Ars Pharmaceutica
https://revistaseug.ugr.es/index.php/ars
E-ISSN: 2340-9894 ISSN: 0004-2927

doi: 10.30827/ars.v63i3.24625
Artículos originales

# Effect of an intervention New Medicine Service to improve adherence in the Spanish community pharmacies: a protocol of a pragmatic randomised trial

## Eficacia del Servicio de Asistencia en Nuevos Medicamentos para mejorar su adherencia en pacientes con enfermedades crónicas en farmacias comunitarias españolas: protocolo de un ensayo pragmático aleatorizado

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**Recibido:** 12.05.2022
**Aceptado:** 16.06.2022
**Publicado:** 22.04.2022

**Funding**

This study is funded by EP - INTERREG V A Spain-Portugal (POCTEP) (0197_NUMA_5_E) programme, and partially by the Andalusian Council of Official Pharmaceutical Associations.

**Conflict of interest**

The authors of this article state they are not subject to any conflict of interest related to the subject matter that may affect the design, analysis or presentation of results.

**Authorship**

All authors have made substantial contributions to all of the following: (1) the conception and design of the study, acquisition of data, analysis and interpretation of data, (2) drafting the article and revising it critically, and (3) final approval of the version to be submitted. The authors declare that the manuscript has not been submitted in whole or in part to other journals at the same time as Ars Pharmaceutica.
ClinicalTrials.gov Identifier: NCT04195191

## Resumen

**Introducción:** La falta de adherencia a los medicamentos es uno de los desafíos a los que se enfrentan los sistemas de salud. Los pacientes con mala adherencia al tratamiento no se benefician de la eficacia de la medicación, lo que se asocia con peor calidad de vida, aumento en hospitalizaciones y muertes y, en consecuencia, mayores costes sanitarios. Se ha demostrado que las farmacias comunitarias son elementos clave para mejorar la adherencia a los medicamentos prescritos, optimizar los resultados en pacientes con enfermedades crónicas y aumentar la eficiencia de la atención sanitaria.

**Objetivos:** (1) evaluar la efectividad de la intervención Asistencia a Nuevos Medicamentos (ANM) administrada por farmacéuticos comunitarios para mejorar la adherencia al tratamiento en pacientes a los que se les ha recetado un nuevo medicamento para una enfermedad crónica específica; y (2) realizar una evaluación económica de esta intervención.

**Métodos:** Se realizará un ensayo clínico pragmático aleatorizado a nivel de farmacia comunitaria (clúster). Se invitará a unirse al estudio a los pacientes identificados en la farmacia comunitaria que inicien tratamiento para: enfermedad pulmonar obstructiva crónica, hipertensión arterial, diabetes mellitus o en tratamiento con un anticoagulante/ antiagregante plaquetario. La intervención se basa en la comunicación farmacéutico-paciente, con el objetivo de evaluar la relación del paciente con su nuevo medicamento, e identificar posibles problemas, preocupaciones y falsas creencias-expectativas.

**Ética y difusión:** Se ha obtenido el dictamen favorable del Comité de Ética de la Investigación Biomédica de Andalucía. Los resultados de este estudio se difundirán activamente a través de publicaciones y presentaciones en congresos.

**Palabras clave:** Servicios de Farmacia Comunitaria; adherencia; intervención; protocolo

## Abstract

**Introduction:** Non-adherence to medications is one of the challenges health systems faces. Patients with poor adherence to treatment fail to benefit from effective medication, and this is associated with reductions in quality of life, poorer outcomes, increased hospitalisations, deaths, and, consequently, higher healthcare costs. Community pharmacies are shown to be key elements in improving adherence to prescribed medications, optimising patient outcomes and increasing the efficiency of care.

**Objectives**: (1) assess the effectiveness of the New Medicine Service (NMS) intervention delivered by community pharmacists to improve adherence to treatment in patients who have been prescribed a new medicine for a specific chronic condition; and (2) to conduct an economic evaluation of this intervention.

**Methods:** A pragmatic randomized clinical trial at community pharmacy-level (clusters) will be performed. Patients identified in the collaborating community pharmacy as starting treatment for the following conditions, will be invited to join the study: chronic obstructive pulmonary disease, hypertension, diabetes mellitus or on an anticoagulant/antiplatelet agent. The intervention is based on the pharmacist-patient communication, aiming to assess the patient's relationship with his/her new prescription, and identify potential issues, concerns and false beliefs or expectations.

Ethics and dissemination: The study protocol has been reviewed and ethics approval obtained from the regional ethics committee. The results from this study will be actively disseminated through manuscript publications and conference presentations.

**Keywords:** Community Pharmacy Services; Professional Role; Medication Adherence.

# highlights

Community pharmacists are privileged positioned to offer health advice and help patients get the most out of their newly prescribed medicine. In Europe, several studies have been conducted on the effectiveness of an intervention to improve adherence to recently prescribed drugs.

Community pharmacists have a privileged situation that would allow them to improve the efficiency of the system and address chronicity by implementing cognitive pharmaceutical care services, through improving the treatment adherence.

The study should provide important information on the clinical and cost-effectiveness of involving Community pharmacists in interventions in order to improve adherence.

The objective of this protocol is to describe the objectives, methodology and response of the study "Effect of a New Medicines Assistance intervention to improve adherence in Spanish community pharmacies: protocol of a pragmatic randomized trial".

# Introduction

Non-adherence to medications is one of the challenges health systems faces, and an issue that has negative effects both on health outcomes and healthcare costs[1]. The prevalence of non-adherence has remained almost unchanged over the last decades, and according to the scientific literature is around 50%[2]. The reasons for non-adherence are complex and multi-causal phenomenon which includes treatment-related and sociodemographic aspects, problems with the regimen (such as adverse effects), poor instructions, poor provider-patient relationship, poor memory, and patients' disagreement, among others[2-5].

A systematic review of the Cochrane Collaboration (2014)[6], which included a total of 182 clinical trials of interventions to improve medication adherence, concluded that novel approaches are needed to improve adherence rates, due to inconsistences in intervention´s results. This fact, coupled with budgetary constraints, increased chronicity and ageing populations[7], makes it necessary to develop new care proposals that can contribute to the sustainability of the health system. In this scenario, community pharmacists could help improve the efficiency of the system and address chronicity implementing pharmaceutical care cognitive services[8,9]. Cognitive services have been defined as those that are directed towards the patient and carried out by pharmacists who, calling on a specific knowledge, attempt to improve the process of the use of medications or the results of pharmacotherapy.[9-11]

The *New Medicine Service* (NMS), introduced in England in 2011, is an intervention carried out by professionals in community pharmacies accredited by the National Health Service (NHS). This service provides support to improve medication adherence in people starting a new medicine for a long-term condition. This intervention at the beginning of treatment achieves to improve long-term adherence. An economic evaluation made from data collected from NMS in 46 community pharmacies from a total of 504 participants, concluded that this service significantly improves adherence to treatment and that it is also cost-effective. Patients who received the intervention showed a better outcome, measured as quality adjusted life years (mean 0.04; 95%CI: 0.01; 0.13) and a lower cost (mean -£113.9; 95%CI: -1159.4; 683.7) than those who did receive the standard intervention. The study concluded that the extra cost of providing the intervention by the community pharmacy was offset by the reduction in overall healthcare costs related to the NHS[12-13].

The NMS intervention was implemented in other countries, for patients with a first-time prescription for a cardiovascular medicine (Norway) and for asthma (Belgium). In Norway, Medisinstart evaluated

the intervention in 67 pharmacies obtaining those patients in the intervention group 88.7% were adherent after 18 weeks versus 83.7% in the control group (5.0% difference, 95% CI 0.8–9.2, p=0.021), although that difference disappeared at 52 weeks (95% CI -2.0 to 7.8, p=0.24)[14]. In the case of Belgium, the introduction of the NMS program was not sufficiently embedded in the Belgian health care organization, causing low uptake and resistance to its implementation by pharmacists, patients, and other health care professionals; although, as of December 2015, a total of 22855 consultations had been performed[15].

Lastly, a study published on the barriers and facilitators to service (NMS) in UK implementation describes a perceived lack of time and inadequate relationships between pharmacists and GPs as barriers. On the other hand, an appropriate planning and monitoring system was, for example, identified as a potential facilitator. Overall, pharmacists were positive about this service. The study concludes that, despite the progress made in developing interventions delivered by community pharmacists, due to the complexity and challenges they entail, further assessments of these interventions are required[16]. It is interesting to note that the elements that have been identified are similar to those described in Spain by Gastelurrutia[11], who, using qualitative techniques, obtained information from a total of 33 pharmaceutical professionals with experience in professional practice and intervention strategies.

The study described in this protocol aims to: (objective 1) assess the effectiveness of the NMS intervention provided by community pharmacies to improve adherence to treatment, based on patients' specific disease pathology; and (objective 2) to conduct an economic evaluation of this intervention from the healthcare system perspective.

# Methodes

## Methodology Objective-1

Study design: a pragmatic randomized clinical trial at community pharmacy-level (clusters)[17]. Patients from intervention group (IG) will receive NMS and patients from the control group (CG) will receive normal practice.

### Criteria for inclusion/exclusion:

Patients identified in the collaborating community pharmacy as starting treatment for the following conditions, will be invited to join the study: chronic obstructive pulmonary disease (COPD), hypertension, diabetes mellitus or on an anticoagulant/antiplatelet agent. Patients to be excluded: suffer from a physical or mental disorder that prevents them from following the intervention; with seasonal or acute treatment; or those who have serious disease-related complications hampering their continuity in the study. Finally, it shall be deemed to be withdrawn from the study when the patient chooses to voluntarily drop-out, or when non-compliance with the intervention guidelines (failing to attend any of the visits scheduled in the intervention, refusal to complete the questionnaires). In the event of a patient withdrawal, the reason for leaving the study will be recorded, and monitoring will continue as usual.

## Development of the intervention

The intervention is based on the pharmacist-patient communication, by engaging in an open and free-flowing conversation aiming to assess the patient's relationship with his/her new prescription, and identify potential issues, worries and false beliefs or expectations. It has been observed that issues with new prescriptions appear early, causing a significant proportion of patients to stop taking their medication and thus become non-adherent.[13,18] To this end, this intervention will try to identify main medication-related issues (including adverse events) and any needs or support required by the patient including indications to visit his/her doctor for a medication review. The intervention is carried out in 3 steps: In the first one (step 1), recruitment is carried out and commitment to the patient is established. After 14 days (step 2), the intervention will be carried out and a script of questions was available (Table 1). At this visit, adherence to the new medication will be evaluated and problems with the medication will be identified and strategies to minimize them will be established. Finally, after 28 days (step 3), the

follow-up visit is carried out where adherence is checked and the intervention is evaluated (Table 2). To enable the development of the intervention and to standardized, the professionals from the participating pharmacies will be given a programme (Axon Pharma, available at: https://axonfarma.es/) which will provide guidance on the steps to take and record the information. Also supporting the intervention, the pharmacists also have access to explainer videos and other information and dissemination materials (leaflets, etc.) in order to offer to the patient to improve the adherence.

Two training sessions will be held to introduce the project, its objectives, methods and target population to encourage the homogenization and standardization of the intervention (length, procedures, or the use of communication skills and empathy emphasis, among others). Training will also be provided on the use of the Moodle platform. This platform will enable the resolution of any issues or incidents that may arise along the process. It also contains a user guide and a summary including answers to frequently asked questions, which will be fed back and updated periodically along with the development of the intervention. In addition, every six months a telephone meeting of researchers and pharmacist will be held to address potential problems, monitor the progress of the study and ensure adherence to the study protocol.

## General procedure

A total of 20 Andalusian pharmacies will participate in the study (10 in each arm). It is estimated that an average of 20 patients eligible for inclusion will participate in each pharmacy (independently of the conditions). Authors estimate an 20% drop-out rate. Therefore, final population is expected to include around 320 participants. This way, if we consider the proportion of adherence observed in the project evaluating the effectiveness of the NMS intervention in England[12], the power of the study would be enough to detect differences among groups.

The community pharmacies involved will be randomly assigned to the intervention group or the control group. Thus, all participants will be intervention or control to avoid contamination bias (Execution of an intervention bias). Randomisation will be conducted using computer-generated random numbers (Epidat software).

Patient recruitment will be carried out by the pharmaceutical staff from the community pharmacies involved in the study. Pharmacists will inform patients about the purpose and objectives of the study. Once the patient is interested in joining the scheme, he/she will be asked a number of questions to confirm eligibility. Subsequently, the patient will be asked to sign an informed consent. Confidentiality of the information given will be guaranteed. In compliance with the General Data Protection Regulation (Ley Orgánica 3/2018), no information allowing identification of the patient will be collected. Lastly, it is important to stress that the project has the favourable opinion issued by the Andalusian regional ethics committee (code 1202-N-18).

**Variables under study:**

The primary dependent variable will be the "Adherence to new prescription medication". The independent variables will be:

- Sociodemographic variables: age, sex, number of children and social support.
- Clinical variables: indication for the treatment (hypertension or diabetes), number of other treatments (continuous) and total number of pills a day, number of hospitalisations or emergency department visits in the last 6 months, changes in the health-related quality of life (HRQoL), and presence of other diseases or comorbidities. Other clinical variables according to type of population: Hypertension: response and normalisation of blood pressure. Diabetes Mellitus: Glycated hemoglobin.
- Variables regarding satisfaction with both the service and medication.
- Variables regarding healthcare costs: GP or specialist consultant visits, emergency service (at the health centre, hospital or at home), admissions to hospital and reasons.

Measurements will be performed at baseline, and at 10 weeks and 6 months. It is important to bear in mind that 10 weeks is the minimum time required for identifying an effective behaviour change[19].

Measuring instruments:

The working team has the necessary licenses for the use of the measuring instruments:

a. A questionnaire regarding socio-demographic and clinical characteristics, and an instrument for assessing the service, specifically designed by the research team for this particular project.

b. Social support (high, low): This will be measured by Blake and McKay's question: "How many people do you have near that you can readily count on for real help in times of trouble or difficulty, such as watch over children or pets, give rides to hospital or store, or help if you are sick?" Subjects with responses of 0 or 1 are considered as having low social support[20].

c. Health-related quality of life: The EQ-5D instrument will be used to assess the HRQoL. EQ-5D is a generic, self-applicable instrument that consists of two parts. First, it comprises 5 dimensions to enable the patient assess his/her state of health. Second, it also includes a visual analogue scale (VAS) [21]. In addition, patients with COPD will be given the CAT specific questionnaire (COPD Assessment Test), with final scores ranging from 0 to 40, where higher scores denote a worse quality of life[22].

d. SATMED-Q is a generic questionnaire measuring the patient satisfaction with treatment, and designed to be used in patients undergoing treatment for a chronic condition[23].

e. Adherence to medication: This will be measured at 2 and 6 months follow-up. Participants will be classified as adherent when a >80% adherence (or persistence) is achieved under the 3 following criteria:

• Q1: Adherence (main measure). In the last six or three months, have your forgotten to take the medication (medicine under study)? (yes/no).

• Q2: Adherence (control measure) Treatment completion rate from visit [%adherence = (number of pills taken/ number of pills prescribed) x 100].

• Q3: Persistence (control measure) measured by medication possession ratio[24]; by observing the number of medicine packages dispensed within 6 months (using electronic healthcare data, through the patient's health insurance card) and its consistency with adherence.

## Statistical analysis

First, this study will conduct a descriptive analysis. Mean, standard deviation, and maximum and minimum values will be estimated for all quantitative variables. Frequency analysis will be conducted for qualitative variables, to estimate the number and proportion of patients in each category. Then, the relationship between independent and dependent variables will be contrasted using the chi-square test ($\chi^2$) for qualitative variables, and using logistic regression for quantitative variables. Odds Ratio (OR) will be used, with a 95% confidence interval (95%CI), as a measure of association.

Finally, a multiple logistic regression analysis will be performed to control for potential confounding factors. This analysis will include all the variables shown to be statistically significant in the bivariate analysis and other variables of interest. The goodness of the model (goodness-of-fit) will be verified by the Hosmer-Lemeshow coefficient, and the existence of interactions between variables will be explored. A value of $p<0.05$ will establish statistical significance.

## Methodology Objective 2

Using a decision tree, this study will conduct a cost-utility evaluation, according to CHEERS guideline[25], of the NMS intervention compared with standard follow-up. The analysis will be carried out from the healthcare system perspective, with a 6-month time horizon.[26] The probabilities of the different decision branches from the decision tree model will be estimated from data collected to meet objective 1. An alternative analysis will be performed (cost effectiveness analysis) using the adherence to treatment declared by the patient as measure of effectiveness.

Use of resources and costs: direct healthcare costs will be taken into account and will be based on each patient's daily cost. The cost for each contact made with the health system will be estimated using 2005 public rates of the Public Health System of Andalusia.[27] Estimation of the cost of medication will

be based on the cost per unit extracted from the database of the General Council of Official Colleges of Pharmacists.[28] Since the analysis is to be carried out from the healthcare system perspective, direct healthcare costs (e.g. costs assumed by the patients and families), and indirect costs (e.g. costs resulting from the loss of productivity of patients or associated to morbimortality) have not been included.

The following will be calculated for each option: cost (medication, visits, hospitalizations, etc.), incremental cost, effectiveness, incremental effectiveness and the Incremental Cost-Effectiveness Ratio (ICER) showing the cost-outcome relation. This way, ICER result represents the additional amount the health system would pay for an additional unit of Quality-Adjusted Life-Years (QALY) gained attributable to NMS service. These will be calculated as follows:

A univariate sensitivity analysis will be performed in an effort to evaluate uncertainty of the variables included in the model. Data analyses will be performed in Excel 2016.

Missing data can lead to a reduction in precision and can bias estimates, most significantly when there are differences between groups. It is estimated that the main losses occur in data costs due to forgetfulness of information by the patients. Multiple imputation for missing data will include EQ-5D-5L indices at baseline, at 2 months, adherence, sex, type of medication and age as predictor variables. [29] Three scenarios will be considered for this purpose. First scenario: missing at random (MAR). Second scenario: missing data are data missing completely at random (MCAR), assuming that those who completed follow-up are considered fully representative of the entire sample who initiated the study. Third scenario: missing not at random (MNAR) assumes that other issues may be causing the absence of information, i.e. assuming that the probability of absence of information depends on unobserved values. This is consistent with a scenario in which the participants did not attend the interview because they were healthier (or less healthy) than the average. All these analyses will be performed following the approach proposed by Faria.[29] Finally, to establish the robustness of the model and explore the differences between the options, probabilistic sensitivity analyzes were performed; the results will be shown in a cost-effectiveness plan

# Discussion

This project is mainly funded by the INTERREG-EUROPE Interregional Cooperation Programme, which aims to improve the effectiveness of regional development policies and contribute to economic modernisation and increased competitiveness in Europe. In that regard, this protocol is part of a larger study entitled “New Care Model-NUMA”, whose overall objectives are mainly the design and piloting of a new care model. This new care model introduces community pharmacies into the care circuit between health and care services, in an effort to empower people to improve the relationship with patients, monitoring of their health conditions and prevention, as a way to address frailty and chronicity. Thus, the initial hypothesis is that community pharmacies, because of the family-like environment they offer to the community they serve, provide a service that can contribute to improving the monitoring of conditions of patients with chronic diseases, the prevention of frailty and the increase of self-efficacy in the management of their disease. Furthermore, the Professional Pharmaceutical Assistance Services have demonstrated their effectiveness in achieving a safer, more effective and efficient use of medications, which is why they can be a useful strategy in reducing medication errors[8].

The start of the field work has experienced some delay with respect to its initial schedule. This delay is due to the fact that the intervention is being tailored to the local context and circumstances, as recommended by the Medical Research Council.[30] In addition, recruitment is being a slower process than expected, mainly due to the number of patients meeting the study inclusion criteria.[31] To this end, additional recruitment is being considered in those community pharmacies with a higher incidence of patients meeting the inclusion criteria. Then, once editing and translation into English was completed, came COVID-19 pandemic, which hampered the project’s progress. In this respect, in addition to performing routine tasks, patient care and trying to reduce the burden of patients on health facilities, community pharmacists are working to provide home deliveries, as well as dealing with the increasing

number of patients coming through pharmacies with other ailments. All this has hampered the recruitment of patients to the study.[32,33]

This study has several limitations that should be considered when interpreting the results. Subjects who will receive the intervention need not be representative of the population. Furthermore, this intervention should be tailored to the needs of the patient, and therefore a balance must be achieved between the needs of the patient and standardization, which requires methodological rigour. As for the intervention, it is not possible to carry out a "double blind" study as both the pharmacist (who performs the intervention) and the patient are aware of the group they are in. In this sense, to avoid possible contamination between patients assigned to the control and intervention group, randomisation has been carried out at the pharmacy level; preventing the pharmacist from applying part of the intervention to the control group.

Finally, it should be highlighted that EQ-5D-5L normative data for Spanish general population (available from the Spanish National Health Survey) will be used as reference data of the population health status. This will allow for comparisons in health status between the groups of patients and the general population.

## Acknowledgment

The authors would like to thank Rosario Caceres Fernández-Bolaños for her assistance and to Begoña Martínez Vázquez for the translation of this article into English.

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**Table 1:** script of questions from the second visit.

| |
|---|
| Have you already had a chance to take the new medicine? |
| *How many times have you been able to take your new medicine so far, if at all?* |
| How are you doing with it? |
| Are you having a problem with your new medicine or are you worried about taking it? What, if anything, are you concerned about your new medication? |
| Do you think it is working for you? Or does it work for you in a different way than expected? How is the medication working for you? |
| Do you think it is causing any side effects or unexpected? What side effects or unexpected effects have you had since you started taking it? |
| Many people tend to skip a dose, have you missed a dose of your new medication? When was the last time you skipped a shot? How many feeds have you skipped in the last week? |
| Is there anything else you would like to know about your new medicine or is there anything that is not clear to you? What else would you like to know or review? |

**Table 2:** script of questions from the third visit

| |
|---|
| How are you doing on your new medication since we last spoke? (Are you still taking it?) |
| The last time we spoke, he mentioned that he was having some problems with his new medication. We are going to see them one by one to see how she is doing. |
| A: The first problem mentioned [see specific problem] is it correct? |
| B: Did you try [advice/recommended solution in previous contact] to fix it? |
| Have you tried anything else? |
| Did it work? (How did it serve you?) |
| Are you still having problems or concerns related to the medicine? |
| Have there been any other problems/concerns with your new medications since we last spoke? |
| People often forget to take doses of their medications for a variety of reasons. Have you missed a dose of the new medicine, or has the time of taking it changed? When was the last time you missed a dose? |