cohort study. *PLoS One*. 2018;13(7):e0198004. DOI: 10.1371/journal.pone.0198004
5. Hill-Taylor B, Sketris I, Hayden J, Byrne S, O'Sullivan D, Christie R. Application of the STOPP/START criteria: a systematic review of the prevalence of potentially inappropriate prescribing in older adults, and evidence of clinical, humanistic and economic impact. *J Clin Pharm Ther*. 2013;38(5):360-72. DOI: 10.1111/jcpt.12059
6. Hanlon JT, Schmader KE, Samsa GP, Weinberger M, Uttech KM, Lewis IK, et al. A method for assessing drug therapy appropriateness. *J Clin Epidemiol*. 1992;45(10):1045-51. DOI: 10.1016/0895-4356(92)90144-C
7. By the 2019 American Geriatrics Society Beers Criteria® Update Expert Panel. American Geriatrics Society 2019 Updated AGS Beers Criteria® for Potentially Inappropriate Medication Use in Older Adults. *J Am Geriatr Soc*. 2019;67(4):674-94. DOI: 10.1111/jgs.15767
8. Delgado-Silveira E, Montero-Erasquin B, Muñoz-García M, Vélez-Díaz-Pallarés M, Lozano-Montoya I, Sánchez-Castellano C, et al. Mejorando la prescripción de medicamentos en las personas mayores: una nueva edición de los criterios STOPP-START. *Rev Esp Geriatr Gerontol*. 2015;50(2):89-96. DOI: 10.1016/j.regg.2014.10.005
9. Vicens-Caldentey C, Sempere-Verdú E, Arroyo-Aniés MP, Hernández-Rodríguez MA, Palop-Larrea V, Orueta-Sánchez R, et al. Variabilidad en la medición de la calidad de prescripción por comunidades autónomas. *Aten Primaria*. 2010;42(7):380-87. DOI: 10.1016/j.aprim.2009.09.025
10. Slater N, White S, Venables R, Frisher M. Factors associated with polypharmacy in primary care: a cross-sectional analysis of data from The English Longitudinal Study of Ageing (ELSA). *BMJ Open*. 2018;8(3):e020270. DOI: 10.1136/bmjopen-2017-020270
11. Alfaro-Lara ER, Vega-Coca MD, Galván-Banqueri M, Marín-Gil R, Nieto-Martín MD, Pérez-Guerrero C, et al. Selection of tools for reconciliation, compliance and appropriateness of treatment in patients with multiple chronic conditions. *Eur J Intern Med*. 2012;23(6):506-12. DOI: 10.1016/j.ejim.2012.06.007
12. Delgado-Silveira E, Fernández-Villalba EM, García-Mina Freire M, Albiñana-Pérez MS, Casajús-Lagranja MP, Peris-Martí JF. Impacto de la Intervención Farmacéutica en el tratamiento del paciente mayor pluripatológico. *Farm Hosp*. 2015;39(4):192-202. DOI: 10.7399/fh.2015.39.4.8329
13. Campins I, Serra-Prat M, Gózaló I, López D, Palomera E, Agustí C, et al. Randomized controlled trial of an intervention to improve drug appropriateness in community-dwelling polymedicated elderly people. *Fam Pract*. 2017;34(1):36-42. DOI: 10.1093/fampra/cmw073
14. Campins I, Serra-Prat M, Palomera E, Bolívar I, Martínez MA, Gallo P. Reduction of pharmaceutical expenditure by a drug appropriateness intervention in polymedicated elderly subjects in Catalonia (Spain). *Gac Sanit*. 2019;33(2):106-11. DOI: 10.1016/j.gaceta.2017.09.002
15. 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. DOI: 10.1093/ageing/af169
16. Chan AW, Tetzlaff JM, Altman DG, Laupacis A, Gøtzsche PC, Krleža-Jerić K, et al. SPIRIT 2013 statement: defining standard protocol items for clinical trials. *Ann Intern Med*. 2013;158(3):200-7. DOI: 10.7326/0003-4819-158-3-201302050-00583
17. Delgado-Silveira E. "No hacer" en paciente crónico complejo. En: Poveda-Andrés JL, coordinador. *Monografías de Farmacia Hospitalaria y Atención Primaria: "No Hacer", una visión desde la Farmacia Hospitalaria* (N.º 8). Barcelona: Bayer Hispania; 2017.
18. Resolución del Director General del Servicio de Salud de Modificación de los Anexos 1 y 2 de la Orden de la Consejera de Salud y Consumo de 22 de diciembre de 2006. *Boletín Oficial de las Islas Baleares*, n.º 40 (17 de marzo de 2012).
19. Gorgas-Torner MQ, Pàez-Vives F, Camós-Ramió J, De-Puig-Cabrera E, Jolonch-Santusagna P, Homs-Peipoch E, et al. Programa de atención farmacéutica integrada en pacientes con enfermedades crónicas. *Farm Hosp*. 2012;36(4):229-39. DOI: 10.1016/j.farma.2011.06.015
20. Martin P, Tamblyn R, Ahmed S, Tannenbaum C. An educational intervention to reduce the use of potentially inappropriate medications among older adults (EMPOWER study): protocol for a cluster randomized trial. *Trials*. 2013;14:80. DOI: 10.1186/1745-6215-14-80