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Effect of pharmaceutical intervention on medication adherence and blood pressure control in treated hypertensive patients: Rationale, design and methods of the AFenPA pilot study.

Fikri-Benbrahim N[1], Sabater-Hernández D[1], Fikri-Benbrahim O[2], Faus MJ[1], Martínez-Martínez F[1], González-Segura Alsina D[3].

1. Pharmaceutical Care Research Group of University of Granada (Spain); 2. Nephrology Department. Mancha Centro Hospital Complex. Alcázar de San Juan (Ciudad Real, Spain); 3. Medical Department, Almirall S.A., (Barcelona, Spain).

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Correspondence: Narjis Fikri Benbrahim.
Pharmaceutical Care Research Group.
Faculty of Pharmacy. University of Granada.
Campus Cartuja s/n
18071- Granada
e-mail: narjisfikri@yahoo.es

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ABSTRACT

Objective: To assess the effect of a protocol-based pharmacist intervention on blood pressure control and medication adherence among treated hypertensive patients who are users of community pharmacies.

Methods: A quasi experimental study design with control group has been designed to compare the effect of pharmaceutical intervention (intervention group) versus the standard healthcare procedure (control group) on blood pressure and medication adherence among hypertensive patients receiving drug therapy in community pharmacies. The patients will be allocated evenly between the two groups (ncontrol = nintervention), with a 6-month follow-up. The pharmaceutical intervention program will comprise three main parts: 1) patient education / information on issues relating to hypertension and medication adherence; 2) self-monitoring of blood pressure; and 3) interaction with the physician through personalized reports when the mean blood pressure values recorded at home exceed the treatment goal according to the clinical condition of the patient. In order to evaluate the effect of the pharmaceutical intervention upon medication adherence and blood pressure, blood pressure recordings will be made in the pharmacy, while percent medication adherence will be established based on pill count in both groups at the start and end of the study.

Discussion: To our knowledge, this is the first study in the community pharmacy setting in Spain to evaluate the effectiveness of pharmaceutical intervention in combination with home blood pressure monitoring on blood pressure control. In addition, the pharmaceutical intervention has been designed for inclusion as standard practice in the context of Pharmaceutical Care.

KEY WORDS. Hypertension, adherence, community pharmacy services, intervention, home blood pressure monitoring.

RESUMEN

Objetivo: Evaluar el efecto de una intervención farmacéutica protocolizada sobre el control de la presión arterial y la adherencia al tratamiento farmacológico en pacientes usuarios de farmacias comunitarias.

Material y métodos: Estudio cuasi-experimental con grupo control en el que se comparará el efecto de una intervención farmacéutica (grupo intervención) con el proceso de atención habitual (grupo control), sobre la presión arterial y la adherencia al tratamiento de pacientes hipertensos tratados farmacológicamente en farmacias comunitarias. Los pacientes serán distribuidos de

forma equitativa en ambos grupos (n control = n intervención) y serán seguido durante 6 meses. El programa de la intervención farmacéutica constará de tres partes fundamentales: 1) educación/ información al paciente sobre aspectos relacionados con la hipertensión y adherencia al tratamiento farmacológico, 2) automonitorización de la presión arterial y, 3) interacción con el médico mediante informes personalizados cuando la media de las cifras de presión arterial realizadas en el domicilio superen el objetivo terapéutico acorde con la situación clínica del paciente. Para evaluar el efecto de la intervención farmacéutica sobre la adherencia terapéutica y la presión arterial se obtendrán medidas de presión arterial en la farmacia y porcentaje de cumplimiento terapéutico mediante recuento de comprimidos en ambos grupos al principio y al final del estudio.

Discusión: Según nuestros conocimientos, éste es el primer estudio que se realiza en farmacia comunitaria en España para probar la efectividad de una intervención farmacéutica conjuntamente con la automedida de la presión arterial sobre el control de la presión arterial. Además, la intervención farmacéutica se ha diseñado de forma que pueda integrase como práctica habitual enmarcada dentro de la Atención Farmacéutica.

PALABRAS CLAVE: Hipertensión, adherencia, servicios farmacéuticos, intervención, automedida domiciliaria de la presión arterial.

BACKGROUND

Hypertension is a major public health problem. Its prevention and control are therefore a key objectives for the healthcare system[1, 2].

In Spain, the prevalence of hypertension in the general population is estimated to be 35%, affecting a total of 10 million people throughout the country. Specifically, 40% of these patients are middle aged, and 60% are over 60 years old[3].

Drug treatment for lowering blood pressure (BP) has been shown to significantly reduce the risk of ischemic stroke by 31-45%, and the risk of myocardial infarction by 8-23%[4]. However, despite the availability of effective antihypertensive drugs, the control of high BP is far from optimum in this country, since less than 50% of all hypertensive patients are controlled[3].

Difficulties in accessing the healthcare services, non-adherence, inadequate practice organization and physician practice patterns are some of the causes related to the lack of BP control[5, 6]. In order to solve these problems, the World Health Organization, the International Society of Hypertension and other societies (American Society of Hypertension, European Society of Hypertension, and Canadian Hypertension Society) recommend the development of strategies involving the implication and participation of all those healthcare professionals that attend such patients [7-9].

Community pharmacists are the most accessible healthcare professionals in Spain. In addition, as a result of their specific training, they are the ideal professionals for advising patients on proper drug use. These reasons justify the integration of community pharmacists in the multidisciplinary healthcare team setting, where they should play an active role in the follow-up of hypertensive patients with a view to enhancing compliance, reducing adverse events and improving blood pressure control[10]. In this regard, the healthcare activities inherent to pharmacists, set within the concept of Pharmaceutical Care[11-13], could be a good option to be taken into account for improving BP control and medication adherence. Specifically, a number of studies have shown that BP control can be improved when the pharmacist is involved in monitoring patient's BP, offers advice on home blood pressure monitoring (HBPM), provides information on the disease, promotes changes in lifestyle and habits, encourages medication adherence and/or provides recommendations on the pharmacotherapeutic adjustments considered appropriate, in collaboration with the physician[5,14-24].

In a recent systematic review of interventions used to improve control of BP in hypertensive patients[25], the authors discussed the need to implement protocols for hypertensive patient follow-up, and advocated for the promotion of HBPM and for appointment reminders as part of the strategy to improve BP control. Moreover, the authors concluded that pharmacist-led care requires further evaluation.

Three systematic reviews recently published, whose objective were to evaluate the impact of pharmacists´ interventions in the management of hypertensive patients[14-16], highlighted that the studies carried out in a community pharmacy setting are scarce and have limitations that should be solved. Firstly, only one study[17] used a reliable method to measure antihypertensive medication adherence. Secondly, only two studies[6,26] integrated HBPM as a part of

the community pharmacist intervention. Moreover, these studies presented a number of limitations such as: short-time period of follow-up (3 months), lack of a control group or didn't show the proportion of patients with controlled hypertension at the end of the study. As it is well known, HBPM may increase patients' involvement in their care, also increasing medication adherence and improving blood pressure control[27-31]. Furthermore, community pharmacists can play an important role in the implementation of HBPM in daily practice[29,32-34].

Therefore new studies are needed in a community pharmacy setting to draw conclusive data on the benefits of pharmacist intervention in the control of BP and antihypertensive medication adherence.

With the purpose of improving the quality of the research published to date, this study protocol is aimed at providing detailed information on the development of the AFenPA pilot study, specifically, as regards: study design, calculation of the sample size, operational definition of the variables, and operating procedures with a detailed definition of the pharmaceutical intervention or statistical data analysis, amongst others.

Hypothesis: Pharmacist intervention together with HBPM can improve BP control and medication adherence as compared to routine practice in the pharmacy.

Study aims and objectives: To assess the effect of a protocol-based pharmacist intervention on: 1) the control of hypertension; 2) reduction of systolic and/or diastolic BP; and 3) medication adherence among treated hypertensive patients who are users of community pharmacies.

METHODS

Study design. A quasi experimental study design with control group has been designed to compare the effect of pharmaceutical intervention (intervention group) versus the usual care procedure in community pharmacies (control group) upon BP and medication adherence. Each patient will be followed for 6 months.

Study Setting. Community pharmacies of the provinces of Jaén and Granada (Spain).

Community pharmacists' eligibility criteria. Community pharmacists that meet all the following criteria will be eligible to participate in the AFenPA study:

- Pharmacists with previous research experience.
- Pharmacists whose pharmacies have a private counselling area where patients will be shielded from the public eye and ear, and
- Pharmacists able to carry out a follow-up phase for patients during at least six months.

Recruitment of community pharmacists. Community pharmacists will be identified through the local professional pharmacy associations of Jaén and Granada, which will contact pharmacists of their provinces to inform them about the project. Pharmacists who agree to participate will sign the appropriate commitment document and will be instructed on hypertension, medication adherence and the development of the project."

In order to minimize the risk of contamination between the intervention and the control group, trainers will emphasize that patients included in the control group should only receive usual care.

Subjects. The study population will include hypertensive patients receiving drug therapy.

Patient inclusion criteria. Patients of either sex, aged 18-80 years who visit the pharmacy with a personal prescription for any antihypertensive drug.

Patient exclusion criteria. Patients living with other subjects who are taking the same antihypertensive drug(s), pregnant women, patients who during the screening process at the pharmacy show a mean systolic / diastolic BP of ≥ 180/110 mmHg, subjects with difficulties for HBPM or where such monitoring is not recommended, patients lacking motivation for self-control, with secondary hypertension, recent cardiovascular events (less than 6 months), renal or liver insufficiency, patients who have started or have switched their antihypertensive treatment within less than one month, subjects already enrolled in a special hypertensive patient program, or subjects used to performing HBPM at least two days a month.

Any patient who approaches and declines to participate or eventually abandons the study, will be included in a list in order to carry out a non-responder analysis of patients will regard to socio-demographic and clinical data.

Sample size. Sample size determination was based on the difference in the expected percentage of subjects with controlled hypertension between the control group and the intervention group, at the end of the study. The prevalence of controlled hypertension in Spain is 50% [3]. It is assumed that the prevalence of controlled hypertension in the control group at the end of the study will not change from baseline (π_1=0.50) and an increase of 25% in the prevalence of controlled hypertensive patients in the intervention group after the 6 months of follow-up will occur (π_2=0.75). A comparing two binomial proportion test was applied, using a statistical table for the design of clinical trials[35], considering the following assumptions: type II error 20% (ß = 0.80), 95% significance level (α = 0.05).

The contemplated sample size thus included 58 patients in each group (116 in total). To this number we added 20% (24 patients) to make up for possible losses during the study. The final total number of subjects (n=140) will be equally distributed among the 18 participating pharmacists (approximately 10 subjects per pharmacist). The decision to assign 10 patients per pharmacist was based on the experience of other authors, who suggest working with 10-20 patients as a reasonable number for conducting patient healthcare activities at the pharmacy[36].

Trial population and recruitment. Patient screening will be performed on a consecutive basis as the patients visit the pharmacy to receive their antihypertensive drug. Due to the existence of drugs being prescribed either for hypertension or heart failure, the pharmacist will consult the patient's medical report in order to check the therapeutic indication. This personal medical report includes information such as: reason of medical consultation, medical diagnosis, medical tests performed, pharmacological treatments applied and non-pharmacological advice. If the patient does not have a medical record, the pharmacist will contact the physician in order to inquire about therapeutic indication on the drugs prescribed.

The pharmacists will identify patients consecutively until they have recruited 10 subjects. The recruitment stage will be fixed at a maximum of one month. Patient inclusion is contingent on their acceptance to participate in the study and the study's inclusion criteria. The assignment method will consist of a coin toss to determine the group assignment of the first recruited patient per pharmacist. This will be done in each pharmacy. As the aim is to divide the patients evenly between the two groups ($n^{control} = n^{intervention}$), the assignment of the first patient will determine the group of subsequent patients into the intervention or control groups (for example, control/intervention/control/intervention, etc.). This process will be continued until there are10 subjects per pharmacist. The assignment method will only be known to the study coordinator at the beginning of the study.

To minimize the risk of selection bias, after visits 1, 2 and 3 (initial phase, see figure 1) the participating pharmacist will contact the study coordinators to determine the assignment of the patient to the control or intervention group. The pharmacist will contact the coordinators as each patient is included in the study to ascertain their group assignment. The assignment details were revealed to patients as well as study pharmacists only after the completion of baseline data collection.

1.Variables related to the study objectives: primary outcome variables.

BP at the pharmacy. It will be monitored in two different periods: at the start and end of the study (figure 1). In each period, BP will be recorded on three visits scheduled in the same timeline of the day. The time period for the three visits to the pharmacy will cover three weeks. On each visit three BP measurements will be made spaced 2-3 minutes apart, on the control arm (the arm where BP is highest). All pharmacists will use the same clinically validated Visomat Comfort 20/40 monitor (UEBE Medical GmbH, Wertheim, Germany)[37].

The pharmacists were previously instructed on how to monitor BP adequately according to international guidelines[38]: 5 minutes at rest, back supported with feet flat on the floor, proper cuff size at heart level, refrain from drinking coffee or tea, smoking or exercise at least 30 minutes prior to measurement.

Depending on the objective, BP values will be used in their original form (objective 2) or BP will be transformed on a dichotomic basis: controlled / uncontrolled (objective 1).

Mean BP and heart rate in the pharmacy will be calculated, rejecting the measurements obtained on the first day and the first measurement of the next two days. BP control will be defined as systolic BP under 140 mmHg and diastolic BP under 90 mmHg.

Medication adherence. It will be recorded in two different periods: at the start and end of the study (figure 1), based on manual pill count of antihypertensive tablets. This method is an objective and reliable method to assess and investigate adherence to drug therapy in clinical practice[39-41].

A count will be made at the start and end, spaced one month apart. On occasion of the initial count, the date, total number of tablets in the possession of the patient, and number of tablets retrieved with the new prescriptions, if any, will be recorded. After 28-30 days, the patient will be asked to return the drug packs with the complete blisters (consumed or otherwise), and the tablets will be counted (those missing being taken to have been consumed). From this point, calculation will be made of the total number of tablets apparently consumed by subtracting the remaining tablets at the final count from the total tablets at the initial count. Likewise, calculation will be made of the total number of tablets that should have been consumed: tablets a day prescribed, multiplied by the number of days elapsed. Lastly, adherence will be measured as percent medication adherence (PMA), calculated by means of the following formula:

PMA= (Total number. of apparently consumed tablets/ Total number. of tablets that should have been consumed) x 100. Dichotomic transformation of PMA will be used: adherent / non- adherent. Adherence will be defined as PMA 80-110%.

2. In addition to the abovementioned variables, other variables will be recorded at both the start and end of the study, allowing us to describe the study sample and adjust the pharmaceutical intervention effect upon hypertension control, the decrease in systolic/diastolic BP, and medication adherence (evaluation of confounding factors). These variables are the following:

- Age (continuous variable), expressed in years; sex.

- Sociocultural level (polychotomic variable): illiterate / primary education / secondary education or technical training / university.

- Occupational status (polychotomic variable): housewife / employed / student / unemployed.

- Marital status (dichotomic variable): with / without couple.

- Smoking (dichotomic variable): smoker / non-smoker. Smokers will be defined as those subjects who regularly smoke any amount of cigarettes, or who have stopped smoking less than a year ago.

- Physical exercise (dichotomic variable): yes / no. Physical exercise will be defined as walking or any form of aerobic exercise for an average of half an hour a day, three times a week.

- Number of antihypertensive drugs (continuous variable).

- Types of antihypertensive drugs (polychotomic variable): diuretics, beta-blockers, alpha-blockers, calcium antagonists, angiotensin-converting enzyme inhibitors (ACEIs) / angiotensin II receptor antagonists (ARA II) / others.

- Number of antihypertensive drug doses/day (continuous variable).

- Weight (continuous variable), expressed in kg.

- Height (continuous variable), expressed in cm.

In addition, the presence of the following conditions will be documented at the start of the study: diabetes, acute myocardial infarction, chest pain, heart failure, stroke, peripheral artery disease, hypercholesterolemia, hypertriglyceridemia.

Operating procedures: visit scheduling. In broad outlines, the operating procedures can be divided into three main phases: (1) initial phase; (2) final phase, in which pharmacist intervention will be the same in both groups; and (3) intermediate phase, in which the control group will receive the usual pharmacy care and the intervention group will receive the pharmaceutical intervention designed to the effect.

Initial study phase. Intervention and control group.
The initial phase comprises three visits scheduled in three consecutive weeks (figure 1), in which the following activities will be performed: (1) BP measurement at the pharmacy; (2) collection of the initial patient data; (3) checking of the exclusion criteria; (4) signing of the informed consent sheet; and (5) start of manual tablet count.

Intermediate study phase. The intermediate phase will begin once assignment of the patient to the control or intervention group is known. Tablet counting will end on the first visit of this phase (independently of the group to which the patient has been assigned).

After this visit the patients in the control group will not be appointed until 20 weeks later. During this period, the pharmacist will attend these patients as usually done at the pharmacy.

In turn, the patients in the intervention group will start the pharmaceutical intervention program. Thus, on the first visit of the intermediate phase, the patients will be instructed on the use of HBPM in a 20-minute training session by their pharmacist. At the end of the session, the HBPM technique will be tested by three consecutive self-measurements made in the presence of the pharmacist. Patients will also receive written guidelines to reinforce the training provided. Patients will monitor their HBPM over a 5-day period, taking three measurements in the morning (each measurement spaced 2 minutes apart, between 6.00 a.m. and 9.00 a.m.) and three in the evening (between 6.00 p.m. and 9.00 p.m.). At home, the same device as in the pharmacy will be used.

After this first visit, the patients will have 5 additional planned visits over a period of 5 months.

On the second visit of this intermediate phase, the patients will be instructed (verbally and in writing) on aspects related to adherence, using an information leaflet designed to the effect. In this context, the pharmacist will try to identify the educational needs of each patient by means of a specifically designed questionnaire (appendix 1), in order to individualize and better adapt the educational intervention to these needs.

On this same visit, the mean systolic / diastolic BP value of the 5 days of home measurement will be assessed. If the recorded value is ≥ 135/85 mmHg, the patient will be referred to the physician with a personalized report, for introduction of the treatment adjustments considered appropriate. The patient will be seen again four weeks later (visit 3). It will be determined whether the physician has made any treatment changes, and the patient will be asked to continue HBPM at least one day a week.

Four weeks later (visit 4), the patient again will be asked to continue HBPM for 5 consecutive days, in order to again assess the efficacy of the antihypertensive treatment received.

At the end of HBPM, the mean home BP value will be assessed, and the patient will be referred to the physician if ≥ 135/85 mmHg (visit 5).

Four weeks later (visit 6), it will be checked whether the patient complies with HBPM, and whether the physician has introduced treatment changes.

Final study phase. The final study phase will take place 6 months after patient inclusion in the study. This final phase will include four visits involving a new tablet count, and BP again will be measured in the pharmacy in the course of three scheduled visits (figure 1).

Statistical analysis. The data will be filed and analyzed using the SPSS version 15.0 statistical package for Microsoft Windows (SPSS Inc., Chicago, Illinois, USA).

The sample characteristics will be described based on frequency tables for the qualitative variables and tendency measures (arithmetic mean and standard deviation) for the quantitative variables. In addition, the 95% confidence intervals will be calculated.

The Student t-test for paired samples will be used to compare means of one same group between the start and end of the study. If the test application conditions are not met, a nonparametric test will be used: the Wilcoxon test. The McNemar test will be used to compare proportions of one same group between the start and end of the study.

The Student's test for independent samples will be used to compare means between the control group and the intervention group, provided the test applicability conditions are met. Otherwise, the Welch test would be used (for two means that follow a normal distribution, but which show heterogeneous variances). If the applicability conditions of this test are not met, a nonparametric test will be used: Mann-Whitney U-test. The chi-squared test in turn will be used to compare proportions between the control group and the intervention group. When the chi-squared test cannot be used because some expected frequency in the 2 x 2 tables is ≤ 5, the Fisher's exact test will be applied.

Multivariate logistic regression analysis will be used to evaluate the effect of the pharmaceutical intervention. To this effect, two models will be developed: one where the dependent variable is BP control at the end of the study, and another where the dependent variable is medication adherence at the end of the study. The following variables will be entered in both models to control the effect of the intervention: age, sex, body mass index, physical exercise, number of antihypertensive drugs, presence of diabetes, presence of cardiovascular disease (acute myocardial infarction, chest pain, angina pectoris, stroke and/or peripheral artery disease), presence of dyslipidemia (hypercholesterolemia and/or hypertriglyceridemia), and initial BP values.

Likewise, evaluation will be made of the effect of the intervention upon the lowering of BP. To this effect, two analysis of covariance (ANCOVA) will be developed in which the dependent variables will be systolic and diastolic BP, respectively.

Ethics and trial registration. Patient participation is voluntary, and all subjects will give informed consent.

The AFenPa study was evaluated and approved by the Clinical Research Ethics Committee of the University of Granada (Spain).

DISCUSSION

To our knowledge, this is the first study in the community pharmacy setting in Spain to evaluate the effectiveness of pharmaceutical intervention together with home HBPM upon BP control. In addition, the drug intervention has been designed for inclusion as routine community pharmacy practice.

Study limitations. The AFenPA study is a pilot study, whose aim is to assess on the effect of a specific pharmaceutical intervention in a community pharmacy setting. It should be noted that, although quasi-experimental studies are a valid alternative to randomized control trial in the evaluation of health interventions, in future studies a randomized control trial design should be performed. Caution should be exercised when interpreting our results as behavioural intervention studies run the risk of contamination between the intervention and the control groups happening. Other limitations include short-term assessment of BP control and treatment adherence. Caution should be exercised when interpreting our results as behavioural intervention studies run the risk of contamination between the intervention and the control groups happening. Furthermore, in this study researchers who conduct the intervention are not blinded.

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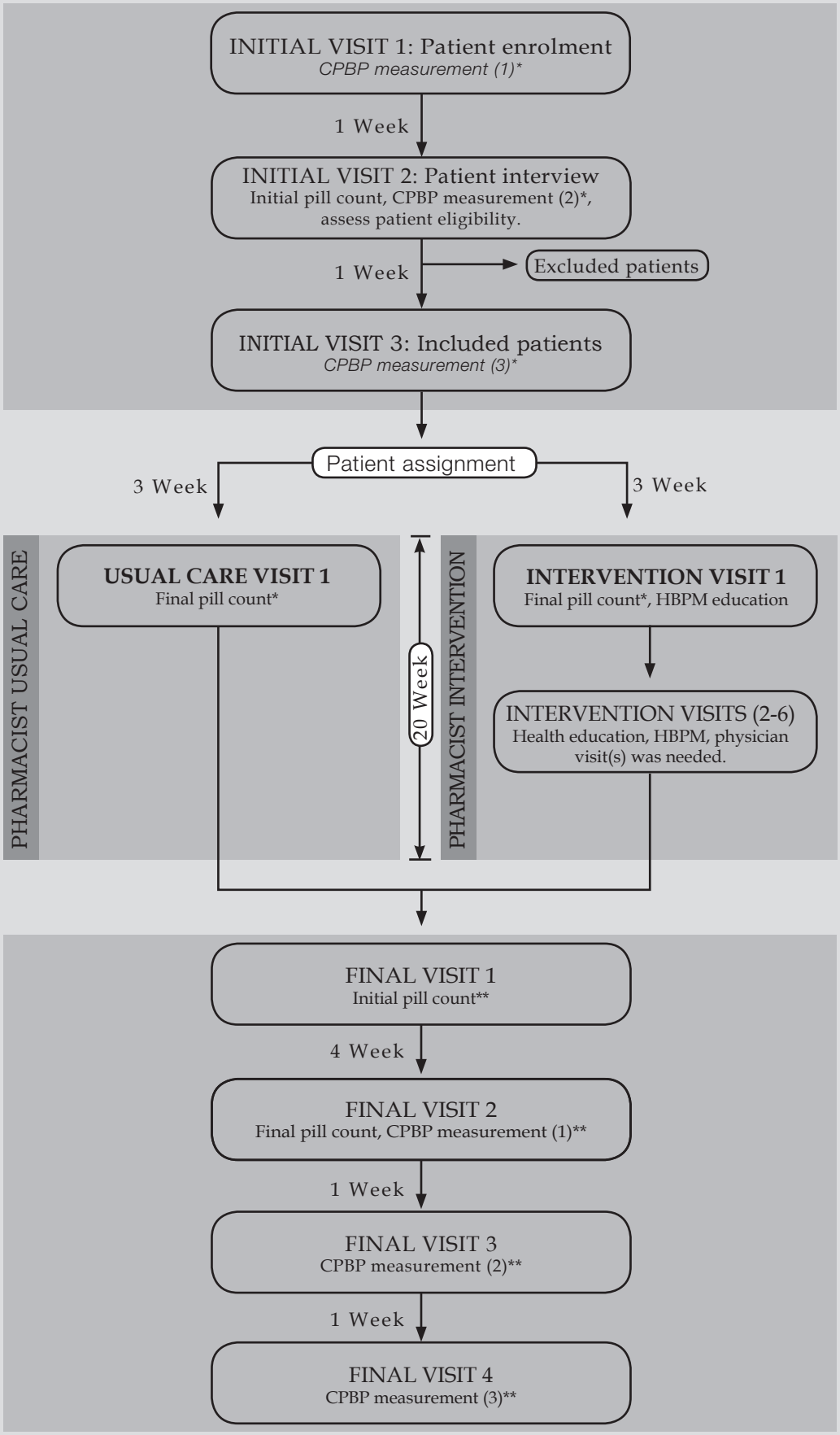
Figure 1. General Procedure of the study.



* Baseline measurements; ** End points measurements; CPBP: Community Pharmacy Blood Pressure; HBPM: Home Blood pressure monitoring.

Mrini, María Ángeles Carrascosa Medina, Miguel Alberto Moreno Carrascosa, María Luisa Díaz Rodríguez, Juan Pedro Lorca González, Sebastián Ramón Martínez Pérez, María Jesús Molina Fernández, Andrea Cecilia Molina Guerra, María Rocío Rivas Pinto, Francisco Javier Sánchez Alonso, Jesús Sierra Ávila, María del Mar Trigo Hervas

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Appendix 1. Question form on the main factors of non-adherence (pharmacological and non-pharmacological)

1. Do you take the medicines at the times indicated by your doctor?
   a) Yes
   b) Sometimes
   c) No

How many pills do you take to control your blood pressure? One ☐ Two ☐ More than two ☐ Don't know ☐

2. How many times a day do you take the medication to control your blood pressure?

Medicine	Taken since	Regimen prescribed	Regimen used

3. People often have difficulties taking their pills. Do you ever forget to take them?
   a) Yes
   b) Sometimes
   c) No

Why?

4. Do you stop taking your medicine when you feel well?
   a) Yes
   b) No

5. If you feel ill, do you ever stop taking your medicine?
   a) Yes
   b) No

6. Do you notice anything unusual or have you experienced some unpleasant effect that you have attributed to the medicine or medicines you take for high blood pressure? No ☐ Yes ☐ Which ☐

7. Are you aware of the possible consequences of failing to take your medicine?
   a) Yes. Which?
   b) No

8. Is high blood pressure a life-long condition?
   a) Yes
   b) No

9. Can it be controlled by diet and medication?
   a) Yes
   b) No

10. Indicate two or more parts of the body that can be damaged by high blood pressure

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