# Better outcomes for everybody evaluates the effectiveness and cost-effectiveness of a pharmacist-led intervention, delivered by community pharmacists in collaboration with physicians, in improving disease control, compared with usual care, in asthma and COPD patients during and after COVID-19

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*DOI:*
10.1097/MD9.0000000000000158

Medicine
Case Reports and Study Protocols

Study Protocol Clinical Trial

OPEN

# Better outcomes for everybody evaluates the effectiveness and cost-effectiveness of a pharmacist-led intervention, delivered by community pharmacists in collaboration with physicians, in improving disease control, compared with usual care, in asthma and COPD patients during and after COVID-19

## A protocol for a pragmatic, parallel randomised controlled trial

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**Abstract**

**Introduction:** In 2025, more than 400 million people will have asthma, and chronic obstructive pulmonary disease (COPD) will be the third leading cause of death by 2030. This trial, called better outcomes for everybody, will evaluate the effectiveness and cost-effectiveness of a pharmacist-led intervention delivered by community pharmacists in collaboration with physicians to asthma and COPD patients to improve disease control compared with usual care.

**Methods:** A pragmatic parallel 2-arm randomized controlled trial will be conducted in one Italian region (Sicily). A 2:1 randomization and sample size of 900 adult patients (450 with asthma, 450 with COPD) will be sufficient to detect a difference of 15% between the intervention and control groups using a dichotomized score (controlled versus non-controlled) of the Asthma Control Test (ACT) and the Clinical Chronic Obstructive Pulmonary Disease Questionnaire (CCQ) with a two-tails, 99% power and 5% significance level. A hundred pharmacists will recruit 9 consecutive patients each and administer either ACT or CCQ according to the patients' disease. Patients will be followed up for 12 months, and the pharmacists will meet their patients every three months. The control group will receive usual care, the intervention a bespoke, structured, and systematic consultation immediately after baseline and 6 months later. The primary outcomes are asthma and COPD control at baseline and 12 months. Secondary outcomes: risk of uncontrolled asthma and COPD, number of active ingredients, pharmaceutical care issues, adherence to medications, minimal clinically important differences in asthma and COPD, and a full health economic evaluation. The analysis will follow an intention-to-treat principle. Generalized estimating equations will be used to test the primary outcomes. Ethics approval was obtained.

*This work was supported by SOFAD srl, Via Comunità Economica Europea, 31, 95045 Misterbianco CT, (Italy), tel. +39 095 305811.*

*The sponsor (SOFAD) did not have any role in the study design and will not have any role in the collection, management, analysis, and interpretation of data, writing of the report, or the decision to submit the paper(s) for publication.*

*Consent was received for publication.*

*The authors have no conflicts of interest to disclose.*

*Data sharing not applicable to this article as no datasets were generated or analyzed during the present study.*

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*How to cite this article: Manfrin A, Jackson C, Campisi R, Oteri A, Copani A, Desideri E, Tsiachristas A, Candio P, Di Tomaso G, Vitale M, Crimi N. A protocol for better outcomes for everybody evaluates the effectiveness and cost-effectiveness of a pharmacist-led intervention, delivered by community pharmacists in collaboration with physicians, in improving disease control, compared with usual care, in asthma and COPD patients during and after COVID-19: a protocol for a pragmatic, parallel randomised controlled trial. Med Case Rep Study Protoc 2021;2:9(e0158).*

*Received: 23 July 2021 / Accepted: 2 August 2021*

*http://dx.doi.org/10.1097/MD9.0000000000000158*

**Discussion:** This is the first study conducted in Italy to assess the effectiveness and cost-effectiveness of a pharmacist-led intervention in asthma and COPD patients at the same time. This research could introduce a new model of care that can be adapted to other chronic conditions in primary care settings. The results will be disseminated to service users and their families via media, healthcare professionals via professional training and meetings, and researchers via conferences and publications.

**Trial registration:** ISRCTN, ID: 38734433 Registered on June 15, 2021

**Abbreviations:** ACT = asthma control test, CCQ = clinical COPD questionnaire, CG = control group, CI = chief investigator, COPD = chronic obstructive pulmonary disease, COVID-19 = coronavirus, CRC-MUR = chronic respiratory conditions medicines use review, EQ-5D-5L = EuroQol Five Dimensions Five Levels, GDPR = General Data Protection Regulation, GEE = Generalized Estimating Equation, HEREMOS = Health REmote MOnitoring System, I-MUR = Italian Medicines Use Review, MCID = minimal clinically important difference, MUR = Medicines Use Review, NNT = number needed to treat, QALY = Quality Adjusted Life Year, RCT = randomized controlled trial.

**Keywords:** asthma, community pharmacy, chronic obstructive pulmonary disease, cost-effectiveness, effectiveness, randomized controlled trial

## 1. Introduction

### 1.1. Background and rationale

The health burden of chronic respiratory disease suggests that in 2017, 544.9 million people worldwide had a chronic respiratory disease, representing an increase of 39.8% compared to 1990.[1] The most recent revised global estimate of asthma suggests that as many as 334 million people have asthma, the burden of disability is high.[2] With a projected surge in the world's urban population, it is estimated that by 2025, an additional 100 million people may develop asthma.[3] Hence, asthma is becoming one of the most prevalent chronic diseases worldwide. The prevalence of chronic obstructive pulmonary disease (COPD) varies according to country, age, and sex, and increases with age due to increased life expectancy.[4] Moreover, infections seem to play an essential role in COPD occurrence; repeated exacerbations, viral or bacterial, could also contribute to lung function decline.[5]

Since the onset of the coronavirus (COVID-19) pandemic in 2020, patients and primary care practitioners have canceled or postponed visits and appointments due to a shortage of healthcare resources and the risk of infection.[6] The full impact of COVID-19 on society and the economy is not fully understood. Still, it has been estimated that the gross domestic product (GDP) will decline by about 5% for each month of partial economic shutdown, which equates to 1.07 trillion dollars in the United States of America.[7] The COVID-19 outbreak poses a major threat to patients suffering from chronic lung conditions. Some researchers and institutions suggest that uncontrolled asthma could increase the risk of COVID-19,[8,9] and the same applies to COPD.[10]

Asthma and COPD erode the health and well-being of patients and harm families and societies.[3] The total cost of respiratory conditions accounts for more than €380 billion annually in Europe, which includes the costs of primary and hospital care (€55 billion), the cost of productivity loss due to sickness (€42 billion), and the monetized value of disability-adjusted life-years lost (€280 billion). Healthcare costs and lost productivity due to COPD are estimated at €48.4 billion. Those due to asthma amounted to €33.9 billion per year.[11] A link between disease control (asthma[12] and COPD[13]) and costs to the National Health Service and society has been demonstrated. The treatment of chronic disease includes the long-term use of medication,[14] which applies to asthma and COPD. The National Institute for Care and Clinical Excellence issued guidelines regarding medicine optimization, a person-centered approach to safe and effective medicine use, to ensure that people obtain the best possible outcomes from their medicines.[15,16]

Nevertheless, the use of medications without support is not sufficient for patients to achieve good clinical outcomes, quality of life, and cost containment.[11] Practitioners working in primary care are well placed to provide support for their patients, and community pharmacists are easily accessible even during the COVID-19 outbreak.[17] An activity often undertaken by community pharmacists to help people improve their use of medication is the medicine use review, which is considered a complex intervention according to Craig et al.[18] The evaluation of this intervention is far from easy. A recent systematic literature review, published in 2019, pointed out that an "*ideal*" method for evaluating complex interventions cannot be proposed. Instead, methods can be used according to the research questions that need to be addressed.[19] Besides objective outcome measures (e.g., blood tests, smoking status, date of death), patient-reported outcome measures in clinical practice have the potential to enhance care for people by identifying problems and improving patient–clinician communication.[20]

One of the earliest funded advanced pharmacy services in England was the Medicines Use Review (MUR) introduced in 2005, which up until now, showed little evidence to support either its effectiveness or cost-effectiveness.[21,22] In 2017, a systematic review and meta-analysis of randomized controlled trials (RCTs) of medication review suggested that an isolated medication review has minimal effect on clinical outcomes, no impact on the quality of life, and lack evidence of economic outcomes. However, studies have shown a decrease in the number of drug-related problems and dosage, more changes in medication, and a greater decrease or smaller increase in the number of medications used.[23] Newman et al[24] evaluated the impact of community pharmacist-led interventions in chronic disease management on clinical utilization and economic outcomes. Other positive results were identified in other reviews,[25–27] but more robust studies are needed to assess their economic outcomes.[28]

In 2012, the Italian Pharmacists' Federation founded a research project called Italian Medicines Use Review (I-MUR), aiming to develop, test, and evaluate the effectiveness and cost of the first community pharmacist-led intervention using asthma as a chronic condition. The Medical Research Council framework for complex intervention informed the development of I-MUR, which was conducted in different steps: 1) a literature review, 2) development and testing, 4) feedback from the main stakeholders, 5) evaluation, and 6) further analysis.[29–32]

The success of the I-MUR project raised the pharmacy profession's profile to a new challenge: the introduction and delivery of these services at the national level. The results of the project significantly impacted policy and practice, and the Italian government allocated funds for such services. Following this experience, SOFAD srl (the sponsor), part of the FARVIMA group, a privately owned company and its stakeholders, decided to provide funds to explore the possibility of developing a pharmacist-led intervention that can be used for asthma and COPD patients as well.

A Belgian study suggested that pharmacists could improve outcomes in patients with COPD.[26] Hesso et al[33] assessed the impact of pharmacists on COPD management, looking at inhalation technique and medication adherence; the results demonstrated that these activities were cost-effective. In India, a study evaluated the direct impact of clinical pharmacist interventions on medicine costs in patients suffering from COPD. The study was an RCT conducted for 24 months; the results showed a reduction of 30.6% in the cost of medicines.[34] The United States is suggesting an emerging role for pharmacists in managing patients with COPD.[35] Pharmacists' roles are evolving, and they seem to work increasingly more often as part of multidisciplinary care teams.[35]

Asthma control is important because it improves the quality of sleep and life in general, reduces days lost at work or school, enhances productivity, reduces the use of rescue medications, and reduces the healthcare system's economic burden (e.g., the number of doctors' appointments), and society.[36] Likewise, COPD control improves quality of life, reduces symptoms, mental and physical dysfunction, and mortality rate.[37,38] In this study, the primary outcome was patient-reported outcome measure. Therefore, the study protocol was designed according to the Standard Protocol Items: Recommendations for Interventional Trials (SPIRIT-PRO) extension [39] and mapped against the SPIRIT checklist (Appendix 1). The comparator is usual care, defined as pharmacists' safe supply of medicines and medication-taking advice to the patient.

## 2. Objectives

### 2.1. Key research questions

The key research questions of this study are:

Is the pharmacist-led intervention called chronic respiratory conditions medicines use review (CRC-MUR) provided by community pharmacists in collaboration with physicians.

Effective in

a) Improving asthma or COPD control as assessed by the Asthma Control Test (ACT) and Clinical COPD Questionnaire (CCQ) scores?
b) Reducing the risk of having asthma and COPD uncontrolled?
c) Optimizing the number of active ingredients used by asthma and COPD patients?
d) Identifying and resolving pharmaceutical care issues?
e) Improving patients' adherence to asthma or COPD medications?
f) Achieving the minimal clinically important differences (MCID) in asthma and COPD control?

Cost-effective for

a) The healthcare system and society (compared to usual care) in terms of cost per quality-adjusted life-year gained (QALY) using the EuroQol five dimensions five levels (EQ-5D-5L).

### 2.2. Trial design

It is a pragmatic, parallel randomized controlled superiority trial that aims to mimic routine practice as closely as possible, except that patients will be randomly allocated to the intervention or control group.[40] The patient follow-up period was 12 months. The study should begin in January 2022 (COVID-19 permitting).

## 3. Methods

### 3.1. Study setting

The study will be conducted in community pharmacies in southern Italy, in one region only, Sicily, which has over 5 million inhabitants.

### 3.2. Eligibility criteria

Participants will be selected according to the following eligibility criteria:

Pharmacies must have

- a private area for private consultation with patients;
- and/or telephone, smartphone, tablet, or other devices allowing remote consultation with their patients if required due to COVID-19 restrictions;
- an internet connection;

Pharmacists must

- be qualified and registered with the Italian Pharmacy Board practicing in Italy;
- have experiences in providing advice to patients;
- have already provided one or more services, such as blood pressure monitoring, smoking cessation, cholesterol monitoring, signposting, and food intolerance testing (this will be verified during the recruitment process asking for a self-declaration).
- be able to attend the full training session(s).

Pharmacies must be excluded if they

- have no internet access;
- no consultation room or no telephone, smartphone, tablet, or other devices allowing remote consultation with their patients if required due to COVID-19 restrictions;
- are currently involved in any other clinical pharmacy research project.

Patients

Patients must:

- be at least 18 years of age;
- have been diagnosed with either asthma or COPD for at least six months before enrollment in the study.
- have prescription(s) for asthma/COPD medications with R03 as Anatomical, Therapeutic Chemical Classification code, or drugs for obstructive airway disease.

Patients must be excluded if they

- have a terminal illness (defined as an advanced stage of a disease with an unfavorable prognosis and no known cure) as identified by the pharmacists through prescription coding.
- are currently enrolled in another clinical trial;
- do not self-administer their medications (e.g. inhaler);
- are not able to communicate well in Italian, both written and spoken.

To minimize diagnostic inaccuracy, asthma and COPD diagnosis will be reviewed in every patient at baseline, before enrollment, following the global initiative for asthma (40) and global initiative for chronic obstructive lung disease (GOLD) (41) strategies.

### 3.3. Intervention

***3.3.1. Description of the intervention.*** The name of the pharmacist-led intervention is CRC-MUR. Community pharmacists will deliver interventions in the primary care setting. The delivery format is verbal (face-to-face or remotely using phone or video facilities). The development of the intervention was informed by its affordability (cost associated with the design and delivery), practicability (pharmacists/patients), effectiveness and cost-effectiveness, acceptability (patients/pharmacists/physicians), side effects/safety (patients), consistency, and replicability. CRC-MUR is a theoretically informed pharmacist-led intervention.[41–44] It consists of a bespoke, systematic, structured face-to-face or remote consultation (due to COVID-19) with a patient, covering asthma/COPD symptoms, health and social care received, medicines used, attitude towards medicines, adherence to medication, recording pharmacist-identified pharmaceutical care issues. If required, pharmacists advise patients, including healthy living advice; they advise physicians on patients' conditions using a standard template. Pharmacists will be trained to advise patients and send recommendations to their general practitioners and/or hospital consultants during the training session before the beginning of the study. The CRC-MUR intervention was mapped against the template for intervention description and replication.[45] Following each consultation, pharmacists will be required to enter the information on a web-based platform, maintaining patient anonymity. The details of the data collection are provided in Table 1 and Figure 1.

***3.3.2. Control group.*** Patients in the control group will receive usual care.

### 3.4. Criteria for discontinuing or modifying allocated interventions

1) Participant withdraws consent
2) The trial is discontinued
3) Participant requires hospitalization

The reasons for discontinuation will be documented. Participants will be invited to participate in an outcome-related assessment to determine the effectiveness of the intervention.

### 3.5. Strategies for monitoring and improving protocol adherence

Measures suggested to maintain and improve adherence to the trial protocol include telephone calls, text reminders, social support provided by community pharmacists and physicians to their patients, and educating patients on the management of the disease.

Community pharmacists will have to

- create a welcoming, non-judgmental, and accepting environment;
- establish an effective tracking system that will be provided by the online web platform used for data entry.
- educate patients about their role as research participants;
- establish a routine while maintaining flexibility;
- provide incentives for participation, such as transportation, parking spaces, home visits, and videoconferences.

### 3.6. Relevant concomitant care and interventions that are permitted or prohibited during the trial

Patients were hospitalized, but overall, no other intervention restriction was imposed in this study.

**Table 1**

**Schedule of enrollment, intervention and assessments.**

| | Study period | | | | | |
|---|---|---|---|---|---|---|
| | **Enrollment** | **Allocation** | **Post-allocation** | | | **Closeout** |
| Timepoint | -T0 | T0 | T3 | T6 | T9 | T12 |
| Enrollment | | | | | | |
| Eligibility screen for pharmacists | x | | | | | |
| Informed consent for pharmacists | x | | | | | |
| Eligibility screen for patients | x | | | | | |
| Informed consent for patients | x | | | | | |
| List of other procedures | x | | | | | |
| Patients' randomization | | x | | | | |
| Intervention: it will be delivered twice to group A, after baseline and at 6 months | | | | | | |
| Intervention Group A | | x | | x | | |
| Control Group B | | | | | | |
| Assessments | | | | | | |
| Baseline characteristics | | x | | | | |
| ACT and CCQ scores | | x | x | x | x | x |
| Number of active ingredients | | x | x | x | x | x |
| Pharmaceutical care issues | | x | x | x | x | x |
| Adherence to medications | | x | x | x | x | x |
| EQ-5D-5L | | x | x | x | x | x |
| Healthcare resource utilization | | x | x | x | x | x |

ACT = Asthma Control Test, CCQ = Clinical COPD Questionnaire, EQ-5D-5L = EuroQol five dimensions five levels.

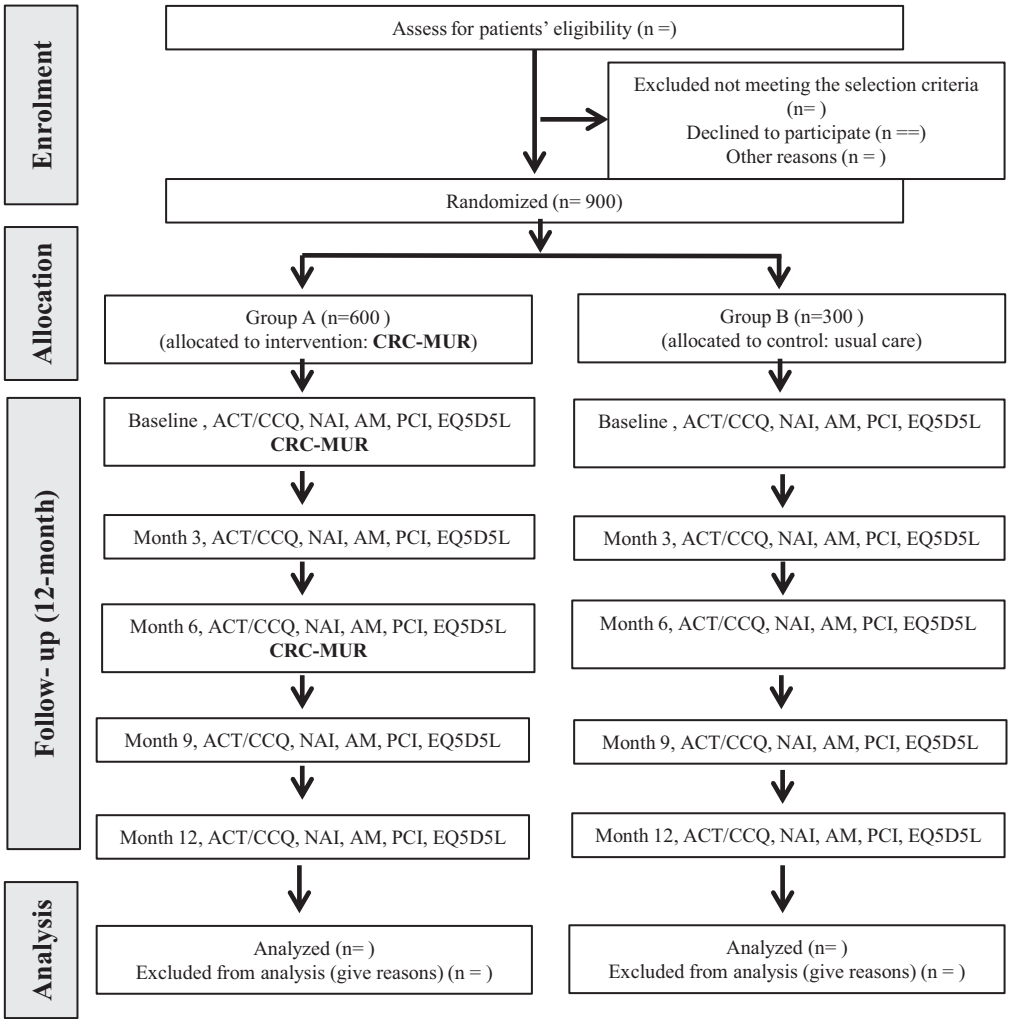


**Figure 1.** CONSORT flowchart of the study design. ACT = asthma control test, AM = adherence to medications, CCQ = clinical COPD questionnaire, EQ5D5L = EuroQol, NAI = number of active ingredients, PCI = pharmaceutical care issue.

### *3.7. Outcomes*

***3.7.1. Primary outcomes: Asthma and COPD control.*** The primary outcomes are asthma and COPD control at baseline and 12 months (according to the patients' disease), assessed at 3-months intervals, using the ACT score and the CCQ score.

ACT score was defined by international guidelines as

- ACT≤14=not controlled;
- 15≤ACT≤19=partially controlled;
- ACT≥20 controlled [154].

The MCID is defined as an increase of ≥ 3-point of the ACT score.

The CCQ was developed by van der Molen et al[46], and it assesses COPD control according to a scale-out of ten.

The CCQ scores are defined as

- CCQ<1 = Acceptable;
- 1≤CCQ<2 = Acceptable for moderate disease (controlled);
- 2≤CCQ≤3 = Instable-severe limited;
- CCQ>3 = Very instable-very severe limited.

The MCID is defined as a reduction of ≥0.4 points of the CCQ score. Furthermore, the CCQ assesses three main domains:

Symptoms = (Item 1 + 2 + 5 + 6)/4, Functional = (Item 7 + 8 + 9 + 10)/4, Mental = (Item 3 + 4)/2.[38]

***3.7.2. Justification for the use of ACT and CCQ.*** The ACT was previously used in Italy in a study conducted by the Italian Society of General Medicine (Societá Italiana di Medicina Generale) and in the I-MUR study. The International Primary Care Respiratory Group proposed creating a user's guide for primary healthcare practitioners to assess "wellness" in COPD patients in an everyday clinical setting. They ranked the CCQ as the most recommended among the eight questionnaires examined in their study.[47] Moreover, the CCQ was used in another study by a member of our research team.[48]

#### *3.7.3. Secondary outcomes.*

1. Reduction of the risk of having asthma and COPD uncontrolled, assessed using the ACT and CCQ scores assessed at baseline and 3-month intervals, as reported by patients.
2. The number of active ingredients used by patients at baseline and 12 months assessed at 3-month intervals, as reported by patients.

3. Patients' self-reported adherence to asthma/COPD medications at baseline and 12 months assessed at 3-month intervals using the questions used in the I-MUR study.
4. Pharmaceutical care issues at baseline and 12 months assessed at 3-month intervals using the questions used in the I-MUR study.
5. The MCID in ACT and CCQ scores at baseline and 12 months assessed at 3-month intervals, as reported by the patients.
6. Cost-effectiveness of CRC-MUR asthma/COPD service compared with usual care, measured in terms of cost per QALY as a measure of disease burden, including both the quality and the quantity of life gained, at the 12-month follow-up.

***3.7.4. EQ-5D-5L.*** The EQ-5D-5L questionnaire will be used to measure health-related quality of life at baseline and at each subsequent 3-month data collection time point. The EQ-5D-5L was selected for use in calculating QALYs using Italian utility tariffs. It is more "sensitive" than the 3-level version, including dimensions of anxiety and depression and daily activities that may have been impacted by the COVID-19 pandemic. Individual patient data on visits to the GP and outpatient departments, attendance to the Accidents and Emergency department, hospital admissions, and medication will be retrieved from electronic patient records for the 12-month follow-up. The Italian unit costs of these services are used to monetize resource use into costs. Trial management will provide intervention costs allocated to each patient in the intervention arm using a top-down costing approach.

### *3.8. Participant timeline*

Pharmacists will encounter their patients at baseline (T0) and every three months. Table 1 was designed according to the SPIRIT 2013;[49] summarizes the enrollment, intervention, and assessment schedule.

### *3.9. Sample size*

The power calculation was conducted using the z-test family, calculating the proportion of the difference between two independent groups with two tails using the dichotomized scores of ACT and CCQ: controlled (ACT≥20; CCQ<2) versus non-controlled (ACT<20; CCQ≥2). A 2:1 randomization and sample size of 887 patients (591 in the IG and 296 in the control group [CG]) will be enough to detect a difference of 15% between the intervention and control groups using a dichotomized score (controlled vs. non-controlled) of the ACT/CCQ, a 99% power and 5% significance level. The 15% difference represents the difference between the percentage of controlled (65%) and non-controlled (50%) patients at the end of the study. The power calculation was conducted using G*Power version 3.1.9.4; the results were assessed and confirmed by a senior statistician working at the UCLan's Clinical Trial Unit.

***3.9.1. Recruitment.*** We decided to round up the number for simplicity; therefore, we aim to recruit 100 pharmacists and 900 consecutive patients (asthma = 450; COPD = 450). Our recruitment strategy will focus on increasing potential participants' awareness of the health problem being studied, its potential impact on their health, and engagement in the learning process.

***3.9.2. Pharmacist patient ratio.*** The pharmacist-patient ratio was 1:9, meaning that each pharmacist will recruit and follow-up nine patients.

### *3.10. Randomization, sequence generation, allocation and blinding*

***3.10.1. Randomization.*** An academic from the UCLan expert in the use of statistics will oversee the randomization process. The randomization procedure was simplified as follows. Thus, the 2:1 allocation was rounded up to 600 in the intervention group (instead of 591) and 300 in the control group (instead of 296) (Fig. 1). The 2:1 randomization was requested by the lead clinician, who reviewed the results of the I-MUR study and did not want to prevent patients from getting the potential benefits from the intervention.

***3.10.2. Unit of randomization and intervention.*** The patient is the unit of randomization and intervention.

***3.10.3. Block size.*** The choice of using the block equal to nine will be adopted because large blocks reduce predictability but will not restrict randomization as closely as small blocks.

***3.10.4. Sequence generation.*** Sequence generation will be conducted using block permutation without stratification, followed by randomization, owing to the expected large sample size (n = 900), as suggested by the senior statistician of the Lancashire Clinical Trial Unit (LCTU). The procedure will be performed by a member of the research team at UCLan using the sealed envelope online system.

***3.10.5. Allocation concealment.*** Allocation concealment will be performed by a member of the research team using the sealed-envelope online system, which generates an allocation schedule. In this study, two lists will be produced. The first list will be given to the pharmacist before patient recruitment, where a unique three-digit code (e.g., relative risk 3, TS7, VS5) will be assigned to each participant. A second list will be released at the end of the recruitment process and will allocate each three-digit code (participant) to either IG or CG. This approach will be adopted because it will not be possible to produce 900 sealed envelopes and circulate them on the starting date (before baseline) while maintaining the cost within the allocated budget.

***3.10.6. Blinding.*** In our study, blinding will not be possible either at the pharmacist or patient level because the nature of the intervention requires their full knowledge. However, the chief investigator (CI), as an assessor of the main outcome measures, asthma and COPD control, will remain blind. As group allocation is intrinsic to the data gathered for each patient, to maintain blindness, the CI will access the data only after all patients have been followed up at three months (see Table 1). Friedman et al[50] suggested that an unblinded trial might not be simple, but it more accurately reflects clinical practice.

### *3.11. Data collection*

Data will be collected by the pharmacists at baseline and 3-month intervals using a bespoke web platform (FarmPro) already in use in many pharmacies in Sicily following the procedure illustrated in Table 1 and Figure 1. All questionnaires will be available in two languages: Italian and English. The CI is proficient in both languages and has translated the CRC-MUR from English to Italian. Another member of the research team, proficient in both languages, has back-translated CRC-MUR into English, and the two English versions were compared to avoid discrepancies. ACT, CCQ, and EQ-5D-5L are also available in English and Italian. A small test will be conducted during the summer of 2020

to verify that the platform will respond to all requirements. The platform will allow the use of different digital devices, such as personal computers,, laptops, tablets, and smartphones. The platform also complies with the General Data Protection Regulation (GDPR) procedure. Primary and secondary outcomes were collected according to the timeline of the study. The length of the patient consultation was expected to be between 30 and 45 minutes. A small number (subgroup) of COPD patients (n = 45), 30 in the IG and 15 in the CG, will have their vital signs monitored using a wearable device named Health REmote MOnitoring System (HEREMOS). The vital signs monitored will be heart rate, respiratory rate, and saturation of peripheral oxygen. Additionally, body temperature, blood pressure, heart rate variability, step count, and pain may be included. Furthermore, we will capture pollen concentration, air pollution (108), particulate matter 10 micrometers or less in diameter, and sulfur dioxide. Monitoring will mostly take place at the patients' home premises and during patient consultation when necessary.

### 3.12. Data management

Data will be managed following the procedure used in a previous study.[29] Input data will be saved and stored on a password-protected system. Only individuals authorized by the CI will be allowed to access the data. Paper data, such as pharmacists' informed consent, will be kept in a locked cabinet by the research team. Patients' informed consent will be kept in a locked cabinet by the pharmacists.

### 3.13. Statistical methods

The primary analysis will be the intention-to-treat, including all randomized participants in the group where they were randomly assigned, regardless of their adherence to the protocol or their withdrawal.

Missing data: The previous experience of the CI suggests that data will be missing at random (MAR); therefore, multiple imputations will be applied.

Each variable will be analyzed using the Shapiro-Wills and Kolmogorov-Smirnov test to check for normality.

Primary outcomes: The primary outcome measures will be dichotomized, controlled (ACT≥20; CCQ<2) and not controlled (ACT<20; CCQ≥2) and analyzed using generalized estimating equations (GEEs) at 12 months. The GEE model will be used to calculate the odds ratio and 95% confidence interval (CI) without adjustment. It will then be adjusted using the ACT/CCQ values obtained at baseline, sex, and age. The relative risk, relative risk reduction, absolute risk reduction, and number needed to treat will be calculated. The proportion of controlled and non-controlled patients will be presented using descriptive statistics at each time point.

Secondary outcomes: Survival analysis will be conducted using the Kaplan-Meier curve, with the log-rank (Mantel-Cox) option, aiming to estimate the survival curve, using the ACT/CCQ control as the event of interest. The risk of uncontrolled disease will be estimated using Cox regression. The mean/median number of active ingredients and PCI will be assessed at each time point using either the unpaired Student *t*-test or Mann Whitney *U* test; GEE at 12 months. Adherence to medications and MCID will be assessed, dichotomizing the variable (adherent and non-adherent; MCID yes or no); the analysis will be conducted using Pearson chi-square or Fisher exact test at each time point and GEEs at 12 months.

An economic evaluation will be undertaken to assess the cost-effectiveness of CRC-MUR at 12 months. Cost effectiveness will be expressed in terms of incremental cost per QALY gained. Bootstrapping will be performed to address uncertainty in the estimates. Uncertainty will be displayed in cost-effectiveness planes and cost-effectiveness acceptability curves.

Method for additional analysis: A small cohort of COPD patients (30 in the IG and 15 in the CG) will have their vital parameters monitored through the smart sensors of the HEREMOS platform. The data collected: Saturation of Peripheral Oxygen, respiratory rate, heart rate, blood pressure, body temperature, heart rate variability, step count, and pain will be analyzed with the help of machine learning technology. Additionally, the patients' data collected through the study questionnaires will be included in the analysis. Different classification techniques, such as support vector machines and random forests, will be considered to evaluate the level of disease control.

Statistical significance was set at $P < 0.05$. In addition, the effect size between the two groups and the 95% confidence interval will be reported (when appropriate). Data analysis will be performed using the SPSS 27 (IBM).

### 3.14. Data monitoring

This trial was designed to minimize the risk, as demonstrated in a previous trial.[29] Therefore, no formal committee has been organized, and no interim analysis of the impact of the intervention has been planned. The coordinating center for the study in Italy is the Catania Policlinico (Hospital), supported by UCLan.

### 3.15. Risk and safety issues

During this study, there will be no risks for the patients. Patients receiving the CRC-MUR service will be at no greater risk than those receiving usual care. Pharmacists will not dispense or administer any medications based on the ACT, CCQ, EQ-5D-5L scores, or CRC-MUR results. Pharmacists will not be involved in the interpretation of diagnostic tests or their results.

### 3.16. Harm

We do not expect adverse events or other unintended effects. All information regarding the trial will be included in the pharmacists' and patient information sheets. Patients using the remote monitoring system HEREMOS will not be exposed to any harm. The HEREMOS sensor system is intended for the sole purpose of monitoring vital signs. This system is not intended for use in cardiac pacemakers. In addition, the system is not intended for use during an MRI scan or when using an internal or external defibrillator. Strong electromagnetic fields can damage the system and make it dangerous.

### 3.17. Auditing

No audit has been planned at this time.

## 4. Research and dissemination

### 4.1. Research ethics approval

Ethics approval was obtained from the Catania Ethics Committee (Italy) (ref. 47/2021/PO; February 22nd, 2021), and the

University of Central Lancashire (UK) (ref HEALTH 0163; March 29th, 2021).

### 4.2. Protocol amendments

We are not expecting to make any changes to the eligibility criteria, outcomes, and analyses during our study.

### 4.3. Consent, invitation and confidentiality

All documentation related to information and consent for pharmacists and patients has been enclosed in the protocol and approved by the ethics committees in Italy and the UK. The procedures followed for consent and confidentiality are described in the following paragraphs.

***4.3.1. Informed consent.*** The chief investigator (CI; AM) obtained consent from the participating pharmacists.

Participating pharmacists will recruit their patients and obtain consent from them.

***4.3.2. Who will write to the pharmacists?.*** An invitation letter and a summary of the study will be prepared by the CI and sent to SOFAD and Federfarma Sicilia, which will distribute the letter with information regarding the study to all community pharmacists in all the identified locations inviting pharmacists to participate in the study.

***4.3.3. How will pharmacists consent?.*** Pharmacists who express interest in participating will be invited to attend presentations. At presentation, which will take place between January and February 2022 (COVID permitting), the CI will outline the study protocol and enrollment criteria. Participants received a detailed participant information sheet. The president of SOFAD and Federfarma Sicilia will collate the names of pharmacists who will express interest over the next few weeks. The first 100 pharmacists who met the inclusion criteria will be selected for inclusion in the study.

***4.3.4. Patients' recruitment and informed consent.*** After assessing patients' eligibility for the study, pharmacists will provide an information letter and consent form to each patient, who will get a week to consider their participation. The pharmacist will retain all signed consent forms in the pharmacy in a locked cabinet.

***4.3.5. Confidentiality.*** Written informed consent will be obtained from all participants included in the study. All data will be handled following the requirements of the Data Protection Act (2018) and/or the GDPR 2016, according to European Union law. Therefore, the data will be anonymized and stripped of any identifiable reference to the participants.

***4.3.6. Declaration of interest.*** None

***4.3.7. Dissemination policy.*** The dissemination of the study will begin immediately after the publication of the protocol. Then, it will continue throughout the study using social media posts, patient events, the third sector, and public engagement events. The results of this trial will be presented at national and international conferences. They will be submitted as scientific manuscripts to peer-reviewed journals, and subsequently published in non-peer-reviewed publications in Italian and maybe other languages. The trial results aim to inform policymakers, the Italian Ministry of Health, the Italian National Health Services, and all other stakeholders that might benefit from the results. The results will be disseminated to service users and their families via media, healthcare professionals via professional training and meetings, and to researchers via conferences and publications.

***4.3.8. Ancillary and post-trial care.*** We are not envisaging the need for the provision of post-trial care. Nevertheless, all participants will be provided with an emergency contact number to reach the study investigators so that they can receive the necessary support when they have any questions or problems.

***4.3.9. Plans, if any, for granting public access to the full protocol, participant-level data set, and statistical code.*** The research team aims to publish the research protocol before starting the trial in a gold open-access journal. Therefore, everyone will have free access to trial protocols. Once the study is completed and the main paper submitted for publication, the data set will be available at the University of Central Lancashire's repository, and all data will be anonymized in line with GDPR requirements.

## 5. Patient and public involvement

The research team developed a protocol during the COVID-19 outbreak (February-July 2020). Hence, it was not possible to organize meetings with patients to obtain their views and opinions. Therefore, the research team contacted Active Citizenship (Cittadinanza Attiva), an Italian national body looking after patients' health and safety. They assessed the research protocol considering its clarity and patients' overall burden during the study, providing positive feedback, and praising the initiative.

## 6. Discussion

Many studies conducted in community-pharmacy settings have assessed the effectiveness and cost-effectiveness of pharmacist-led interventions. However, there is a lack of consistency in the intervention designs and assessments. In Italy, the only study that used a randomized controlled trial design to assess the effectiveness and cost-effectiveness of a pharmacist-led intervention in a chronic condition. To the best of our knowledge, this is the first study conducted in Italy, aiming to assess pharmacists' contribution to improving disease control in two very common chronic lung conditions: asthma and COPD. It is one of the largest studies conducted in one region, and it introduces a new systematic and quantitative bespoke research instrument, CRC-MUR. In Italy, it appears to be the first RCT protocol drafted according to the SPIRIT-PRO extension guidelines,[39] assessing the effectiveness and cost-effectiveness of a pharmacist-led intervention delivered by community pharmacists during and after the COVID-19 outbreak. The effect of COVID will be long-lasting and will impact the healthcare system and the availability of patients' appointments with their general practitioners (GPs). Thus, this intervention aims to reduce GPs' workloads, allowing them to concentrate on more serious conditions, such as cancer. Furthermore, this study will test the intervention and evaluate a model that can be adapted to other chronic conditions if successful.

The study included only adults and patients who will be followed up for 12 months. Given the study's size, we anticipate that problems may arise, for example, due to COVID-19, with the pharmacist and patient recruitment, resulting in the loss of

power. However, we considered this in our power calculation by evaluating two possible options based on the actual results of our previous studies. A potential/expected drop-out rate has already been factored into the power calculation. Assuming that we aim to recruit 900 consecutive patients, we expect a dropout rate of 25% (n=225 patients) in an unlikely scenario. The number of participants will then be reduced to 675, but the study will still retain 96% of the power. In the worst-case scenario, if the number of participants dropped to 413, the study retained 90% of the power.

## 7. Conclusions

This is the first study conducted in Italy to assess the effectiveness and cost-effectiveness of a pharmacist-led intervention in asthma and COPD patients at the same time. The potential benefits of this study are multifold. Thus, the intervention could 1) improve patients' quality of life, 2) reduce the cost to the national healthcare service and society, 3) upskill community pharmacists, 4) introduce a new remuneration scheme for such services, 4) contribute to better integration of community pharmacies in the primary healthcare team, and 5) free up physicians' time to allow them to concentrate on other difficult conditions. This research could introduce a new model of care that can be adapted to other chronic conditions in primary care settings.

## 8. Protocol version

The study protocol version was 1.1.1; 30.09.2020. Important amendments to the study protocol or other changes will be periodically updated at the trial registration site.

## Acknowledgments

The authors would like to acknowledge the ongoing support provided by Dr Gaetano Cardiel, President of SOFAD SRL, Dr Gioacchino Nicolosi, President of Federfarma Sicilia, the Sicily region, and Dr Antonio Gaudioso, Secretary-General of Active Citizenship. The research team is deeply thankful to Dr. Izabella Penier for editing the manuscript and Dr. Miland Joshi, a senior research fellow in statistics from the Lancashire Clinical Trial Unit, for checking the power calculation and sample size.

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