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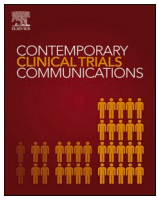

Clinical impact of pharmaceutical consultations in patients treated for chronic obstructive pulmonary disease: Study protocol for a randomized controlled trial (BPCObs study)

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ABSTRACT

Background: Chronic obstructive pulmonary disease (COPD) is an irreversible chronic respiratory disease which outcome depends on medication adherence. Pharmacists may increase this adherence by advising patients on inhaler devices proper use. This paper presents the protocol for a randomized controlled trial, which assesses impact of pharmaceutical consultations on COPD exacerbations, medical care, adherence to inhaler devices and quality of life.

Methods: This trial will include 226 COPD patients treated with inhaler devices: 94 in a control group, 66 receiving a pharmaceutical consultation at hospital and 66 receiving up to 12 pharmaceutical consultations corresponding to dispensing at their community pharmacy. The aim of these interventions is to inform patients about COPD medication, train them in the use of inhaler devices and improve adherence. Patients included by hospital pharmacist will be randomly assigned to the control and hospital experimental groups. Community pharmacists (CP) will include patients in the experimental community group. CPs will follow-up all study patients for 12 months. Primary outcome is the mean number of COPD exacerbations. Secondary outcomes include number of medical consultations, emergency visits and hospitalizations, patients' adherence devices and quality of life.

Discussion: This is the first French trial which assesses both hospital and community pharmaceutical interventions on COPD patients. Study limitations include recruitment and CP adherence to follow-up. Indeed, the success of this trial depends on the willingness of CPs to collect the data. This work is the first step towards building a network of CPs trained for clinical research.

Trial registration: Clinicaltrials.gov, NCT03704545. Registered on October 12th, 2018. https://clinicaltrials.gov/ct2/show/NCT03704545?cond=COPD&cntry=FR&city=nimes&draw=2&rank=1.

1. Background

Chronic obstructive pulmonary disease (COPD) is an irreversible chronic respiratory disease, which was the third leading cause of death in the world in 2019 [1]. In France, COPD affected about 2.6 million people in 2016 [2]. Exacerbations are the main complications of COPD. They result in a worsening of symptoms and can lead to hospitalization and accelerate progression of the disease [3]. The occurrence of exacerbations as well as the progression of the disease depend on adherence to medication, administered by inhalation devices [4]. Indeed, a significant decrease in the number of exacerbations has been found in patients who correctly take their inhalation device. Different kinds of

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devices are available according to the form of the active substance (powder, aerosol, etc.). Thus, a patient may use several different devices, successively or simultaneously. However, the advanced age of patients and the lack of information on the use of inhalation devices contribute to their misuse, resulting in poor adherence to medication estimated at 15–50 % [5–8].

Pharmacists play a leading role in adherence to medication therapy. At the hospital, clinical pharmacists advise patients on correct use of their medication. One study conducted in a French hospital has shown that a pharmaceutical outpatient consultation improves patients' adherence to all medication by 30 % when they return home [9]. In primary care, community pharmacists (CP) may inform and educate the patient on treatment at each monthly visit. Therefore, pharmaceutical interview programs have been implemented to reinforce the follow-up of patients with asthma and patients treated with oral anticoagulants [10,11]. For older patients, medication reviews performed by CP can also improve patient safety [12].

Regarding COPD, the intervention of health professionals such as pharmacist improves the management and burden of the disease. A Norwegian study [13] showed that therapeutic education sessions reduced the number of general practitioner (GP) visits by 85 % (3.4 versus 0.5, $p < 0.001$) and decreased the consumption of short-acting beta2-adrenergic agonists used in the acute phase by 57 % ($p < 0.03$). This resulted in a decrease in healthcare costs, particularly for consultations with GPs. A literature review of CP interventions highlighted a positive impact on medication adherence and on the patient's ability to use inhaler devices to manage COPD [14]. Moreover, CP interventions in Belgium increased the rate of adherent patients, reduced the occurrence of severe exacerbations and shortened the length of hospital stays [15]. This study conducted by Tommelein and al also shows that adherence to inhalation devices increases with repeated pharmacist intervention over time.

To our knowledge, no pharmaceutical interventions in the management of COPD have yet been studied in France. No studies have also explored the potential benefits provided by hospital clinical pharmacists. This trial aims to assess whether pharmaceutical consultations in primary care and/or hospital could have a clinical impact in patients treated for COPD at home.

2. Methods/design

2.1. Design

In this study the objective is to evaluate if the pharmaceutical consultation has a clinical impact in patients treated for COPD at home. Therefore, a 2 group randomized clinical trial was proposed. In the experimental one, the pharmaceutical intervention was proposed at the end of the stay before the hospital discharge. In the control group, patients received the usual care, ie without pharmaceutical intervention.

Nevertheless, this design was not sufficient to answer the question of the relevant frequency of pharmaceutical consultation. For obvious reasons, it was not possible to make pharmaceutical following at hospital but the community pharmacists can. The best choice would have been to follow all patients of experimental group regardless of their usual CP, but that was not possible due to feasibility and methodological reasons. Indeed, it would have been difficult for the pharmacist to follow patients of both control and experimental group, and would have unintentionally delivering information or consultation of control group patient. Moreover, the risk of finding a CP that refusing to perform consultations was too important, and therefore patients without complete data was expected. Finally, to ensure the homogeneity of the process, we chose to select few CP for this pilot study. Therefore, we selected ten CP (5 urban and 5 rural) and trained them to the community consultations. The patients, enrolled directly by these ten CP, make up the experimental community group. This group enables to assess the relevance of the repetition of the pharmaceutical consultation on a 12-months period. Patients of this group were not randomized but matched on the 3 stages of the disease (Stage 1 patients are not recruited in the study).

A pilot committee composed of pharmacists and methodologists oversaw the study methodology to ensure the relevance of research arrangements and the quality of data collection. The first two committee meetings were held upon acceptance of the project and prior to the start of inclusions. A final meeting will be held when the results are exploited, at statistic report writing. A clinical research associate will carry out an audit during the course of the study. This study was approved by the committee for the protection of persons (Comite de Protection des Personnes Sud Mediterranee III, # 2018-A01699-46) and the French National Agency for the Safety of Medicines. It was prospectively registered at clinicaltrials.gov (NCT03704545). This article is written according to the Standard Protocol Items: Recommendations for Interventional Trials (SPIRIT) checklist [see additional file 1].

2.2. Setting and participants

Patients on inhaler device treatment for Stage 2 to Stage 4 COPD according to the Global Initiative for Chronic Obstructive Lung Disease classification [3] are eligible for inclusion. Patients with Stage 1 COPD are ineligible, as their treatment does not require chronic inhalation therapy. Patients must be aged over 18, living at home and agree to 12 months of monthly follow-up.

The control and experimental hospital groups comprise patients hospitalized in care units with a clinical pharmaceutical activity in a single university hospital in France. Clinical pharmacists will identify eligible patients at admission by medication reconciliation and will contact their CP to ensure their participation throughout follow-up. The clinical pharmacist will also make recruitment and randomization once hospital discharge will be confirmed. Regarding the experimental community group, patients will be recruited directly by their usual CP.

For all three groups, patients will receive an information letter specifying the purpose and conduct of the study, as well as their right to refuse to participate in the study or leave at any time. Patient consent will be obtained before patients enter the study. One copy of the signed consent will be given to the patient, one will be retained by the investigator, and one will be retained by the sponsor.

The study visits, procedures and assessments are outlined in Tables 1 and 2.

2.3. Outcomes

2.3.1. Primary outcome

The primary outcome is the impact of the intervention on COPD exacerbation, assessed by the mean number of exacerbations per patient that occurred during the follow-up period. The coordinating pharmacist will phone the patient's GP or pulmonologist at 3, 6, 9 and 12 months to collect the data. Exacerbations are defined as periods of increased COPD symptoms (dyspnea, cough, sputum) requiring consultation with a GP, pulmonologist or hospitalization.

2.3.2. Secondary outcomes

Secondary outcomes include the mean number of: [1] hospitalizations, [2] emergency visits, [3] visits to the GP and [4] visits to the pulmonologist during the follow-up period. The coordinating pharmacist will phone the patient's GP or pulmonologist at 3, 6, 9 and 12 months to collect these data. Two other secondary outcomes relate to adherence to inhaler devices. First, [5] COPD medication compliance is measured by calculating the Medication Possession Ratio (MPR). This is the ratio of the actual number of doses/capsules taken compared with the theoretical number of doses/capsules taken [16]. Then, [6] correct use of inhalation devices is measured by observing the number of steps common to all inhalation devices performed (i.e., exhale slowly, inhale and then hold the breath for 5 s). Patient's usual CP collects both

Table 1
Visits, chronology and procedures for the **Control and Experimental Hospital groups** (CP: Community Pharmacist; HPC: Hospital Pharmaceutical Consultation).

EVENT	Pre- inclusion visit	Inclusion visit	Follow-up		Final visit
	Hospital stay	Hospital discharge	First dispensing by the CP (Dispensing 1)	Dispensing 2 to Dispensing 11	Dispensing 12
ENROLMENT					
General information	✖				
Presentation of the briefing note	✖				
Validation of inclusion and non-inclusion criteria	✖				
Collection of informed consent		✖			
Randomization		✖			
INTERVENTION					
HPC (hospital experimental group)		✖			
EVALUATION					
Collection of remaining doses/capsules				✖	✖
Ability score to inhalation device				✖	✖
Collection of exacerbations, consultations, hospitalizations, visits to the emergency service				✖* * Month 3,6,9	✖
BPCO VQ11 Questionnaire			✖	✖** **Month 6	✖

Table 2
Visits, chronology and procedures for the **Experimental Community group** (CP: Community Pharmacist; ICC Initial Community Pharmacy Consultation; FCC: Follow-up Community Pharmacy Consultations).

EVENT	Pre-inclusion visit	Inclusion visit	Follow-up	Final visit
	Dispensing prior to the inclusion visit	First dispensing by the CP (Dispensing 1)	Dispensing 2 to Dispensing 11	Dispensing 12
ENROLMENT				
General information	✖			
Presentation of the briefing note	✖			
Validation of inclusion and non-inclusion criteria	✖			
Collection of informed consent		✖		
INTERVENTION				
ICC		✖		
FCC			✖	✖
EVALUATION				
Collection of remaining doses/capsules			✖	✖
Ability score to inhalation device			✖	✖
Collection of exacerbations, consultations, hospitalizations, visits to the emergency			✖* * Month 3,6,9	✖
BPCO VQ11 Questionnaire		✖	✖** **Month 6	✖

adherence outcomes by using a specific data collection book, at each medication dispensing during 12 months. The final outcome is the impact on [7] patient quality of life (QoL) measured by the BPCO-VQ11 self-questionnaire, which is specific to COPD [17]. This outcome will be collected at inclusion by clinical pharmacist (control and experimental hospital group) or CP (experimental community group) and at 6 and 12 months by patient's CP for all three groups.

2.4. Intervention

The flow of the intervention is outlined in Fig. 2.

2.4.1. Experimental hospital group intervention

Patients in the experimental hospital group will receive a Hospital Pharmaceutical Consultation (HPC). At the end of hospitalization, the HPC will be carried out by a trained clinical hospital using a consultation guide. This guide was written especially for the study by two clinical pharmacists and validated by two pulmonologists from the hospital. During the HPC, lasting approximately 20 min, the patient will be informed about their disease and the treatment principles (i.e. how it works, adverse effects and how to use the inhaler with a demonstration with placebo inhalers). The aim of this consultation is to explain the importance of good adherence and answer any questions.

2.4.2. Experimental community group intervention

Patients in the community group will receive an Initial Community Pharmacy Consultation (ICC) and if required, up to twelve monthly Follow-up Community Pharmacy Consultations (FCCs) with their CP.

Before starting the study, the community experimental group CP's will receive a group training by the study coordinating pharmacist to form them on both types of consultations. At the same time, a consultation guide specially made for the study will be delivered to them. This guide is the same as this used for HPC. This prior step will allow to ensure uniformity of the consultation content.

a) Initial Community Pharmacy Consultation

The ICC will be performed at the inclusion visit and will contain the same information as the HPC. Demonstration placebo inhalers provided by the sponsoring hospital center are also used during this consultation.

b) Follow-up Community Pharmacy Consultations

At the 11 visits to the pharmacy following the ICC, the CP will check the patient's adherence and ability to use the devices. If any device misuse is identified, the pharmacist will give a FCC lasting approximately 10 min, consisting of a new demonstration of how to use the inhaler and a reminder of the information given at the ICC. In all cases, the pharmacist will answer any questions. The tools used are the same as those used for the ICC.

Patients in the control group will receive usual practice without ICC and FCCs. All patients recruited in the study will be followed up monthly by their CP.

2.5. Blinding

Because of the nature of the interventions, blinding will not be possible for either patients or care providers. Therefore, this study is fully open.

2.6. Sample size calculation

This study is composed of three groups allowing two comparisons: the control group will be compared with each experimental group. The expected number of exacerbation by patient was 0,61 a year [15]. We assume a minimum of 20 % of decrease with one of the two experimental arms and a standard deviation of 0,2. At 5 % risk level, and a statistical power of 90 %, we obtain 60 patients per group. Since the control group will be used for two comparisons, its size was increased by a 2 square root factor, i.e. 85 patients. Anticipating a 10 % loss to follow-up, a total of 226 patients will be enrolled in the study: 94 in the control group and 66 in each experimental group (hospital and community pharmacy) (Fig. 1).

The average number of hospitalized patients at our institution on treatment for COPD and eligible for management by a clinical pharmacist is estimated at 1200 per year. Recruitment was firstly planned for a period of 12 months but has been extended for 36 months due to the Sars-COV 2 health crisis.

2.7. Data collection and data management

Only those involved in the research project and identified will have access to the RedCap® data entry software. All data entered in the electronic case report form will be checked and formatted to prevent the entry of out of bounds data or outliers. In the event of an input change, traceability will be ensured. This software is hosted on our University Hospital's website and access to the application is protected by a login and password. All data collected via this software are backed up daily on a secure network.

All clinical data from the study will be stored on a specific server directory. Only network administrators and authorized persons in the Department of Biostatistics, Epidemiology, Public Health and Innovation in Methodology (BESPIM) will have access to this directory.

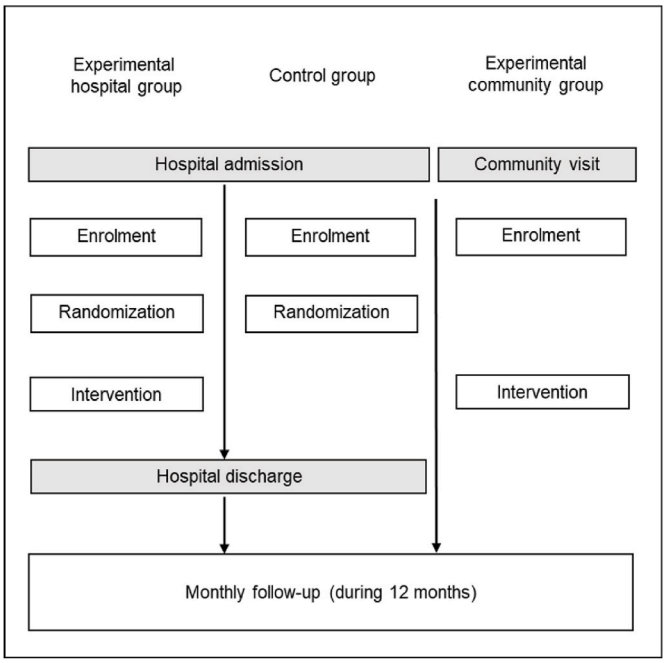

Fig. 1. BPCObs study flowchart.

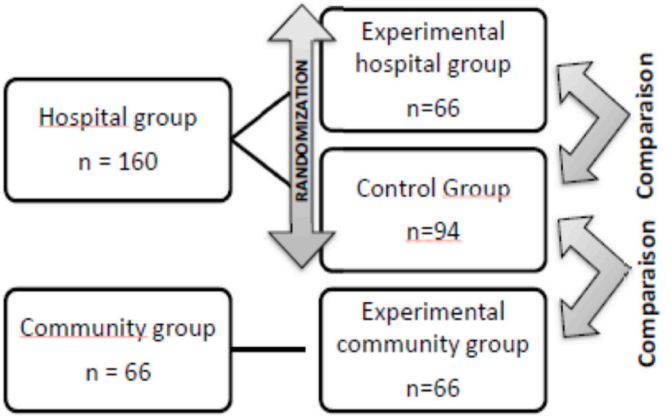

Fig. 2. BPCObs study design.

A clinical research associate delegated by the promoter will regularly monitor the study in accordance with the regulations: at the outset, during the study and at the end. The frequency of visits will depend on the inclusion rate. The monitoring will verify compliance with the protocol, verify informed consent, ensure quality control and alert any possible protocol deviations. All visits will be the subject of a written monitoring report (traceability of visits).

2.8. Data analysis

2.8.1. Description of the population and main parameters under study

An initial data analysis will be performed to describe the total population and by group. Statistical results will be presented as means ± standard deviations for quantitative variables with Gaussian distribution, and medians and interquartile ranges for other variables. For qualitative variables, the numbers and associated percentages will be presented.

2.9. Statistical analysis

The statistical analysis will be conducted by the BESPIM at Nîmes University Hospital using statistical analysis software (SAS Institute, Cary, NC, USA) version 9 or R 4.2.1. All analyses will be made according the intention-to-treat principle and all statistical tests will be conducted at 0.05 two-sided significance level.The number of exacerbations per patient will be compared for the three groups using a Kruskal-Wallis test to assess the overall differences at 12 months. Each experimental group will then be compared with the control group using a Mann-Whitney-Wilcoxon test.

A subgroup analysis is planned to estimate the number of exacerbations per patient compared via a Kruskal-Wallis test for all three groups. Finally, the rate of patients with at least one exacerbation will be compared for the three groups using a Chi-squared test.

The number of consultations, emergency room visits and hospitalizations will be estimated and compared for the three groups using a Kruskal-Wallis test. Each experimental group will be compared with the control group using a Wilcoxon-Mann-Whitney test.

The MPR and the number of completed successive steps common to all inhalation devices will be described per group at each month. Furthermore, the median MPR and the number of completed successive steps common to all inhalation devices estimated will be compared with a repeated measures model. Change in quality of life over time will be described via a graphical analysis. The average scores for the three groups will also be presented and compared using a repeated measures model.

2.10. Dissemination

The corresponding author will be responsible for the publication of the results of the study and any publications ancillary to the project. No intermediate publication of results will be made.

3. Discussion

We describe the protocol for a clinical trial designed to evaluate the impact of pharmaceutical consultations at the hospital or community pharmacy on the occurrence of COPD exacerbations in patients using inhaler devices. We also wanted to assess the potential contribution of follow-up of patients by their CP, particularly in terms of the proper use of inhalation devices. Indeed, monthly dispensing of treatments in pharmacies allows CP to provide short follow-up consultations directly at the counter. This repetition of pharmaceutical consultations, which is difficult to set up in the hospital, could also allow for a better education of the patient in the handling of his inhalation devices. To our knowledge, this is the first controlled trial which evaluate the effects of this kind of intervention in France. Due to the nature of the intervention, blinding will not be possible for patients or pharmacists. Therefore, this study is fully open. Two critical parameters will be taken into account to guarantee the study's feasibility: patient recruitment and availability for follow-up. Recruitment may be complicated by the fact that patients with COPD are older, frail patients, generally suffering from several comorbidities. Despite a high number of hospitalized COPD patients, the proportion of eligible subjects available for a 12-month follow-up upon their return home is limited. There are several reasons for this: the life expectancy of certain patients, the transfer to follow-up care and the intervention of nurses at home. These patients risk becoming lost to follow-up.

Concerning outcomes, there is a potential information bias due to the method used for collecting data on exacerbations, physician (GP and pulmonologist) visits, hospitalization and emergency visits. Indeed, the exhaustiveness of data collection by telephone call is limited as this depends on the physicians' availability.

To standardize the information provided during consultations, pharmacists were trained by the coordinating pharmacist using the guide developed in collaboration with the pharmacy and pulmonology teams. For patients recruited at hospital (control and experimental hospital groups), their CP will only monitor and collect data without any intervention. There is a risk of bias due to potential information given to the patient by the pharmacist during dispensing.

Finally, another potential limitation will be all pharmacists' adherence to follow-up. Indeed, the willingness of these pharmacists and the team's availability to collect data will have an impact on the quality and quantity of data collected. Throughout the study, the coordinating pharmacist will provide follow-up and telephone assistance as required. However, this study could be the first stage towards building a network of CP trained in clinical research. With this in mind, we would like to provide a model for future studies in which patients can be monitored over long periods with real-life data collected by their CP.

4. Trial status

This trial was registered on October 12th, 2018 in clinicaltrials.gov under the number NCT03704545. The study opened on 18th January 2019. After the initial inclusion period of 12 months, recruitment was extended for 36 months due to the health crisis related to the sars-COV-2 pandemic. Despite this additional time, the number of patients to be recruited could not be reached and the follow-up is currently performed on 174 patients recruited out of the 226 initially planned.

Ethics approval and consent to participate

This study will be performed in accordance with the Declaration of Helsinki and has been approved by the committee for the protection of persons, CPP Sud Méditerranée III; reference no. 2018.10.01 six_18.07.09.52123) and by the French National Agency for the Safety of Medicines (ANSM; reference no. 2018-A01699-46). Written informed consent will be sought from all patients recruited.

Consent for publication

Not applicable.

Availability of data and materials

All datasets generated from the study are available from the corresponding author.

Declaration of conflicting interests'

The authors declare that there is no conflict of interest.

Funding

This trial is supported by Nimes University Hospital internal funding through the NimAO 2017 call for tenders. The study protocol has undergone peer-review by the funding body. The funders have no role on this study in protocol drafting, data collection, data analysis and interpretation.

CRediT authorship contribution statement

Djamila Hachemi: Investigation, Writing – original draft. **Géraldine Leguelinel-Blache:** Supervision, Writing – review & editing. **Sophie Bouvet:** Formal analysis, Validation, Writing – original draft. **Clarisse Roux-Marson:** Project administration. **Nathalie Plouvier:** Conceptualization, Funding acquisition, Project administration. **Jean-Marie Kinowski:** Conceptualization, Funding acquisition, Project administration. **Christel Castelli:** Methodology, Writing – review & editing. **Florent Dubois:** Conceptualization, Funding acquisition, Methodology, Writing – review & editing.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Abbreviations

BESPIM	Department of Biostatistics, Epidemiology, Public Health and Innovation in Methodology
COPD	Chronic obstructive pulmonary disease
CP	Community Pharmacist
FCC	Follow-up Community Pharmacy Consultations
GP	General Practitioner
HPC	Hospital Pharmacy Consultation
ICC	Initial Community Pharmacy Consultations
SPIRIT	Standard Protocol Items: Recommendations for

Interventional Trials

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.conctc.2023.101249.

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