# PROTOCOL FULL TITLE:

# Supported Rescue packs post-discharge in chronic obstructive pulmonary disease: An open-label multicentre randomised controlled trial

## Protocol Short Title/ Acronym:

## RAPID

### Trial Identifiers

| | | | |
|---|---|---|---|
| **IRAS Number:** | 331831 | | |
| **ISRCTN Number/ Clinical trials.gov Number:** | ISRCTN44283921<br><br>NCT06347536 | | |
| **Funders Number:** | NIHR156698 | | |
| **Protocol Version Number:** | 4.0 | **Date:** | 05/11/2024 |

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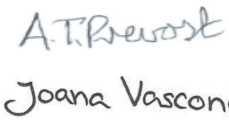
| **Signature** |  | Date: 31/01/2025 |

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# Study Synopsis

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|---|---|
| **TITLE OF CLINICAL TRIAL:** | SUPPORTED RESCUE PACKS POST-DISCHARGE IN CHRONIC OBSTRUCTIVE PULMONARY DISEASE: AN OPEN-LABEL MULTICENTER RANDOMISED CONTROLLED TRIAL |
| **Protocol Short Title/ Acronym:** | RAPID |
| **Study Phase:** | Phase 3 |
| **Sponsor Name(s):** | King's College London and Guy's and St Thomas Hospital NHS Foundation Trust |
| **Chief Investigator(s):** | Professor Mona Bafadhel |
| **Academic co-lead:** | Professor John Hurst |
| **Medical Condition or Disease Under Investigation:** | Chronic Obstructive Pulmonary Disease (COPD) |
| **Purpose of Clinical Trial:** | To test the hypothesis that provision of a rescue pack of antibiotics and corticosteroids, together with written (and translated) education on their use and twice-weekly telephone (or text) based support for when to use rescue packs, can reduce all-cause hospital re-admission in the 90-day high-risk period following discharge from hospital after an exacerbation of COPD. |
| **Primary Outcome:** | Time to first all-cause readmission within 90 days of discharge from hospital |
| • **Secondary Outcome(s):** | • Time to and frequency of COPD-related readmissions at 30 and 90 days<br>• Days alive and out of hospital at day 90<br>• Time to and frequency of all COPD exacerbations at days 30 and 90<br>• Cumulative systemic oral corticosteroids use over 90 days<br>• Cumulative systemic antibiotic use over 90 days<br>• Health care contacts at baseline, days 90 and 180, and 1 year<br>• All cause readmission at 30 days<br>• All cause-, cardiovascular- and COPD- related mortality at day 90 and over 12 months<br>• Quality of life (COPD assessment Test (CAT) score and EQ-5D-5L) at days 90 and 180, and 1 year<br>• Incremental cost-effectiveness ratio (ICER, a ratio of the additional cost divided by the additional effectiveness of SRP compared to UC) at days 90 and 180 and 1 year |

| | |
|---|---|
| | • Qualitative description of usual care<br>• Qualitative examination of fidelity to and adaptation of the plan in the intervention arm<br>• Serious adverse events<br>• Antimicrobial resistance |
| **Trial Design:** | Open label randomised controlled trial, with internal pilot |
| **Sample Size:** | 1400 patients recruited for 1331 analysed to ensure 515 primary outcome events needed for 90% power |
| **Summary of Eligibility Criteria:** | INCLUSION:<br>• Adults aged 40 and over<br>• Patient to be discharged from hospital with exacerbation of COPD<br>• Able to provide informed consent<br><br>EXCLUSION:<br>• Requirement for invasive ventilation during the hospital admission<br>• Patients who have an expected survival of less than 90 days<br>• Patients with signs of new consolidation on chest X-ray (if available)<br>• Discharge to residential or nursing home<br>• Inability to engage with supported self-management<br>• No access to telephone.<br>• Existing participation in an interventional trial.<br>• Previous participation in the RAPID trial. |
| **Intervention (Description, frequency, details of delivery)** | Patients allocated to the intervention arm will receive:<br>1. a rescue pack (prednisolone and antibiotics for 5-7 days). The prescription will conform to local prescribing guidelines for antibiotic and systemic corticosteroids for exacerbations of COPD.<br>2. a written rescue pack management plan.<br>3. twice-weekly automated telephone symptom reminder calls and/or text messages for 90 days. |
| **Comparator Intervention:** | Usual care (to be studied and described) – but no provision of a rescue pack at discharge. |
| **Maximum Duration of Treatment of a Participant:** | One year from the point of discharge from hospital. |
| **Version and Date of Final Protocol:** | V2.0 20/06/2024 |

# Revision History

| Protocol version | Description of changes from previous revision | Effective Date |
|---|---|---|
| Protocol Version 4.0 | - Addition of further exclusion criteria:<br>- Patients with signs of new consolidation on chest X-ray (if available)<br>- Previous participation in the RAPID trial. | |
| Protocol Version 3.1 | - Clarification around pneumonic exacerbations of COPD and pneumonia on X-ray | 24/09/2024 |
| Protocol Version 3.0 | - Removal from exclusion criterion: Individuals discharged from hospital to a non-physical virtual ward.<br>- Addition of Dyspnea VAS as part of standard practice<br>- Clarification on the definition of discharge from hospital<br>- Addition of definition of moderate and severe exacerbations of COPD<br>- Addition of clarifications regarding randomisation strata<br>- Clarifications around SAEs added as additional source data for primary outcome alongside HES data | 20/09/2024 |
| Protocol Version 2.0 | - Additon of exclusion criterion: Individuals discharged from hospital to a non-physical virtual ward.<br>- Addition of modified MRC measure.<br>- Clarification of safety reporting procedures. | 03/07/2024 |
| Protocol Version 1.0 | First approved version of Protocol | |

# Glossary of terms

| | | | | |
|---|---|---|---|---|
| **AE/AR** | Adverse Event/Adverse Reaction | | **ITT** | Intention to Treat |
| **AMR** | Anti-mircrobial Resistance | | **KCL** | King's College London |
| **ARG** | Andibiotic Resistance Gene | | **KCTU** | King's Clinical Trials Unit |
| | | | **KHP-CTO** | King's Health Partners Clinical Trials Office |
| **BNF** | British National Formulary | | | |
| | | | | |
| **CA** | Competent Authority | | **MAR** | Missing at Random |
| **CAT** | COPD Assessment Test | | **MTA** | Material Transfer Agreement |
| | | | **NHS** | National Health Service |
| | | | **NIHR** | National Institute for Health and Care Research |
| **CI** | Chief Investigator | | **NACAP** | The National Asthma and COPD Audit Programme |
| **CONSORT** | Consolidated Standards of Reporting Trials | | **ONS** | Office of National Statistics |
| **COPD** | Chronic Obstructive Pulmonary Disease | | **PI** | Principal Investigator (at site) |
| **CRF** | Case Report Form | | **PIN** | Participant Identification Number |
| **CRT** | Community Respiratory Team | | **PIS** | Participant Information Sheet |
| **CSV** | Comma-Separated Values | | **PP** | Per Protocol |
| **CTU** | Clinical Trials Unit | | **QALY** | Quality-Adjusted Life-Years |
| **DCR** | Data Clarification Request | | **R&D** | Research and Development |
| **DMC** | Data Monitoring Committee | | **RA** | Regulatory Agency |
| **DOB** | Date of Birth | | | |
| **DSUR** | Development Safety Update Report | | **REC** | Research Ethics Committee |
| | | | | |
| **eCRF** | Electronic Case Report Form | | **RN** | Research Nurse |
| | | | | |
| **EDC** | Electronic Data Capture | | **SAE** | Serious Adverse Event |
| | | | **SAP** | Statistical Analysis Plan |
| **eSMS** | Emergency Scientific and Medical Services | | **SDV** | Source Data Verification |
| **EU** | European Union | | | |
| | | | **SS** | Senior Statistician |
| **GDPR** | General Data Protection Regulation | | **SDW** | Source Data Worksheets |
| **GP** | General Practitioner | | | |
| **GCP** | Good Clinical Practice | | | |
| **HES** | Hospital Episode Statistics | | | |
| **HRA** | Health Research Authority | | **TM** | Trial Manager |
| | | | **TMG** | Trial Management Group |
| | | | | |
| | | | **TS** | Trial Statistician |
| | | | **TSC** | Trial Steering Committee |
| | | | **UCL** | University College London |
| **ICER** | Incremental Cost-effectiveness Ratio | | **UK** | United Kingdom |
| **ICF** | Informed Consent Form | | **VAS** | Visual Analogue Scale |
| **ID** | Identifier | | **VDI** | Virtual Desktop Infrastructure |
| **IME** | Important Medical Event | | | |
| **IP** | Intellectual Property | | | |
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# PROTOCOL CONTENT

# 1. INTRODUCTION

## 1.1 BACKGROUND AND RATIONALE

**What is the problem being addressed?**

Chronic obstructive pulmonary disease (COPD) is a common lung condition in the United Kingdom, with a prevalence of 4.5% in population ≥40 years and rising[4]. In addition to daily symptoms such as cough and breathlessness that limit physical activity, people living with COPD are prone to unpredictable deteriorations in their health called 'exacerbations'. Exacerbations are sometimes severe enough to lead to hospital admission and are often driven by infections. A systematic review of patient outcomes in COPD identified exacerbations, especially severe hospitalised exacerbations, as the aspect of COPD that patients found most difficult to live with[5]. Prior to the pandemic there were around 115,000 admissions to hospital with COPD exacerbations per annum[6] and admissions are now returning to that level. Exacerbations are more common in the winter with greater circulation of respiratory viruses, and thus the burden of hospitalised exacerbations contributes to winter National Health Service (NHS) bed pressures and cost to the NHS. The annual healthcare cost for people with moderate and severe exacerbation of COPD in England was estimated to be nearly £1 billion in 2022[7]. A particular problem after a hospitalised COPD exacerbation is re-admission to hospital. The National Asthma and COPD Audit Programme (NACAP) has shown that the re-admission rate is 23% at 30 days and 43% at 90 days[2]. Our systematic review identified comorbidities, previous exacerbations and increased length of stay as risk factors for 30- and 90-day all-cause readmission[5].

There are many interventions that can reduce the risk of COPD exacerbations but these are incompletely effective[8]. There is also evidence to suggest that earlier intervention with standard exacerbation treatment of antibiotics and/or corticosteroids (called a 'rescue pack') can hasten recovery, with a lessened chance of hospital admission[9]. As part of standard NHS care[2], patients with COPD should have a 'discharge bundle' implemented, although this is often poorly delivered and has not been definitively shown to impact outcomes (likely because the wrong outcomes were chosen, and the bundle was poorly implemented)[10]. The provision of rescue packs is not a standard component of discharge bundles but these are sometimes provided according to local service preference[3]. Additionally, in usual clinical practice, some patients will have been prescribed rescue packs from primary care (GP) or a community respiratory team (CRT) prior to being hospitalised with COPD. Furthermore, patients may or may not have access to rescue packs from the GP or the CRT after hospital discharge.

Although rescue packs are part of NICE guidance[2], the available evidence suggests they are not effective unless provided in the context of a more comprehensive management/education plan that supports patients in their appropriate use[11]. In practice this usually does not happen[3], with evidence that a patient with COPD will receive variable or often no support; with some patients receiving rescue packs on demand without considering antimicrobial resistance, predictable side-effects from steroid overuse, or reviewing appropriateness. The investigators have pilot data that show receiving a rescue pack on hospital discharge is controversial as the hospital team is not, in general, the team that provides ongoing support to use these. There is thus recognised over- and under-use of rescue packs, associated harm from these medicines and variable provision. Providing a rescue pack, with education on how to use and support for when to use, has not been specifically tested in the high-risk 90-day period for readmission following a hospitalised exacerbation. We hypothesise that rescue packs on discharge from hospital in addition to a comprehensive self-supported management plan, consisting of the Asthma+Lung UK written management plan and twice weekly automated phone and or text messaging during this 90 day high risk period, will reduce readmissions by 20% compared to standard care.

**Why is this research important in terms of improving the health of patients and health and care services?**

Reducing re-admission through provision of supported rescue pack use would benefit people living with COPD and the NHS. A reduction in readmissions of 20% could save the NHS £86 million per quarter (£344 million per annum). Conversely, demonstrating that rescue packs are not effective when used in this way will address controversy about use, and reduce pressure on antimicrobial resistance and harm from over-use of oral corticosteroids. Integrated care systems are rapidly developing out-of-hospital support for people with exacerbations of COPD including digitally supported virtual wards. The proposed trial will define the role of supported rescue pack provision in the design and implementation of these programmes, enhancing their ability to reduce demands on urgent and acute care. Whether positive or negative, this trial will help to reduce the current variation in service provision by providing a definitive answer to the study question. Furthermore, preventing exacerbations of COPD have been identified as a priority by the James Lind Alliance (JLA) Priority Setting Partnership (PSP)[12].

# 2. TRIAL DESIGN

Open label randomised controlled trial, with internal pilot.

## 2.1 OBJECTIVES

### 2.1.1 PRIMARY OBJECTIVE

To assess whether rescue packs and a comprehensive supported self-management plan reduce readmissions following exacerbation of COPD.

This study objective is not to test safety or efficacy of rescue packs. The focus is rather on the treatment support strategies therefore constituting a non-CTIMP study as per current regulatory requirements.

### 2.1.2 SECONDARY OBJECTIVES

- Time to and frequency of COPD-related readmissions at 30 and 90 days
- Days alive and out of hospital at day 90
- Time to and frequency of all COPD exacerbations at days 30 and 90
- Cumulative systemic oral corticosteroids use over 90 days
- Cumulative systemic antibiotic use over 90 days
- Health care contacts at baseline, days 90 and 180, and 1 year
- All cause-, cardiovascular- and COPD- related mortality at day 90 and over 12 months
- Quality of life (COPD assessment Test (CAT) score and EQ-5D-5L) at days 90 and 180, and 1 year
- Incremental cost-effectiveness ratio (ICER, a ratio of the additional cost divided by the additional effectiveness of SRP compared to UC) at days 90 and 180 and 1 year
- Qualitative description of usual care
- Qualitative examination of fidelity to and adaptation of the plan in the intervention arm
- Serious adverse events
- Antimicrobial resistance

# 3. PARTICIPANTS

## 3.1 STUDY SETTING & RECRUITMENT

The study will be open across NHS-based sites in the United Kingdom. Participants in the trial will be recruited during the hospital admission.

## 3.2 ELIGIBILITY CRITERIA

### 3.2.1 INCLUSION CRITERIA

- Age ≥ 40 years
- Individuals admitted to hospital with COPD exacerbation. Admission is defined as an episode in which a patient with an exacerbation of COPD is admitted to a ward and has stayed in hospital for 4 hours or more, including Emergency Medicine Centres, Medical Admission Units, Clinical Decision Units, short stay or virtual wards or similar but excludes patients treated transiently before being discharged from Emergency Department.
- Ability to provide written informed consent.

### 3.2.2 EXCLUSION CRITERIA

- Individuals who require invasive ventilation during the hospital admission
- Patients who have an expected survival of less than 90 days
- Patients with signs of new consolidation on chest X-ray (if available)Individuals who have been discharged to residential or nursing home.
- Individuals who are unable to manage a supported self-management plan.
- Individuals with no access to telephone.
- Individuals who are already taking part in an interventional trial.
- Previous participation in the RAPID trial.

## 3.3 IDENTIFICATION OF ELIGIBLE PARTICIPANTS

Patients admitted to hospital with an exacerbation of COPD could be potential participants for recruitment into the study. While some controversy exists around pneumonic COPD exacerbations[46], for the purposes of the trial, patients with COPD background and signs of consolidation on X-ray should be classified as diagnosed with pneumonia. At time of hospital admission, the direct clinical care team will identify potential participants admitted with COPD exacerbation and inform the study team who will then provide study information sheets at the earliest opportunity. This will all happen in the hospital setting. In this study, as patients admitted with COPD exacerbations are routinely looked after by the respiratory team (respiratory consultants, respiratory trainee doctors, respiratory nurse team, respiratory pharmacist team, respiratory physiotherapists) identification of potential participants will be part of research practices for each site and direct and rapid communication with the study team is expected. The direct clinical care team will notify the study team of the following personal identifiable data: name, DOB, Hospital Number. If potential participants are interested in taking part, then the study team will be informed for potential recruitment. In scenarios where the patient is not admitted under the respiratory team, then the direct clinical care team will identify potential participants and ask if they are interested in taking part in the study; and if potential participants are interested in taking part, then the study team will be informed for potential recruitment.

## 3.4 INFORMED CONSENT

Informed consent must be obtained before any trial related procedures or assessments can be done. The participant will be given a copy of the Patient Information Sheet (PIS) and Informed Consent Form (ICF) and the investigator or designated person must ensure participants are informed about the trial, their participation and any associated risks. Consent will be taken by any suitably qualified person as delegated by the PI (including research nurses, clinical trial practiotioners, etc). The investigator will retain one copy of the original

signed consent forms for the investigator site file, a second copy will be given to the participant to keep and a copy will be uploaded to the participant's medical records.

# 4. DATA COLLECTION & DATA ENTRY

## 4.1 PARTICIPANT TIMELINE

### *TABLE 1 SCHEDULE OF EVENTS*

| **Timepoint** | **Screening** | **Baseline (-3 to 0 days)*** | **Day 30 +/- 3** | **Day 90 +/- 3** | **Day 180 +/- 7** | **1 year +/- 7** | **Ongoing** |
|---|---|---|---|---|---|---|---|
| 1. Registration form & consent | **X** | | | | | | |
| 2. Eligibility | **X** | | | | | | |
| 3. Medical history | **X** | | | | | | |
| 4. COPD history | **X** | | | | | | |
| 5. Demographic data | **X** | | | | | | |
| Collation of routine investigations and and data on this admission eg LOS | | **X** | | | | | |
| Clinical Frailty Scale | | **X** | | | | | |
| The modified MRC Scale | | **X** | | **X** | **X** | **X** | |
| Dyspnea VAS | | **X** | | **X** | **X** | **X** | |
| 6. Randomisation | | **X** | | | | | |
| 7. Status form to include VITAL STATUS, READMISSIONS and COMMUNITY TREATED EXACS | | | **X** | **X** | **X** | **X** | |
| 8. Study Follow-Up Telephone call | | | **X** | **X** | **X** | **X** | |
| 9. EQ-5D-5L | | **X** | | **X** | **X** | **X** | |
| 10. COPD Assessment Test (CAT) | | **X** | | **X** | **X** | **X** | |
| 11. Resource use questionnaire | | **X** | | **X** | **X** | **X** | |
| 12. Text messaging/tel call[¥] | | | **X** | **X** | | | |
| 13. Seriousadverse events log | | | | | | | **X** |
| 14. Concomitant medications log | | **X** | | | | | |
| 15. Withdrawal form | | | | | | | **X** |
| 16. Rescue packs dispensing | | **X** | | | | | **X**[†] |
| 17. Interview[¶§] | | | | **X*** | | | |
| 18. Biological sample collection (including stool, nasosorption, sputum)§ | | **X** | | **X** | | | |

*in relation to discharge from hospital; [¥] twice-weekly for 90 days in the intervention arm; [¶]window for interviews +/- 14 days; § sub-study; [†]resupply of rescue pack(s) if used within 90 day window.

### 4.1.1 VISIT WINDOWS

Telephone calls at 30 and 90 days will be +/- 3 days (one week window), with the day 180 and 365 calls +/- 7 days (two week window).

#### 4.1.2 SCREENING

Patients will be identified and screened whilst in hospital before they are discharged.

#### 4.1.3 BASELINE

Patients will be randomised following eligibility checks and consent. Baseline data will be collected as per the Schedule of Events in Table 1 prior to patient being discharged.
Participants in the intervention arm will receive a rescue pack prior to being discharged from hospital.

#### 4.1.4 DAY 30, 90 AND 180 TELEPHONE CALLS

Follow up data will be collected as per the Schedule of Events in Table 1 above. At each follow up timepoint, a status form is completed; in the event of a missed visit, the status form must be completed. The following will be collected:

- Time to and frequency of all COPD-related readmissions
- Time to and frequency of all COPD exacerbations
- Time to first all cause readmission
- Time to and frequency of COPD related readmissions
- Days alive and out of hospital at 90 days
- Cumulative oral corticosteroids and antibiotic use
- Healthcare contacts
- All cardiovascular and COPD related mortality
- Use of secondary healthcare services
- SAEs
- Subject to optional consent, a qualitative telephone interview will be scheduled with a subsample of intervention-arm participants at approximately 90 days post-discharge (+/-14 days). For further details, see section 4.11

In the event that the participant in the intervention arm uses the rescue pack within the first 90 days, a new pack will be provided by the research team.

#### 4.1.5 DAY 365 OR END-OF-STUDY TELEPHONE CALL

Day 365 data will be collected as per the Schedule of Events in Table 1 above. In the event a participant wishes to stop the study and withdraw from further data collection, a withdrawal form must be completed. Where possible a withdrawal call should be scheduled to undertake a final set of outcome assessments. In cases where the participant completes the study to month 12, a withdrawal form should be completed at the final visit to indicate they never withdrew.
The following data will be collected:

- Healthcare contacts
- Use of secondary healthcare services
- All cardiovascular and COPD related mortality – to be collected over 12 months
- SAEs

#### 4.1.6 TWICE WEEKLY TEXT MESSAGING/TELEPHONE

In the intervention arm, Patients will receive twice weekly telephone calls or text messages for 90 days following randomisation. This will ask patients about their level of symptoms and remind patients that if there is a sustained increase in their symptoms consistent with an exacerbation, to use their education plan, consider using their rescue pack and to contact their usual clinical provider.

Frequent repeated patient contact is believed to lead to

•Earlier recognition of symptoms

•Earlier intervention by appropriate use of rescue pack

•Reduced severity of exacerbation

•Reduced rate of readmission

• Earlier recognition of signs of exacerbation and knowledge of appropriate action

## 4.2 DATA ENTRY

Authorised staff at sites will transcribe baseline and follow up participant data from source data (SD) to the study eCRF by going to www.ctu.co.uk and clicking the link to access MACRO Version 4. A full audit trail of data entry and any subsequent changes to entered data will be automatically date and time stamped, alongside information about the user making the entry/changes within the system.

Study site staff will be delegated by the site PI to access the eCRF and randomisation systems via a Study Site Delegation Log. The request for user access must go to the UK Trial Manager, who will submit user requests for all sites to the KCTU team upon receipt of completed Study Site Delegation Logs. Requests for user access will be processed within a maximum of 5 working days.

Training videos for data entry staff, study site monitors and trial managers / trial co-ordinators are available at www.ctu.co.uk under the 'Training' section. Users can self-register and should select the MACRO related training videos.

## 4.3 BASELINE DATA COLLECTION

### 4.3.1 REGISTRATION

When the participant has signed consent, the study site staff should register the participant in the MACRO eCRF system. Upon registration, the system will assign a unique study PIN, to be used for the participant throughout the study.

### 4.3.2 ELIGIBILITY

All eligibility checks must be completed and eligibility confirmed prior to randomisation.

### 4.3.3 MEDICAL HISTORY

Relevant medical history must be recorded. If the participant is taking any medications at baseline, the relevant condition should be recorded in the medical history.

### 4.3.4 DEMOGRAPHICS

Relevant demographic information will be collected prior to randomisation. This includes age, gender, ethnicity, smoking history and social/home situation.

### 4.3.5 CLINICAL DATA

Relevant data from the clinical episode, including blood tests, x-rays (where applicable), clinical frailty[43], dyspnea VAS[44], modified MRC[45] scores, treatment and length of stay will be collected and entered into the eCRF.

### 4.3.6 RANDOMISATION

Sites must confirm in the eCRF system whether participants were randomised into the study or not. Age at randomisation will be entered in the eCRF. The randomisation procedure and access to the randomisation system is described in the trial specific procedures.

## 4.4 EFFICACY DATA

Participant self-report measures should ideally be completed in the absence of the caregiver.

#### 4.4.1 MEASURE 1:COPD ASSESSMENT TEST

The COPD Assessment Test (CAT) is an eight-item health status instrument in COPD that is used to quantify the impact of COPD on the patient's health

#### 4.4.2 MEASURE 2: EQ-5D-5L

The EQ-5D-5L[28] is a validated and widely used generic measure used to collection patients' health-related quality of life.

#### 4.4.3 MEASURE 3: RESOURCE USE QUESTIONNAIRE

A resource use questionnaire[27] will be used to collect patients' use of primary healthcare services, social care services and out of pocket expenditure and their carers' productivity losses.

### 4.5 SAFETY DATA

#### 4.5.1 SERIOUS ADVERSE EVENTS

During each assessment, participants will be asked about adverse events. All serious adverse events will be recorded in an ongoing serious adverse event log. Symptoms of disease progression need only be recorded if treatment is required or if the physician is concerned that the rate of progression is unexpected.

#### 4.5.2 CONCOMITANT MEDICATIONS

During each assessment, participants will be asked about their current medication. All concomitant medication will be recorded in an ongoing concomitant medication log.

#### 4.5.3 WITHDRAWAL

A withdrawal form must be completed in the event of participant death or where the participant has stopped taking study medication and is no longer prepared to provide any follow up data or have their caregiver or family doctor provide any follow up data. Where the participant has stopped study intervention but is still being followed for primary outcome data, a withdrawal form should not be completed, but a status update must be recorded in the eCRF every 3 months.

### 4.6 LABORATORY DATA

The results of any routine clinical blood results will be entered into the eCRF. Routine sputum antibiotic sensitivity collected data will also be stored in the eCRF at admission and at any readmission for assessment of AMR. In a sub-study of patients, stool samples will be collected at baseline prior to discharge from the index exacerbation and at 90 days to assess the effect of rescue packs on AMR rates. Assuming that the comparator group has less AMR than the intervention group, and 20% drop out, it is estimated that 34 patients from each study arm will need to be sampled and sequenced for antibiotic resistance genes (ARGs) to determine a clinically meaningful effect of rescue packs on AMR. The results of any routine nasal/throat swabs and nasal absorption will also be collected during the admission and discharge.

### 4.7 MEASURES TO PROMOTE PARTICIPANT RETENTION

There are no in person visits in this study and so we do not anticipate challenges with retention. We will work flexibly with patients regarding scheduling of phone calls, sending reminders before-hand.

### 4.8 QUALITATIVE SERVICE EVALUATION TO CHARACTERISE STANDARD-OF-CARE

Reflecting patterns in the UK[10] and notwithstanding NICE guidance, standard of care in the participating sites is likely to vary greatly. Understanding the nature and level of support offered as standard of care to participants will be essential to interpretation of results. To address this need, prior to the delivery of the study described in this protocol, we will undertake a service evaluation as part of a sub-study using qualitative interviews with

relevant healthcare staff (providers and commissioners) to characterise standard of care in participating sites prior to site initiation, to identify the key aspects of variation that may have a bearing on the primary and secondary outcomes, and to inform collection of participant-level data relating to these variations in the trial. We will supplement data from these interviews with information derived from local protocols, guidance and other documents.

## 5. QUALITATIVE SUB-STUDY TO UNDERSTAND INTERVENTION DELIVERY

The delivery of a complex intervention with several component parts such as rescue packs and their associated interventions including education and reminders, is subject to mutation at various points in the process. This may include appropriate adaptions of the intervention to local circumstances, and changes that are likely to undermine positive impact. Both to understand the impact of the intervention (and particularly variability in impact) and to equip practitioners to make the best use of it if adopted in routine care, it is important to understand the nature of those variations and the extent to which fidelity to the intervention as intended has been achieved. We will carry out interviews after the 90-day follow-up period with patients in the study's intervention arm. We will seek a sub-sample that exhibits strong heterogeneity in characteristics that may affect participants' attitudes towards and use of rescue packs and the associated package of supporting measures.

As part of the consent process for the study, participants will be asked (optionally) to consent to being contacted by the study team regarding participation in an interview about experiences of the intervention at around 90 days. Contact details of patients who give consent to this, will be collated on a monthly basis and passed to the qualitative research team, along with basic demographic details (site, sex, age, ethnicity, language, date of discharge), to inform identification of a subsample. At follow-up calls, the research team will address eligibility for, and agreement to undertake the qualitative interviews and pass contact details on to the qualitative research team. The qualitative team will contact participants using the information provided at 90 days (+/-14 days). At this point, participants will have the chance to ask further questions about the study, and consent will be reaffirmed verbally; information sheets will be re-supplied upon request. Where a participant's preferred language is not English, this contact will be supported by a professional interpretation service. The qualitative team will keep an ongoing record of participants who agree to be interviewed, with a view to securing variation in the following characteristics and constructing a diverse sample:

- Gender
- Age
- Ethnicity
- Preferred language
- Site of recruitment

As recruitment proceeds, the profile of the sample according to each of these variables will be kept under review, and further recruitment will be targeted at groups that are less well represented in the sample to date. Up to approximately 60 participants will be recruited across all sites (around two per site on average).

Where participants agree to be interviewed, the researcher will agree an appropriate time and date for the interview. Interviews will be conducted by telephone, will take up to approximately 60 minutes, and will be audio-recorded using an encrypted device. They will follow a topic guide focusing on the participant's experience of the post-discharge intervention, including their knowledge of the use of rescue packs, whether they used a rescue pack and in what circumstances, their views on the support and guidance provided (written, telephone, and text message), and the fit of the intervention into their day-to-day lives. Topic guides informed by constructs from the COM-B framework[40] and from Burden of Treatment Theory[41], with a view to understanding both the individual-level and social influences on reception and use of the rescue packs and associated support.

Following completion of interviews, audio recordings will be moved to the University of Cambridge Safe Haven storage space, and then transferred securely to a professional transcription service with appropriate confidentiality and data-sharing agreements in place. In the course of transcription, identifying features will be anonymised. Anonymised transcripts will be returned to the Safe Haven, at which point they will be checked

against audio recordings to ensure full anonymity and accuracy. Once this has been verified, audio recordings will be destroyed the anonymous transcripts will then be transferred from the University of Cambridge Safe Haven to the University of Cambridge research drive for analysis. Analysis will be based on the constant comparison approach, adapted to incorporate sensitising concepts from COM-B and Burden of Treatment theory, and will focus in particular on: (i) the impacts of participants' diverse backgrounds and circumstances on their attitudes towards and use of the rescue packs and other components of the intervention; (ii) the consequences for adherence to intended use; and (iii) the implications for refining protocols for administering rescue packs and supporting resources and how these might best be tailored to individual patients' situations.

# 6. INTERVENTIONS

## 6.1 EXPLANATION FOR THE CHOICE OF COMPARATORS

The comparator is usual care, which will vary by site, and will be studied via a qualitative sub-study.

## 6.2 INTERVENTION AND COMPARATOR DESCRIPTION, DOSING AND LABELLING

The intervention arm consists of 3 components: i) a written (and/or translated) management plan for COPD exacerbations as per Asthma+Lung UK; ii) medication in the form of a rescue pack and iii) reminder text or telephone messages, twice per week as per section 4.1.6. A 'rescue pack' according to local prescribing guidelines, will be allocated to the intervention arm. This typically consists of 5-7 days of prednisolone (30mg to be taken once a day) and 5-7 days of amoxicillin (500mg to be taken three times a day). If participants in the intervention arm use their rescue packs a further rescue pack will be provided by the study team, up to 90 days following randomisation. The control study arm will not receive a rescue pack on randomisation, by the study team. However, participants in the control study arm may have access to rescue packs in the community, their homes or their community care team for which we will record this use on study visit telephone calls.

# 7. ASSIGNMENT OF INTERVENTIONS

## 7.1 RANDOMISATION METHOD

The method of randomisation in the trial is stratified randomisation with two stratifiers defined by COPD hospitalisations (severe exacerbation) in the last year and previous exacerbations (moderate or severe) in the last year and (excluding the index hospitalisation).

I) Prior versus no prior severe exacerbations in the last year
II) >=2 or <2 moderate/severe exacerbations in the last year

Randomly permuted blocks will be used within the four strata defined by the categories of these stratifiers.

Severe exacerbation is defined as a COPD exacerbation requiring hospitalisation, moderate exacerbation is defined as a COPD exacerbation that is treated with steroids and/or antibiotics, but that does not require hospitalisation.

## 7.2 RANDOMISATION IMPLEMENTATION

### 7.2.1 ALLOCATION SEQUENCE GENERATION

The randomisation sequence will be generated dynamically by the KCTU team via the KCTU web based randomisation system, in accordance with the specification agreed with the CI and Senior Statistician. The Chief Investigator, Senior Statistician and TMG will be blinded to the sequence generation.

#### 7.2.2 ENROLMENT OF PARTICIPANTS

Participants will be enrolled in the study for the purpose of CONSORT reporting at the point of signing a consent form to being screened for eligibility and will be part of the target N=1400 at the point of randomisation.

#### 7.2.3 ASSIGNMENT OF PARTICIPANTS TO INTERVENTIONS

Recruiting sites will assign participants to interventions by logging into the 'KCTU randomisation and IMP management system' at www.ctu.co.uk (click 'randomisation' and select 'XXXX study) and entering the participant's year of birth and age and stratifiers.

## 8. LABORATORIES

### 8.1 SAMPLE COLLECTION

In participants who provide consent, stool and nasal fluid samples for exploratory analysis will be collected at baseline prior to discharge and at 90 days. These samples will be collected by sites and in bulk will be transported for laboratory analysis to University College London (UCL) for stool and to King's College London (KCL) for nasal fluid. Samples will be stored in -20C or -80C freezers.

### 8.2 SAMPLE ANALYSIS PROCEDURES

All processed samples will be cell-free and not have any human genetic material. Stool samples will be analysed to understand anti-microbial resistance, including measurement of antibiotic resistance genes. Nasal fluid samples will also be analysed to measure inflammatory proteins, including chemokines and cytokines.

### 8.3 SAMPLE DATA RECORDING

As exploratory data, results will be recorded in a safe password controlled held spreadsheet at UCL and KCL.

### 8.4 SAMPLE INCIDENTS

As this is a sub-study with exploratory analysis, any incidents of sample handling or loss will not be required to be reported to the sponsor. Incidents of sampling handling or loss will be reported according to local guidelines as part of standard practice.

Sample incidents taking place at the Guy's and St Thomas' NHS Foundation Trust should also be reported on the Trust risk register Datix: http://gti.gstt.local/services/healthsafety/health-safety-main-pages/i-am-interested-in/accidents-and-incidents-reporting.aspx

## 9. DATA MANAGEMENT

### 9.1 DATA MANAGEMENT

There are two datasets in the trial: the KCTU randomisation dataset and the KCTU Elsevier Macro 4 eCRF system dataset. Source data worksheets will be supplied to all recruiting sites by the co-ordinating centre for the region. These will be prepared after the database specification is finalised and database testing is complete. Laboratory results may be reviewed directly in hospital laboratory systems where appropriate and need not be transcribed in full to the source data work. The source data worksheet must confirm that the samples were processed, and any abnormal results must be recorded and transcribed. Normal results need not be transcribed. Data will be transcribed from the source to the MACRO eCRF system, ideally within 7 days of the study visit. Participating Sites will complete source data location lists defining the source data at their site. The CI will act as custodian for the trial data. The flow of trial data is outlined in Figure 1.

§.

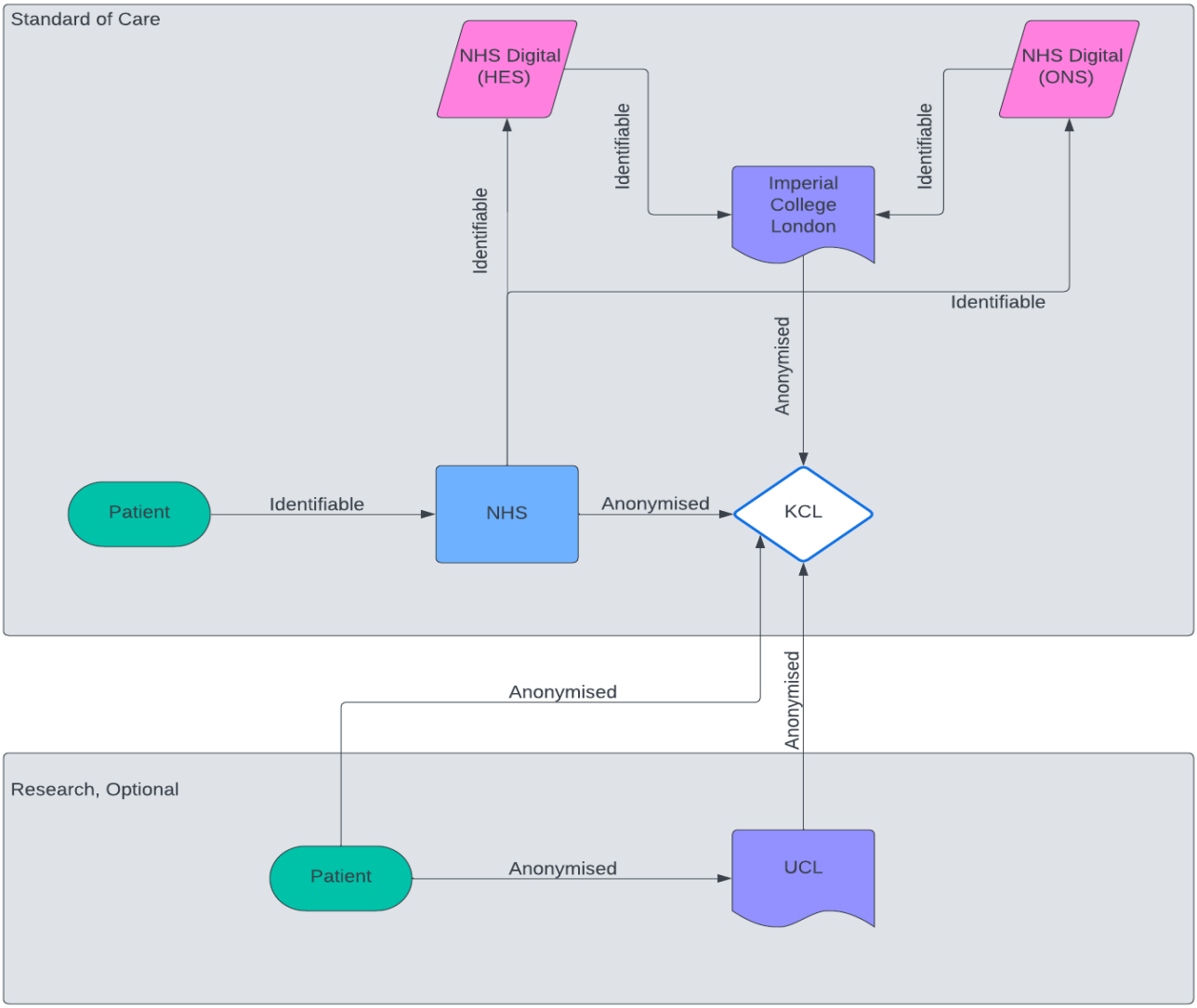


**Figure 1.** Data Flow

## 9.2 DATA SECURITY

Clinical trial will involve the sharing of deidentified data and samples of subjects for research purposes, both during and after the trial for the purposes of monitoring and analysis. All applicable statutory requirements and mandatory codes of practice in respect of confidentiality (including, where applicable, medical confidentiality) in relation to such trial subjects or their legal guardians. Data flow will be governed by UK-specific requirements.

Data Management Plans will be provided to the Trial Manager, detailing relevant security information about both data systems. Systems access will be strictly restricted through user-specific passwords to the authorised research team members. It is a legal requirement that passwords are not shared, and that only those authorised to access the system are allowed to do so. If new staff members join the study, a user-specific username and password must be requested and a request for access to be revoked must be requested when staff members leave the project.

Participant year of birth and age will be entered into the systems. No more identifiable data will be entered into the eCRF system. Trial sites will maintain a master participant log linking participant identifiers to study numbers. No data will be entered unless a participant has signed a consent form to participate in the trial

### 9.3 DATA QUALITY PROCESSES

At the database design stage, validations will be programmed into the systems to minimise data entry errors by querying the data entered in real time with sites.

The CI team will undertake appropriate reviews of the entered data, in consultation with the project analyst, where appropriate for the purpose of data cleaning and will request amendments to the MACRO eCRF system data as required. No data will be amended independently of the study site responsible for entering the data.

No data can be amended in the randomisation system, however CI or delegate (e.g., Trial Manager) may request King's Clinical Trials Unit to add notes against individual participant entries to clarify data entry errors. Any errors should be reported by site staff to the Trial Manager as soon as possible once they are detected. The trial manager will onward report errors to KCTU and retain records in the TMF.

The KCTU will provide the Trial Manager with Data Management Plans for both the Elsevier Macro eCRF system and the randomisation system once the systems are made live. Those documents will be filed in the Trial Master File.

A regular Data Management Report will be produced by KCTU and passed to the Trial Manager, who will raise Data Clarification Requests (DCRs) with sites in the eCRF system. The Trial Manager will raise DCR's. Study sites will periodically review raised DCR's and respond to the queries raised.

During site monitoring visits, the Trial Manager will raise any queries with sites via the Source Data Verification (SDV) function.

### 9.4 DATABASE LOCK

At the end of the trial, the site PI's will review all the data for each participant in the MACRO eCRF system and provide electronic sign-off to verify that all the data are complete and correct.

The trial manager will confirm all checks are complete and all monitors queries have been resolved prior to database lock. At this point, with the agreement of the senior statistician, all data can be formally locked for analysis.

When the final data extract is requested, KCTU will remove all data entry user access prior to data extract and will retain only 'monitor' access for site PI's and other relevant individuals.

Upon request, KCTU will provide a copy of the final exported dataset to the CI in .csv format and the CI will onward distribute to sites as appropriate. Once sites have received copies of their individual datasets and confirmation of receipt has been received, the Trial Manager will request that all user access is removed from the MACRO eCRF system. A copy of the dataset will be stored in the TMF at the end of the study.

## 10. SUMMARY OF KNOWN AND POTENTIAL RISK OF RESCUE PACKS

Administration of rescue packs for this study is not anticipated to induce any potential risk other than the known potential side effects as listed in the British National Formulary (BNF).

**Undesirable effects of prednisolone**
A wide range of psychiatric reactions including affective disorders (such as irritable, euphoric, depressed and labile mood, and suicidal thoughts), psychotic reactions (including mania, delusions, hallucinations, and aggravation of schizophrenia), behavioural disturbances, irritability, anxiety, sleep disturbances, and cognitive dysfunction including confusion and amnesia have been reported. Reactions are common and may occur in both adults and children. In adults, the frequency of severe reactions has been estimated to be 5-6%. Psychological effects have been reported on withdrawal of corticosteroids; the frequency is unknown. The

incidence of predictable undesirable effects, including hypothalamic-pituitary adrenal suppression correlates with the relative potency of the drug, dosage, timing of administration and the duration of treatment (see Section 4.4 'Special warnings and special precautions for use').

# 11. ADVERSE EVENT MANAGEMENT AND REPORTING

All serious adverse events will be recorded in the participants medical notes, the study source data worksheets, and the eCRF. SAE's will be additionally reported, within 24 hours of site becoming aware of the event, to KCTU.

All SAEs, SARs and SUSARs (except those specified in this protocol as not requiring reporting) will be reported immediately (and certainly no later than 24hrs) as per the instructions on the SAE report form.

In research other than CTIMPs, a Serious Adverse Event (SAE), Serious Adverse Reaction (SAR) or Suspected Unexpected Serious Adverse Reaction (SUSAR) is defined as any adverse event, adverse reaction or unexpected adverse reaction, respectively, that:

- results in death
- is life-threatening
- required hospitalisation or prolongation of existing hospitalisation
- results in persistent or significant disability or incapacity
- consists of a congenital anomaly or birth defect
- is otherwise considered medically significant by the investigator

An SAE occurring to a research participant should be reported to the main REC (the REC that gave favourable opinion of the study) where in the opinion of the Chief/Principal Investigator the event was:

- "Related" – that is, it resulted from administration of any of the research procedures, and
- "unexpected" – that is, the type of event is not listed in the protocol (section10)/BNF as an expected occurrence.

The Chief/Principal Investigator or Sponsor must submit reports of related and unexpected SAEs within 15 days of the Chief/Principal Investigator becoming aware of the event, using the SAE report form for non-CTIMPs available from: https://www.hra.nhs.uk/approvals-amendments/managing-your-approval/safety-reporting/

Important Medical Events (IME) & Pregnancy: Events that may not be immediately life-threatening or result in death or hospitalisation but may jeopardise the participant or may require intervention to prevent one of the other outcomes listed in the definition above should also be considered serious. Although not a serious adverse event, any unplanned pregnancy will also be reported via the SAE reporting system.

## 11.1 EVALUATING SAES

### 11.1.1 ASSESSMENT OF INTENSITY

The Investigator will make an assessment of intensity for each SAE reported during the study. The assessment will be based on the Investigator's clinical judgement. The intensity of each SAE recorded in the eCRF should be assigned to one of the following categories:

- Mild; An event that is easily tolerated by the participant, causing minimal discomfort and not interfering with everyday activities
- Moderate; An event that is sufficiently discomforting to interfere with normal everyday activities
- Severe; An event, which is incapacitating and prevents normal everyday activities

An AE that is assessed as severe should not be confused with an SAE. Severity is a category utilised for rating the intensity of an event; and both AEs and SAEs can be assessed as severe.

#### 11.1.2 ASSESSMENT OF CAUSALITY

The Investigator is obligated to assess the relationship between intervention and the occurrence of each SAE. The Investigator will use clinical judgment to determine the relationship. Alternative causes, such as natural history of the underlying diseases, concomitant therapy, other risk factors, and the temporal relationship of the event to the investigational product will be considered and investigated.

The causal relationship to the study procedures assessed by the Investigator (or medically qualified delegate) should be assessed using the following classifications:

- Not Related: In the Investigator's opinion, there is not a causal relationship between the study intervention and the SAE.
- Unlikely: The temporal association between the SAE and study internevtion is such that the study intervention is not likely to have any reasonable association with the SAE.
- Possible: The SAE could have been caused by the study participant's clinical state or the study intervention.
- Likely: The SAE follows a reasonable temporal sequence from the time of study intervention administration, abates upon discontinuation of the study intervention and cannot be reasonably explained by the known characteristics of the study participant's clinical state.
- Definitely: The SAE follows a reasonable temporal sequence from the time of study intervention administration or reappears when study interventionis reintroduced.

There may be situations when an SAE has occurred, and the Investigator has minimal information to include in the initial report to the Sponsor. However, it is very important that the Investigator always assesses causality for every event prior to transmission of the SAE form to the Sponsor. The Investigator may change his/her opinion of causality considering follow-up information, amending the SAE form accordingly. The causality assessment is one of the criteria used when determining regulatory reporting requirements.

#### 11.1.3 ASSESSMENT OF EXPECTEDNESS

A reasonable possibility of a relationship conveys that there are facts, evidence and/or arguments to suggest a causal relationship, rather than a relationship that cannot be ruled out.

- Expected: An adverse reaction, the nature or severity of which is consistent with the applicable Reference Safety Information in the Summary of Product Characteristics for an approved medicinal product
- Unexpected: An adverse reaction, the nature or severity of which is not consistent with information in the relevant source document

#### 11.1.4 FOLLOW-UP OF SAES

After the initial SAE report, the Investigator is required to proactively follow each participant and provide further information to the Sponsor on the participant's condition. All SAEs documented at a previous visit/contact and are designated as ongoing, will be reviewed at subsequent visits/contacts. All SAEs will be followed until resolution, until the condition stabilises, until the event is otherwise explained, or until the participant is lost to follow-up. Once resolved, the adverse event log will be updated. The Investigator will ensure that follow-up includes any supplemental investigations as may be indicated to elucidate the nature and/or causality of the SAE. This may include additional laboratory tests or investigations, histopathological examinations, or consultation with other health care professionals. New or updated

information will be recorded on the originally completed SAE form, with all changes signed and dated by the Investigator. The updated SAE form should be resent to the Sponsor.

#### 11.1.5 POST-STUDY SAES

A post-study SAE is defined as any event that occurs outside the SAE detection period. Investigators are not obligated to actively seek SAEs in former study participants. However, if the Investigator learns of any SAE, including death, at any time after a participants has been discharged from the study, and he/she considers the event reasonably related to the investigational product, the Investigator will promptly notify the Sponsor.

#### 11.1.6 SAES

SAEs that lead to hospitalisation within 90 days of randomisation will be source data for the primary endpoint and will detail cause of hospitalisation to determine if this was related to COPD or not.

### 11.2 ADVERSE EVENT PROCESSING RESPONSIBILITIES

The Trial Statistician will report relevant adverse events to the Data Monitoring Committee.

## 12. ETHICS APPROVAL

This protocol and related documents will be submitted for review to Health Research Authority (HRA), and Research Ethics Committee (REC).

### 12.1 PROTOCOL AMENDMENTS AND VERSION CONTROL OF STUDY DOCUMENTS

The Trial Manager will be responsible for preparing and submitting protocol amendments to the Sponsor and ethics committee/HRA.

TheTrial Manager will be responsible for updating the ISRCTN register subsequent to relevant protocol amendments.

## 13. STATISTICAL METHODS

### 13.1 PRIMARY OUTCOME

1. Time to first all-cause readmission within 90 days of discharge from hospital. The day of discharge will be the 1st day in the countdown to 90-day timepoint

### 13.2 SECONDARY OUTCOMES

- Time to and frequency of COPD-related readmissions at 30 and 90 days
- Days alive and out of hospital at day 90
- Time to and frequency of all COPD exacerbations at days 30 and 90
- Cumulative systemic oral corticosteroids use over 90 days, measured as proportion of period used and number of occasions used
- Cumulative systemic antibiotic use over 90 days, measured as proportion of period used and number of occasions used
- Health care contacts at baseline, days 90 and 180, and 1 year
- All cause readmission at 30 days

- All cause-, cardiovascular- and COPD- related mortality at day 90 and over 12 months
- Quality of life (COPD assessment Test (CAT) score and EQ-5D-5L) at baseline, days 90 and 180, and 1 year
- Incremental cost-effectiveness ratio (ICER, a ratio of the additional cost divided by the additional effectiveness of SRP compared to UC) at days 90 and 180 and 1 year
- Qualitative description of usual care
- Qualitative examination of fidelity to and adaptation of the plan in the intervention arm
- Serious adverse events
- Antimicrobial resistance

## 13.3 SAMPLE SIZE JUSTIFICATION

A sample size of 1400 participants randomised has been chosen to achieve a target of 515 primary outcome events. Population estimates of the 90-day and 30-day all-cause readmission rates of 43% and 23%[42]respectively have been reported previously. In the absence of a minimum clinically important effect size defined for the 90-day all-cause readmisstion primary outcome, we performed a national survey of respiratory COPD secondary care specialists via the British Thoracic Society, with responses from 80 participants. This supported a 20% relative reduction as the minimum required to be considered clinically meaningful. This corresponds to an intervention arm readmission rate of 34.4%. As the 30-day and 90-day rates are not consistent with an exponential time-to-event survival distribution, the log rank test was chosen for the sample size and the primary analysis. With 515 first readmission events, there is 90% power to detect a reduction from 43% to 34.4% in the 90-day reasdmission rate using a two-sided log rank test at the 5% level of significance and 1:1 allocation to the goups. In the absence of withdrawals, 1331 participants would be required. This was inflated to a sample size of 1400 participants randomised, representing a 5% participant withdrawal rate, and this is expected to maintain the target of 515 events. The randomisation is stratified but the primary analysis will use the log rank test, for simplicity and to match the sample size calculation, as the purpose of the stratifiers is predominantly as foundation for subgroup analyses given that the large sample size limits chance confounding effects.

## 13.4 STATISTICAL METHODS FOR PRIMARY AND SECONDARY OUTCOMES

### 13.4.1 STATISTICAL METHODS FOR PRIMARY OUTCOME

The log-rank test will be used to test the null hypothesis of no difference in readmission-free survival distributions between arms at the two-sided 5% significance level. These data will be collected primarily from HES. If HES data is not available, then other sources of data will be used (patient-reported data, SAE forms). These distributions will be described using the Kaplan-Meier plot. The univariate Cox proportional hazards model will be used to estimate the unadjusted hazard ratio with 95% confidence interval. In our previous meta-analysis, comorbidities, previous exacerbations and hospitalisation, and increased length of stay were significant risk factors for 30-day and 90-day all-cause readmission after an index hospitalisation with an exacerbation of COPD. Chance confounding effects are not expected given the planned size of the trial and the number of events. We will however secondarily adjust for the randomisation stratifiers as main effects within the Cox model framework. This model will be extended to explore the consistency of the primary outcome result across categories of the randomisation stratifiers, and other subgroup variables defined in the statistical analysis plan. This will involve including the interaction of a subgroup variable with study arm, Randomised controlled intervention effects within subgroup categories will be estimated with 95% confidence intervals.

We will seek to idenstify an appropriate survival distribution, in order to favilitate the development of predicted probabilities of readmission and to estimate key readmission duration quantiless. The proportionality of hazards assumption will be assessed using recommended methods[26]. The noninformative censoring assumption will be assessed in a sensitivity analysis, where the censoring of the 90-day all-cause first readmission, by a COPD-related death, is dealt with as a composite outcome. Departures from assumptions, and consequently required analysis methods will be desribed in the statistical analysis plan.

Survival analysis methods will be used for the outcome of the number of days alive and out of hospital at day 90I, which may be censored, and for other time-to-event secondary outcomes. Strategies to minimise missing data include obtaining primary outcome dates from more than one source, capturing this in those who move outside the study area, and our PPI group having assessed questionnaire burden. Study dropout, and loss of events, are expected to be at most 5%.

#### 13.4.2 STATISTICAL METHODS FOR SECONDARY OUTCOMES

##### 13.4.2.1 CONTINUOUS OUTCOMES

In secondary continuous outcome analyses, each randomisation stratifier and the baseline of the outcome, will be analysed as a main effect covariate and, if necessary, using the missing indicator method. Each repeated-measures continuous outcome timepoint will be analysed using linear mixed effects models with unstructured correlation structure and with covariates, including arm, interacted with time. This beneficially includes partial responses of the outcome over time because the estimated correlations between the repeated measures act equivalently to impute missing responses applying a “missing at random” assumption given the data included in the model. As nonresponse could instead be “not missing at random”, the impact of this assumption will be investigated according to available collected reasons for withdrawal and missing responses, by means of sensitivity analysis in all randomised participants across a realistic range of values for the intervention effect amongst non-responders. Details of these, and any sensitivity analyses, will be described in the approved statistical analysis plan.

##### 13.4.2.2 BINARY OUTCOMES

Distinct from time-to-event outcomes, binary outcomes will be analysed between groups primarily as a difference in proportions. Methods for obtaining 95% confidence intervals will be reported in the statistical analysis plan.

### 13.5 INTERIM ANALYSES (STATISTICAL)

No formal interim analysis is planned. An internal pilot phase will assess trial parameters but not the between-arm effectiveness measures.The DMC will provide advice to the TSC, who will advise the Sponsor in making the final decision on continuing or stopping the trial.

### 13.6 METHODS FOR PRE-SPECIFIED SUBGROUP ANALYSES

Below are details of two pre-specified sub-group variables:

i) Prior versus no prior severe exacerbations in the last year (excluding the index exacerbation)
ii) >=2 or <2 moderate/severe exacerbations in the last year (excluding the index exacerbation)

The hypothesis is that the first category of each of these subgroup variables is related to worse outcomes, more precisely a higher rate of hospital re-admission. The subgroup analysis will investigate the consistency of the randomised intervention effect on the primary outcome analysis across these subgroup categories.

### 13.7 METHODS TO HANDLE MISSING DATA

Our primary outcome (re-admission within 90 days of discharge from hospital) will be collected from source documentation of SAEs and HES Linkage data which is a robust method of data collection. Missing data from HES Linkage may arise from participants that have not consented for HES linkage to occur. Our experience is that this will be minimal, but to manage this, we will also collect directly from patients this information at 30 and 90 days, using pre-specified questionnaires completed by the local site or central study coordinator at the lead site and SAE forms. For the majority of our secondary outcomes, we will be using HES linkage data, which will minimise missing data. Data will be linked via a third party using NHS number. No NHS numbers will leave the NHS, instead unique study IDs will be used and data will be stored in the Safe Haven at King's College London. Named researchers will have virtual desktop infrastructure (VDI) access to log in and analyse the data as appropriate. For other secondary outcomes, including Health Economic analysis we will be using questionnaires collected over 4 timepoints. For missing EQ-5D index values at baseline, we will use mean imputation to fill in each missing index value independent of the treatment arm. We will follow the same approach for the total and different categories of costs at baseline. For missing EQ-5D index values at all follow up points, we will assume that the data are missing at random (MAR). We will replace the missing observations with a set of imputed values through multiple imputations drawn from posterior predictive distribution given the missing observed data31. For missing cost data at all follow up points, we will impute at the costs level using the same approach outlined for dealing with missing EQ-5D index values at follow up. We have limited questionnaires to the EQ-5D-5L and resource use questionnaire and the COPD assessment tool. These have been selected and prioritised to reduce burden of questionnaires to manage missing data. We have discussed this questionnaire limits with PPI and this was agreed that this design would reduce missing data, whilst not being overburdensome to patients and their carers.

### 13.8 PLANS TO GIVE ACCESS TO THE FULL PROTOCOL AND PARTICIPANT LEVEL-DATA

It is anticipated the full protocol and all results will be available as open access according to the rules of the funding bodies.

## 13.9 HEALTH ECONOMIC ANALYSIS

A cost-utility analysis will be conducted to compare the cost-effectiveness of the self-supported rescue pack intervention at day 90, 180 and one-year. In line with the recommendation of National Institute for Health and Care Excellence (NICE), a healthcare and societal costing perspective will be adopted[34]. The primary outcome of the economic analysis will be total cost per patient, total quality-adjusted life-years (QALYs) per patient, and incremental cost-effectiveness ratio (ICER). Interventions with an ICER less than £20,000-30,000 per QALY are considered cost effective.

**Data collection:** Patients' use of secondary healthcare services will be collected from the trial and the HES database. Patients' use of primary healthcare services, social care services, their productivity losses and their carers' productivity losses will be collected using a resource use questionnaire adapted from a previous UK RCT[35] for patients with COPD at baseline, days 90, 180 and 1 year. For all health and social care services, nationally applicable unit costs will be taken from the annual Personal Social Services Research Unit (PSSRU) compendium. National Health Service reference costs and national tariffs will be used to estimate the cost of inpatient, accident and emergency and day hospital attendances where necessary. Cost of steroid medicines, antipsychotic medications and other drugs will be calculated using daily dose information and the cost of the generic drugs as listed in the British National Formulary (BNF). EQ-5D-5L[36], a validated and widely used generic measure will be used to collect patients' health-related quality of life data. Both the EQ-5D-5L and resource use questionnaire will be administered at baseline, days 90, 180 and 1 year.

**Missing data:** For missing EQ-5D index values at baseline, we will use mean imputation to fill in each missing index value independent of the treatment arm[37]. We will follow the same approach for the total and different categories of costs at baseline. For missing EQ-5D index values at all follow up points, we will assume that the data are missing at random (MAR). We will replace the missing observations with a set of imputed values through multiple imputations drawn from posterior predictive distribution given the missing observed data[38]. For missing cost data at all follow up points, we will impute at the costs level using the same approach outlined for dealing with missing EQ-5D index values at follow up.

**Analysis:** The utility scores derived from EQ-5D will be used to calculate QALY accrued over the follow-up period using area-under-the-curve methods and assuming a linear change between any two adjacent time points. Costs will be calculated using data on the type, number and length of contacts received by each participant. No discounting is needed as the maximum time horizon of the economic analysis is one year. Uncertainty of the results will be quantified by bootstrapping and reported as the cost-effectiveness planes and cost-effectiveness acceptability curve (CEAC)[39]. Cost-effectiveness planes plot the adjusted mean differences in total cost and QALYs based on the bootstrapped results. The CEAC curve will be derived by calculating the proportion of bootstrapped estimates that are cost-effective across a range of willingness-to-pay thresholds, to show the probability that the intervention is cost-effective across different threshold values. A Health Economic Analysis Plan (HEAP) will be developed which will describe their plans in more detail.

# 14. OVERSIGHT AND MONITORING

## 14.1 TRIAL MANAGEMENT GROUP (TMG)

| Title | Name | Role |
|---|---|---|
| KCL Chief Investigator | Mona Bafadhel | Co-Chair |
| UCL Academic co-lead | John Hurst | Co-Chair |
| Senior Statistician | Toby Prevost | Member |
| Trial Statistician | Joana Carvalho Vasconcelos | Member |
| Health Economist | Huajie (Lily) Jin | Member |
| KCTU Trial Manager (UK) | Olena Said | Member |
| KCTU Trial Manager (UK) | Stephen Lisk | Member |
| KCTU Operations Director (UK) | Caroline Murphy | Member |
| KCTU Data Centre Lead (UK) | Joanna Kelly | Member |
| Participant Representative (UK) | Anna Goodman | Observer |

***TABLE 4 TRIAL MANAGEMENT GROUP MEMBERSHIP IN RAPID STUDY***

Members of the TMG are listed in Table 4 above. Changes in individuals filling these roles will not require a protocol update but will be documented in the TMG minutes.

## 14.2 TRIAL STEERING COMMITTEE (TSC)

The TSC will be composed of a majority of independent members. The TSC is an executive committee, reporting to the funder (NIHR) and the sponsor. The TSC is formally appointed by NIHR and members will receive individual letters from NIHR confirming their role. Independent members will be independent of the Sponsor organisations and of any recruiting study sites.

The trial may be prematurely discontinued by the Sponsor, Chief Investigator or Regulatory Authority on the basis of new safety information or for other reasons given by the Data Monitoring Committee / Trial Steering Committee regulatory authority or ethics committee concerned.

If the trial is prematurely discontinued, active participants will be informed, and no further participant data will be collected. The Competent Authority and Research Ethics Committee will be informed within 15 days of the early termination of the trial.

## 14.3 DATA MONITORING COMMITTEE (DMC)

The DMC will be composed of three independent members: a statistician and two clinicians. The DMC is an advisory committee, reporting to the Trial Steering Committee. The DMC is formally appointed by NIHR and

members will receive individual letters from NIHR confirming their role. Members will be independent of the Sponsor organisations and of any recruiting study sites. The DMC will work to the DAMOCLES guidance[39].

### 14.4 MONITORING

The Investigator(s) will permit trial-related monitoring, audits, REC review, and regulatory inspections by providing the Sponsor(s), Regulators and REC direct access to source data and other documents (e.g., participants' case sheets, blood test reports etc.). The routine site monitoring activities will be performed remotely by the Trial Manager.

## 15. MISCELLANEOUS

### 15.1 PLANS FOR INDEPENDENT AUDIT

There are no current plans to commission an independent audit of study conduct.

### 15.2 DISSEMINATION PLANS

The primary and secondary outcomes will be published in a peer reviewed open-source medical journal within 12 months of the end of trial. Recruiting sites will be informed of the results and will be asked to disseminate the findings to participants. Patient groups will be informed of the results for dissemination among their members.

### 15.3 END OF TRIAL

The end of the trial will be defined as database lock.

### 15.4 CONFIDENTIALITY

When consent forms are signed, a copy will be provided to the participant, a copy will be filed in the medical records and the original will be retained in the Investigator Site File. Participant's year of birth and age will be entered into the study database from countries where this is permitted, but no more identifying information will be collected outside the recruiting study site. Within site, an Investigator Site File will be maintained by the site PI. Participants will be fully identifiable within these files.

When the study is complete, a data sharing dataset will be created from the raw data by the study analyst, which will not include any other identifiable data and study PIN will be altered so that individuals are not recognisable from the dataset.

The study will comply with the General Data Protection Regulations (GDPR).

### 15.5 FUNDING

This study has been funded by the NIHR HTA (application NIHR156698).

### 15.6 INSURANCE AND INDEMNITY

This study is co-sponsored by King's College London (KCL) and Guys and St Thomas' NHS Foundation Trust (GSTFT). The co-sponsors will, at all times, maintain adequate insurance for the design, management and conduct of the study: (a) KCL through its' own professional indemnity (Clinical Trials) & no fault compensation policy; and (b) GSTFT through NHS Resolution cover, in respect of any claims arising as a result of negligence by its employees, brought by or on behalf of a study participant.

### 15.7 ARCHIVING

Upon request, KCTU will provide a copy of the final exported dataset to the CI in .csv format and the CI will distribute as appropriate for the purpose of archiving. The CIs will appoint named individuals within the

research team to be responsible for archiving the documents which are, or have been, contained in the trial master file and, access to those documents shall be restricted to those appointed individuals. At the end of the trial, all trial data will be stored and archived in line with Sponsor requirements.

### 15.8 DATA CONTROLLER

Guy's and St Thomas' NHS Foundation Trust (GSTFT) and King's College London (KCL) as co-sponsors of the research study have shared Data Controller responsibilities and agree to comply with the Data Protection Legislation including UK GDPR. The data generated in the process of the study will flow into KCL and no data flow outside of KCL will occur.

Where optional samples have been collected (samples containing no human tissue, cells or DNA), they may be stored and used for further research purposes according to the appropriate research protocols and with relevant material/data transfer agreements in place.

### 15.9 INTELLECTUAL PROPERTY (IP)

There will be no IP generated as a result of the study.

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