Tailored Intervention at home for patients with moderate-to-severe COPD and Co-morbidities by Pharmacists and Consultant Physicians

TICC-PCP

STATISTICAL ANALYSIS PLAN (SAP)

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1. INTRODUCTION

1.1. STUDY BACKGROUND

People with moderate-to-severe chronic obstructive pulmonary disease (COPD) are so breathless that they need to stop for breath when walking at their own pace. At home, when breathing gets worse, for example due to infection, hospitalisation often results. Frequent adjustment of medicines for COPD and other medical conditions improves breathing and reduces hospitalisations. However, home-based check-ups for breathing and medicines are uncommon. Our preliminary research has shown that pharmacist home-visits, undertaken with the support of the patient's GP and chest physician, can help ensure that patients are on the right medication and through so doing reduce the risk of a flare-up of COPD and associated hospital admission.

In Scotland, Chronic Obstructive Pulmonary Disease (COPD) exacerbations are the most common cause of emergency hospital attendance for respiratory problems in adults. COPD prevalence and hospitalisations are increasing over time (29% increase expected by 2034 accentuated by rising numbers of older people), impacting negatively on quality of life, mortality and health care costs. Pharmacological treatment optimisation is a key intervention in COPD, including rapid treatment of exacerbations and individualised management of co-morbidities to improve symptoms and reduce exacerbations.

This small-scale pilot study wants to build on preliminary research to see if pharmacist independent prescriber home-visits in this population would be accepted by patients in Glasgow and Edinburgh. If the pilot suggests the intervention and trial procedures all work together in miniature, with favourable patient and stakeholder views, this will allow us to proceed to a full-scale definitive randomised controlled trial (RCT) of our complex intervention.

1.2. STUDY OBJECTIVES

The aim of this study is to generate sufficient information on recruitment, retention, utility of study measures, intervention implementation, fidelity and delivery, randomisation, sample size, resource use, outcomes and perspectives of patients and clinicians, to determine whether we should proceed to a definitive RCT.

Research questions:

1. What are the recruitment and retention rates across sites and between recruitment methods?
2. Are randomisation and data collection procedures suitable?
3. What is the extent of adherence with the delivery of components of the intervention?
4. What are patient/professional perceptions of the intervention and acceptability of trial procedures?
5. What do patients and professionals view as the likely barriers and facilitators to future implementation of the intervention as a form of routine service delivery?

6. What are the sample sizes needed for planned outcomes (exacerbations, A&E and hospitalisations for respiratory causes), and estimates of the outcome variability?
7. Can all relevant resource use data and preference based quality of life data be identified and measured for the purposes of conducting a future full economic evaluation?

1.3. Study Design

Pilot parallel group RCT with embedded qualitative and economic evaluation to test recruitment, retention, acceptability, trial procedures and potential future implementability.

1.4. Randomisation

Patients were randomised at the end of their baseline home visit in a 1:1 ratio to either the intervention group (pharmacist home visits), or to usual care via a central interactive voice response system hosted by the Robertson Centre for Biostatistics. Randomised permuted blocks were used stratified by recruitment centre and number of respiratory hospitalisations in the previous year (0 vs. 1 or more). Patients and study staff were aware of the randomisation decision; however, the statistical team remain blind to group allocation until after the database lock.

1.5. Sample Size and Power

Since this is a pilot study, no formal sample size calculation has been provided. The main aim is the feasibility of trial procedures and providing information required for a subsequent larger scale trial. The aim was to invite 160 patients in order to recruit 100 (50 patients from respiratory clinics serving patients from East, West and Mid Lothian, and 50 from Glasgow's New Victoria or Queen Elizabeth University Hospital), based on an earlier feasibility study with a recruitment rate of ~60%.

If 100 agreed, then the recruitment rate could be estimated as 62.5% (95% confidence interval: 55-70%). The 1-year mortality rate in the previous feasibility study was 4.6%. Therefore, it was anticipated that 11-12 out of 100 recruited patients would die during the planned 30 months follow-up. A conservative retention rate of 80% during the study was assumed, given that pharmacists and researchers conduct home visits, and the information available on additional losses due to mortality from previous work, it was expected approximately 73 patients with follow up data would remain to inform a sample size calculation for a full-scale RCT.

1.6. Interim Analysis and Stopping Rules

No formal interim analysis will be performed.

1.7. STATISTICAL ANALYSIS PLAN (SAP)

1.7.1. SAP OBJECTIVES

The objective of this SAP is to describe the analyses to be carried out for the TICC-PCP final analysis.

This SAP does not cover any statistical issues for any process or economic evaluation.

The current version of the protocol at the time of writing is the protocol dated 07/09/2020. Future amendments to the protocol will be reviewed for their impact on this SAP, which will be updated only if necessary. This will be documented as part of the Robertson Centre Impact Assessment process.

1.7.2. GENERAL PRINCIPLES

Data will be summarised for all participants and by randomised treatment group where appropriate. Categorical variables will be summarised with the number of observations and missing values, and number and percentage of participants falling into each category. Continuous variables will be summarised using the number of observations and number missing, mean, standard deviation (SD), median, 25th and 75th quartiles (Q1 and Q3 respectively), minimum and maximum values.

Any estimates of rates provided (e.g. recruitment rates) will include a corresponding 95% confidence interval (CI).

No formal comparisons between treatment group allocations (intervention vs. control) will be provided.

1.7.3. DEVIATIONS TO THOSE SPECIFIED IN STUDY PROTOCOL

During the study the original follow-up duration of 30 months was reduced to 21 months due to delays initiating recruitment across all sites and researcher capacity for follow-up data collection within the study funding period. Reducing the follow-up duration 1) contributes to our study outcome reporting, which includes reviewing the availability of data collection at the follow-up time points to identify the optimal duration of follow-up from this pilot study, and 2) ensures all recruited participants would be eligible to attend the final follow-up visit. As a result, the information to be reported with regards participant attendance at each of the follow-up visits, the number of participants completing the study and the outcomes captured at specific follow-up time points are updated in this SAP to reflect the updated follow-up duration of 21 months.

The recruitment and retention rates between recruitment methods are also mentioned in the protocol but are not captured in this SAP due to changes in the data available from those initially planned.

1.7.4. Additional Analyses To Those Specified In Study Protocol

The items listed in the exploratory outcomes section of this document will also be analysed and are additional to those specified in the study protocol.

1.7.5. Software

Analyses will be conducted using R version 4.0.0 or higher.

2. Analysis

2.1. Study Populations

The screened population will consist of all patients that were screened for eligibility.

The invited population will consist of all patients that were deemed eligible and therefore sent a letter of invitation.

The consented population will consist of all patients that provided written informed consent regardless of other study involvement.

The intention-to-treat (ITT) population will consist of all randomised patients and will be analysed according to group allocation.

2.2. Study Status

The following information, which will help to prepare the consort diagram, will be summarised:

- Number of patients screened (overall and by site)
- Number of patients ineligible (overall and by site) and the reasons eligibility was not met
- Number of patients invited (overall and by site)
- Number and percentage of patients consented (of those invited, overall and by site)
- Number and percentage of patients in the ITT population (of those consented, overall and by treatment group
- Follow-up visit status of those in the ITT population (overall and by treatment group)
    - Number and percentage of patients attending at least one follow-up
    - Number and percentage of patients attending all follow-ups available

- Number and percentage of patients that withdrew by each follow-up visit, and reasons for withdrawal if known (of those in the ITT population, overall and by treatment group)

- Number and percentage of patients that died by each follow-up visit and primary cause of death (of those in the ITT population, overall and by treatment group)

- Number and percentage of patients who completed the study (of those in the ITT population, overall and by treatment group)

2.3. PROTOCOL DEVIATIONS

There were no protocol deviations during the study.

2.4. BASELINE CHARACTERISTICS

All descriptive summaries will be provided for the ITT population (overall and by treatment group) for the following baseline characteristics, as recorded in the CRF:

- Demographics (age, gender, ethnicity, occupation, SIMD decile and quintile)

- Home Information (telecare, community alarm, stair lift, heating, internal/external stairs, bedroom/bathroom location)

- GP, Pharmacy & Social Care (medication delivered by the pharmacy; social care package in place; current package of care; other teams/people providing help?; If so, who is providing help?; receiving any benefits; and benefits type received)

- Flu & COVID vaccination status (flu vaccine within past year; pneumococcal vaccine within past year; COVID vaccinated and number of COVID vaccinations)

- Lifestyle and Exercise

    - Smoking history (smoking status; number of years as a smoker; age started smoking; number of cigarettes/roll-ups per day; number of years stopped smoking; previous quit attempts?; any support in place for quit attempts?; consider stopping smoking now?; know where to access cessation services?; like to be referred to cessation services?; any other substances smoked?; if yes, what type of other substances?

    - Alcohol (current drinking status; number of days per week alcohol consumed; typical number of units consumed per day; looking to reduce/stop?; require any referral for help?)

    - Exercise (typical level of daily exercise; number of days exercising per week)

    - Diet (typically eat breakfast/lunch/dinner)

- Respiratory history (total number of patient-reported and case note diagnoses; frequency of each patient-reported and case note diagnosis; listing by patient of patient-reported and case note diagnoses; number of hospitalisations in past 12 months due to a respiratory problem; breathlessness in past 12 months compared to year before; self-management plan/rescue pack in house; number of rescue packs used in past 12 months; previous attendance at pulmonary rehab; MRC score; CAT score; usual colour and consistency of spit/phlegm; exacerbation (rescue pack) in past 12 months; experienced any of the following conditions or symptoms - wheezy chest, seasonal or allergic rhinitis/hay fever, night-time cough, productive cough, night sweats/fevers, coughed up blood, reflux/heartburn, recent chest pain)

- Bone health (any past falls; any past fractures; any family history of hip fracture; current rheumatoid arthritis; ever had prednisolone for ≥ 3 months at ≥ 7.5mg/day)

- Non-respiratory medical history of interest (total number of patient-reported and case note diagnoses; listing by patient of patient-reported and case note diagnoses; frequency of each patient-reported and case note diagnosis)

- Current prescribed medications of interest (total number of patient-reported and case note medications; listing by patient of patient-reported and case note medications; frequency of each patient-reported and case note medication)

- Vital signs and Health measures (height; weight; BMI; weight change in past year; if so, lost or gained weight?; SBP and DBP; respiratory rate; heart rate; oxygen saturation; temperature; grip strength; oxygen?; mobility aid(s); inhaler technique check; over past 2 weeks, how often have you felt tired or with little energy? (0-10 scale))

- Mental health questions (individual item responses; PHQ-4 anxiety and depression subscale scores, total score and psychological distress category)

- Mental health medical history of interest (total number of patient-reported and case note diagnoses; frequency of each patient-reported and case note diagnosis; listing by patient of patient-reported and case note diagnoses)

- Quality of Life - EQ-5D-5L Questionnaire (individual questionnaire items; utility index score; visual analogue scale; listing of responses to “How do you think you could improve today’s health number?”)

- Patient Experience with Treatment & Self-Management (PETS) Questionnaire (standardised scale scores; workload and impact summary index scores)

- Healthcare contacts in past 12 months and frequency of contacts:

    - primary care (any; nurse; GP; admin; pharmacist; podiatrist; healthcare assistant; physiotherapist; pharmacy technician; phlebotomist; treatment room; out of hours; COPD specialist/team contact)

  - mental health hospital/outpatient appointments or admissions
  - A&E visit without admission (any; those due to a respiratory cause; those due to a non-respiratory cause)
  - hospital admission (any; those due to a respiratory cause; those due to a non-respiratory cause)
  - secondary care (any A&E visit without admission or hospital admission; those due to a respiratory cause; those due to a non-respiratory cause)
  - outpatient appointment

- Blood results (K, Na, urea, Cr, eGFR, ALT, AST, Alb, ALP, eosinophils, WBC, RCC, platelets, neutrophils, Hb, HCT, MCV, MCH, lymph, folate, B12, CRP, Ca) where these are available from clinical records
  - result status (normal, low or high)
  - time since measurement, in days
- Diagnostic test results (sputum, chest X-ray, ECG, CT scan)
  - result status (change, no change)
  - time since diagnostic test, in days

2.5. EFFICACY OUTCOMES

Information collected will be summarised overall and by randomised treatment group where available.

2.5.1. PRIMARY OUTCOME

The primary outcome for this pilot study, was whether to progress to a definitive RCT based on achievement of four progression criteria:

1. Recruitment of at least 70% invited participants within four months;
2. At least 70% of intervention arm participants receiving TICC PCP as planned (at least monthly for 6 months then every two months) from the date of allocation to intervention arm;
3. At least 80% of participants (excluding those who died or developed incapacity before the end of the study) remaining in the study until 21-month data collection;
4. At least 90% of in-person data collected at each study time point (baseline and every three months for up to 21 months).

The percentage of missing data will be calculated using the expected data available as the: number of missing data points divided by the total number of expected data points. Researchers will not specifically take blood samples during assessments and so the availability of blood results depends on whether the participant has recent blood results already in their clinical records as part of their routine care. Therefore, blood results will be

excluded from the calculation of missing data items. Additionally, a modified version of the Patient Experience with Treatment and Self-management (PETS: a patient-reported measure of treatment burden)[39] will be used, which has not been validated, therefore PETS responses will also be excluded from the missing data calculations.

2.5.2. SECONDARY OUTCOMES

The following secondary outcomes and resource use will be measured by independent researchers extracting data from primary and secondary care health records at 3, 6, 9, 12, 15, 18, and 21 months whilst the participant remains in the study:

- the number of, and the number of people with: Primary care contacts (GP, nurse, healthcare assistant, pharmacist or other), in person or by phone;
- the number of prescribed medicines for respiratory conditions;
- the number of prescribed medicines for: bone health; gastrointestinal problems; pain; skin conditions; cardiovascular disorders; depression; anxiety; anaemia; and vitamin or other dietary insufficiency;
- the total number of prescribed medicines;
- the total number of, the number of people with, and time to first: ED attendances (without admission) for respiratory reasons;
- the total number of, the number of people with, and time to first: ED attendances (without admission) for non-respiratory reasons;
- the total number of, the number of people with, and time to first: hospitalisation for respiratory reasons;
- the total number of, the number of people with, and time to first: hospitalisation for non-respiratory reasons;
- the duration of hospitalisation for respiratory reasons;
- the duration of hospitalisations for non-respiratory reasons;
- the number of out-patient attendances and out-patient non-attendance for respiratory and other reasons;
- the total number of, time to, and causes of death.

The following secondary outcomes will be collected from participants during home visits by independent researchers at the same time points noted above whilst the participant remains in the study:

- the number of COPD exacerbations (confirmed by patient report on use of rescue pack (steroids and/or antibiotics);
- HRQoL using the EQ-5D-5L instrument score and individual domain scores;
- modified Medical Research Council Dyspnoea scale (mMRC) score;
- COPD Assessment Test (CAT) score;
- the total number of, the number of people with, and time to first fall;
- the total number of, the number of people with, and time to first fracture;
- Treatment burden scores (PETS questionnaire) collected at 3, 6, 12, and 21 months); and
- Patient Health Questionnaire-4 Item (PHQ-4) depression and anxiety score and sub scores (anxiety and depression).

2.5.3. EXPLORATORY OUTCOMES

The exploratory outcomes below will be summarised for the ITT population, overall and by randomised treatment group:

- Lifestyle and Exercise
    - Smoking history (smoking status; number of years as a smoker; age started smoking; number of cigarettes/roll-ups per day; number of years stopped smoking; previous quit attempts?; any support in place for quit attempts?; consider stopping smoking now?; know where to access cessation services?; like to be referred to cessation services?; any other substances smoked?; if yes, what type of other substances?)
    - Alcohol (current drinking status; number of days per week alcohol consumed; typical number of units consumed per day; looking to reduce/stop?; require any referral for help?)
    - Exercise (typical level of daily exercise; number of days exercising per week)
    - Diet (typically eat breakfast/lunch/dinner)
- Vital signs and Health measures (weight; BMI; SBP and DBP; respiratory rate; heart rate; oxygen saturation; temperature; grip strength; oxygen?; mobility aid(s); inhaler technique check; over past 2 weeks, how often have you felt tired or with little energy? (0-10 scale))

2.6. SAFETY OUTCOMES

The safety outcomes below will be summarised for the ITT population, overall and by treatment group. Note that intervention adherence outcomes will be summarised in the intervention group only.

2.6.1. INTERVENTION ADHERENCE

The following outcomes will be summarised overall and by delivery method (face-to-face, or telephone/email).

- Number of people who had at least one contact
- Total number of contacts per patient
- Time spent with patient (average contact duration, total duration of all contacts with patient)
- Various information collected on the delivery of the intervention (e.g. whether diagnostics performed, counselling given, new diagnoses given, etc.)

2.6.2. Laboratory Parameters

- Blood results (K, Na, urea, Cr, eGFR, ALT, AST, Alb, ALP, eosinophils, WB, RCC, platelets, neutrophils, Hb, HCT, MCV, MCH, lymph, folate, B12, CRP, Ca)
    - result status (normal, low or high)
    - time since measurement, in days
- Diagnostic test results (sputum, chest X-ray, ECG, CT scan)
    - result status (normal, abnormal, no change)
    - time since diagnostic test, in days

3. Data Conventions

Separate assumptions documents "TICC_PCP_baseline_dataset_assumptions_vX_X" and "TICC_PCP_followup_dataset_assumptions_vX_X" detailing data rules (e.g. formulae used for new variables, assumed categories for unique responses, partial dates, missing data imputation) will be created.

4. Tables and Figures

A draft version of the completed tables and figures will be provided to the study Chief Investigator (CI) prior to database lock, to allow for a full review of the report. Once the CI has agreed the content and accuracy of data within the draft report, database lock can be undertaken.

5. References

1. Morton, F., & Nijjar, J. S. (2024). Package name: eq5d: Methods for Analysing 'EQ-5D' Data and Calculating 'EQ-5D' Index Scores. R package version 0.15.4, https://CRAN.R-project.org/package=eq5d
2. Eton DT, Yost KJ, Lai JS, et al. Development and validation of the patient experience with treatment and self-management (PETS): a patient-reported measure of treatment burden. Qual Life Res 2017; 26:489–503

6. Document History

This is the first version (v1.0) of this document (initial creation).