**Trial Title: To determine whether administration of almitrine bismesylate can ameliorate hypoxaemia in Covid-19 and augment effectiveness of supplementary oxygen therapy and respiratory support**

**Internal Reference Number / Short title: A**lmitrine **B**ismesylate in **C**ovid-**19** (**ABC-19**)

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**Confidentiality Statement**

This document contains confidential information that must not be disclosed to anyone other than the Sponsor, the Investigator Team, HRA, host organisation, and members of the Research Ethics Committee and Regulatory Authorities unless authorised to do so.

TABLE OF CONTENTS

[1. KEY TRIAL CONTACTS 6](#_Toc41035615)

[2. LAY SUMMARY 7](#_Toc41035616)

[3. SYNOPSIS](#_Toc41035617) 8

[4. ABBREVIATIONS 1](#_Toc41035618)1

[5. BACKGROUND AND RATIONALE 12](#_Toc41035619)

5.1 Overview………………………………………………..…………………………………………………………………………….……12

5.2 Pathophysiology of COVID-19 pneumonia ………………………………………………..…………………………….…13

5.3 Almitrine bismesylate ………………….……………………………………………………………………………………………14

5.3.1 Rationale for use of almitrine in COVID-19 ………………………………………………………………………14

5.3.2 Preclinical/mechanistic data on almitrine …..……………………………………………………………………15

5.3.3 Clinical experience with oral almitrine in patients with COPD …………………………………………16

5.3.4 Clinical experience with intravenous almitrine in patients with ARDS …..…………………………16

5.3.5 Clinical experience with intravenous almitrine in patients with COVID-19 ..………………….…17

5.3.6 Dosing and formulation of almitrine in the current trial……………………………………………………18

5.4 Risk benefit analysis…..………………….…………………………………………………………………………………………….20

5.4.1 Potential benefits of almitrine in COVID-19.………………………………………………………………………20

5.4.2 Potential risks of almitrine in COVID-19…..…..……………………………………………………………………21

5.4.3 Risk mitigation………………………………………………………………………..…………………………………………22

5.4.4 Overall risk benefit balance………………………………………………………………. …..…………………………22

[6. OBJECTIVES AND OUTCOME MEASURES 23](#_Toc41035620)

[7. TRIAL DESIGN 24](#_Toc41035621)

[8. PARTICIPANT IDENTIFICATION 25](#_Toc41035622)

[8.1 Trial Participants 25](#_Toc41035623)

8.2 Inclusion Criteria…………………………………………………………………………………………………………………………..25

[8.3 Exclusion Criteria 27](#_Toc41035624)

[9. TRIAL PROCEDURES (STUDY DESIGN)](#_Toc41035625) 27

[9.1 Recruitment](#_Toc41035626) 27

[9.2 Screening and Eligibility Assessment](#_Toc41035627) 28

[9.3 Informed Consent 29](#_Toc41035628)

9.4 Randomisation……………………………………………………………………………………………..………………………..30

[9.5 Blinding and code-breaking 30](#_Toc41035637)

[9.6 Trial Visits/Data Collection 31](#_Toc41035638)

[9.7](#_Toc41035639) [Sample Handling 33](#_Toc41035640)

9.8 [Early Discontinuation/Withdrawal of Participants…………………………………………………………………..34](#_Toc41035641)

[9.9 Definition of End of Trial 35](#_Toc41035642)

[10 TRIAL INTERVENTIONS 36](#_Toc41035643)

[10.1 Investigational Medicinal Product(s) (IMP) Description 36](#_Toc41035644)

[10.1.1. Blinding of IMPs 37](#_Toc41035645)

[10.1.2. Storage of IMP 37](#_Toc41035646)

[10.1.3. Compliance with Trial Treatment 37](#_Toc41035647)

[10.1.4. Accountability of the Trial Treatment 37](#_Toc41035648)

[10.1.5. Concomitant Medication 37](#_Toc41035649)

[10.1.6. Post-trial Treatment 37](#_Toc41035650)

[10.2 Other Treatments (non-IMPS) 38](#_Toc41035651)

[10.3 Other Interventions](#_Toc41035652) 38

[11 SAFETY REPORTING 3](#_Toc41035653)8

[11.1 Adverse Event Definitions](#_Toc41035654) 38

[11.2 Assessment results outside of normal parameters as AEs and SAEs 39](#_Toc41035655)

[11.3 Assessment of Causality](#_Toc41035656) 39

[11.4 Procedures for Reporting Adverse Events 4](#_Toc41035657)0

[11.5 Reporting Procedures for Serious Adverse Events 41](#_Toc41035658)

[11.6 Reference Safety Information 4](#_Toc41035659)1

11.6.1 Expectedness…………………………………………………………………………………………………..………………….42

[11.7 SUSAR Reporting 42](#_Toc41035660)

[11.8 Development Safety Update Reports 42](#_Toc41035661)

[12 STATISTICS AND ANALYSIS 43](#_Toc41035662)

[12.1 Statistical Analysis Plan (SAP) 4](#_Toc41035663)3

[12.2 Sample Size Determination 4](#_Toc41035664)3

[12.3 Analysis Populations](#_Toc41035665) 45

12.4 Decision Points…………………………………………………………………………………………………………………….45

12.5 Stopping Rules……………………………………………………………………………………………………………………..45

[12.6 The Level of Statistical Significance](#_Toc41035666)……………………………………………………………………………………….45

12.7 Procedures for Accounting for Missed, Unused and Spurious Data………………………………………45

12.8 Procedure for Reporting any Deviations from the Original Statistical Analysis Plan……………..45

12.9 Health Economics Analysis……………………………………………………………………………………………………45

[13 DATA MANAGEMENT AND QUALITY ASSURANCE 45](#_Toc41035668)

[13.1 Source Data 46](#_Toc41035669)

[13.2 Access to Data 46](#_Toc41035670)

[13.3 Data Recording and Record Keeping 46](#_Toc41035671)

[14 QUALITY ASSURANCE PROCEDURES 47](#_Toc41035672)

[14.1 Risk assessment 47](#_Toc41035673)

[14.2 Monitoring 47](#_Toc41035674)

[14.3 Trial committees 47](#_Toc41035675)

14.3.1 Trial Management Group…………………………………………………………………………………………..……….47

14.3.2 Data Safety Monitoring Committee…………………………………………………………………………………..47

14.3.3 Trial Steering Committee ……………………..…………………………………………………………………………..48

[15 PROTOCOL DEVIATIONS 48](#_Toc41035676)

[16 SERIOUS BREACHES 48](#_Toc41035677)

[17 ETHICAL AND REGULATORY CONSIDERATIONS 48](#_Toc41035678)

17.1 Declaration of Helsinki…………………………………………………………………………………………………………….48

17.2 Guidelines for Good Clinical Practice………………………………………………………………………………………49

17.3 Approvals………………………………………………………………………………………………………………………………..49

[17.4 Other Ethical Considerations 49](#_Toc41035679)

17.5 Reporting……………………………………………………………………………………………………………………………….49

[17.6 Transparency in Research 49](#_Toc41035680)

17.7 Participant Confidentiality………………………………………………………………………………………………………49

17.8 Expenses…………………………………………………………………………………………………………………………………50

[18 FINANCE AND INSURANCE 5](#_Toc41035681)0

18.1 Funding………………………………………………………………………………………………………………………………..…50

18.2 Insurance……………………………………………………………………………………………………………..…………………50

[18.3 Contractual arrangements 5](#_Toc41035682)0

[19 PUBLICATION POLICY 50](#_Toc41035683)

[20 DEVELOPMENT OF A NEW PRODUCT/ PROCESS FOR THE GENERATION OF INTELLECTUAL PROPERTY………………………………………………………………………………………………………………………………………………](#_Toc41035684)50

21 ARCHIVING………………………………………………………………………………………………………………………………….51

[22 REFERENCES 51](#_Toc41035685)

[APPENDIX A : SAE REPORTING 56](#_Toc41035686)

APPENDIX B: AMENDMENT HISTORY………………………………………………………………………………………………………57

# KEY TRIAL CONTACTS

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| **Committees** | **Trial Management Group**  Dr Nick Talbot  Professor Keith Dorrington  Professor Peter Robbins  Emma Hedley  Gayahri Kagithala  **Trial Steering Committee**  Dr Claire Craig (Chair)  Dr Nick Talbot  Professor Keith Dorrington  Professor Peter Robbins  Professor Naj Rahman  Professor Ian Pavord  Dr Stephen Gerry  Melissa Dobson  Emma Hedley  **Data Safety Monitoring Committee**  Professor John Stradling (Chair)  Professor Christopher O’Callaghan  Professor Chris Pugh  Independent statistician [TBC] |

# LAY SUMMARY

A major feature of severe COVID-19 infection is a very low level of oxygen in the arterial blood. Normally, blood picks up oxygen as it travels through the lungs by passing close to the gas in the lungs. The problem in COVID-19 is that much of that blood is passing through blood vessels in the lungs without ever coming close to the gas. This is called a ‘shunt flow’, and if this leads to an arterial oxygen that is very low, patients need to be admitted to hospital for respiratory support. This may initially take the form of supplementary oxygen, but intubation and mechanical ventilation in the intensive care unit (ICU) may be required, and in some cases the use of an artificial lung (extracorporal membrane oxygenation, ECMO) might be needed. Unfortunately, there are limitations on the availability of ICU beds, and there are very few specialist facilities for ECMO, and in a pandemic situation these services may not be able to cope with the number of patients who could potentially benefit from such therapy. The idea in this study is to trial an old drug called almitrine that selectively reduces the shunt blood flow through parts of the lung where the oxygen is low, and diverts it instead to regions of the lung where the blood can get close to the gas and the oxygen levels are higher. The result should be to increase the oxygen levels in the arterial blood supplying the tissues of the body. This should reduce the number of patients progressing to ever higher levels of dependency on respiratory support.

# SYNOPSIS

|  |  |
| --- | --- |
| Trial Title | To determine whether administration of almitrine bismesylate can ameliorate hypoxaemia in Covid-19 and augment effectiveness of supplementary oxygen therapy and respiratory support. |
| Trial registration | *TBC* |
| Sponsor | University of Oxford  CTRG, Joint Research Office, 1st Floor, Boundary Brook House, Churchill Drive, Headington, Oxon, OX3 7GB |
| Funder | LifeArc |
| Clinical Phase | Phase II/III |
| Trial Design | Double blind randomized controlled with 1:1 randomisation |
| Trial Participants | Hospitalised patients, 18 years old or above, with a clinically confident or proven diagnosis of Covid-19 who require respiratory support, who have not undergone significant de-escalation of respiratory support (i.e. are not in a recovery phase), and who are willing to adhere to contraceptive advice for two weeks after final dose of IMP. For definitions see section 8.2  Patients will have been recently (within the last 48 hours) established on oxygen therapy, which at the least will be oxygen therapy at a moderate level (> 4 l/min O2 flow to mask or nasal cannulae; FiO2 > 0.3 for Venturi mask), to maintain pulse oximeter saturation, SpO2, in the target range set by the treating clinician. Other higher levels of respiratory support involving non-invasive respiratory support (continuous positive airway pressure (CPAP), high-flow nasal oxygen, or bi-level non-invasive positive pressure ventilation (NIPPV)) and invasive mechanical ventilation via an endotracheal tube can all be included.  In participating centres, participants who at the time of recruitment already have an arterial line in place (as part of routine clinical care) AND for whom the inspired oxygen fraction can be measured, will be eligible to take part in the physiological sub-study. |
| Sample Size | Overall total of 116 participants  (58 IMP, 58 placebo) |
| Planned Trial Period | First Participant In - November 2020  Final 30 day mortality data collection – September 2021 |
| Planned Recruitment period | 5-months |

|  |  |  |  |
| --- | --- | --- | --- |
|  | Objectives | Outcome Measures | Timepoint(s) |
| Primary | To determine whether administration of almitrine bismesylate can ameliorate hypoxaemia in Covid-19 and augment the effectiveness of supplemental oxygen therapy and respiratory support. | Change in level of respiratory support over 7 days of treatment (see section 6 for definition). | Baseline and days 1-7 following almitrine/placebo administration |
| Secondary | To measure the time to de-escalation of respiratory support (if it occurs),  To assess the impact of the oral almitrine on daily circulating almitrine levels.  To assess the impact of almitrine on mortality from COVID-19  **Physiological sub-study:**  To understand the relationship between oral almitrine administration and arterial oxygenation.  To understand the relationship between oral almitrine administration and plasma almitrine levels. | Time to de-escalation of respiratory support (if it occurs).  Daily blood almitrine concentrations.  Mortality at 30 days captured via medical records / phone follow up.  Time profile for change in PaO2/FiO2 and blood almitrine concentration hourly over 4 hours post first administration of almitrine/placebo.  Time profile of blood almitrine concentration hourly over 4 hours post first administration almitrine/placebo | Baseline and days 1-7 after administration of almitrine/placebo.  Baseline and days 1-7 after administration of almitrine/placebo.  30 days  During 4 hours after first administration of almitrine/placebo.  During 4 hours after first administration of almitrine/placebo. |
| Intervention(s)   * IMP(s) * nIMP(s) * Other intervention(s) | Loading oral/via NG tube dose 100 mg almitrine (2 x 50mg capsules) followed by 50 mg almitrine (4 hourly for 7 days).  None  None | | |
| Comparator | Loading oral/via NG tube dose 100 mg matched placebo (2 x 50mg capsules), followed by 50 mg matched placebo 4 hourly for 7 days.  Each placebo capsule contains magnesium stearate. | | |

# ABBREVIATIONS

|  |  |
| --- | --- |
| AE | Adverse event |
| API | Active pharmaceutical ingredient |
| AR | Adverse reaction |
| CFS | Clinical Frailty Score |
| CI | Chief Investigator |
| COVID-19 | Coronarvirus disease 2019 |
| CPAP | Continuous Positive Airway Pressure |
| CRA | Clinical Research Associate (Monitor) |
| CRF | Case Report Form |
| CRO | Contract Research Organisation |
| CT | Clinical Trials |
| CTA | Clinical Trials Authorisation |
| CTRG | Clinical Trials and Research Governance |
| DSMC | Data Safety Monitoring Committee |
| DSUR | Development Safety Update Report |
| ECMO | Extracorporeal Membrane Oxygenation |
| GCP | Good Clinical Practice |
| GP | General Practitioner |
| HPV | Hypoxic Pulmonary Vasoconstriction |
| HRA | Health Research Authority |
| IB | Investigators Brochure |
| ICF | Informed Consent Form |
| ICH | International Conference on Harmonisation |
| ICU | Intensive Care Unit |
| IMP | Investigational Medicinal Product |
| IRB | Independent Review Board |
| MHRA | Medicines and Healthcare products Regulatory Agency |
| NHS | National Health Service |
| NIPPV | Non-invasive Positive Pressure Ventilation |
| PI | Principal Investigator |
| PIL | Participant/ Patient Information Leaflet |
| REC | Research Ethics Committee |
| RSI | Reference Safety Information |
| SAE | Serious Adverse Event |
| SAR | Serious Adverse Reaction |
| SARS-CoV-2 | Severe acute respiratory syndrome coronavirus 2 |
| SDV | Source Data Verification |
| SMPC | Summary of Medicinal Product Characteristics |
| SOP | Standard Operating Procedure |
| SUSAR | Suspected Unexpected Serious Adverse Reactions |
| TMF | Trial Master File |

# BACKGROUND AND RATIONALE

**5.1 Overview/Summary**

Between December 2019 and September 2020, over 37 million cases of coronavirus disease 2019 (COVID-19) were reported worldwide, with over 1 million deaths. Over the same period in the UK, over 143,000 patients were admitted to hospital with COVID-19, and >40,000 patients have died after testing positive for the causative virus, the majority of whom died from COVID-19 pneumonia. Although some new treatments (e.g. dexamethasone, remdesivir) have been shown to be effective in hospitalised patients (Bai et al, 2020), the mortality of moderate-severe disease remains high, and further waves of infection are expected. Additional effective therapies are urgently required.

Coronavirus disease 2019 (COVID-19) pneumonia presents with an unusual clinical picture of severe hypoxia without other features of classical acute respiratory distress syndrome (ARDS). There is growing evidence to suggest that an important and specific feature of COVID-19 is the loss of a protective physiological mechanism called hypoxic pulmonary vasoconstriction (HPV), which normally diverts blood flow away from diseased areas of lung. Loss of this mechanism would explain the unusually severe hypoxaeamia (low blood oxygen levels) that characterises COVID-19, and which often leads to a requirement for supplementary oxygen or other forms of respiratory support.

Almitrine bismesylate is the only licenced drug known to enhance HPV. It was previously licenced for the treatment of chronic obstructive pulmonary disease (COPD) and ARDS. Although its efficacy in these conditions, in which HPV may well be operating normally, are relatively modest, there is a strong rationale for believing that its effects in COVID-19 pneumonia, in which HPV appears to be impaired, would be much greater. This rationale, combined with promising case series data in patients (Losser et al, 2020, Barthelemy et al, 2020, Huette et al, 2020, Cardinale et al, 2020; Caplan et al 2020), has led to numerous calls for prospective clinical trials of this compound in COVID-19 (e.g. Archer et al, 2020; Bendjelid et al, 2020; Caplan et al, 2020).

The current trial will randomise patients with moderate to severe COVID-19 pneumonia to receive one week of oral almitrine bismesylate or placebo. The primary aim is to determine whether almitrine improves blood oxygen levels and reduces the need for respiratory support. It is funded by a major (>£400,000) award from the charity LifeArc, in recognition of the novelty of the therapeutic approach, and the potential for rapid deployment of almitrine for the treatment of COVID-19.

**5.2** **Pathophysiology of COVID-19 pneumonia**

The severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) causes respiratory infection by binding to angiotensin coverting enzyme-2 (ACE2) protein, which is expressed on the surface of the epithelial cells lining the respiratory tract (Wiersinga et al, 2020). In most patients, infection produces relatively mild respiratory symptoms, often accompanied by non-respiratory symptoms including headache, fatigue, myalgia and loss of taste or smell. However, many patients develop a more significant respiratory illness (COVID-19 pneumonia), which is characterised by inflammation in the airways and blood vessels of the lung, leading to cough, shortness of breath and hypoxaemia. In an important subset of patients, this illness requires hospitalisation for respiratory support. Patients may initially receive simple supplementary oxygen, but can progress to require higher levels of respiratory support including continuous positive airway pressure (CPAP), invasive mechanical ventilation or extrapulmonary corporeal membrane oxygenation (ECMO).

In common with clinicians across the world, our experience is that patients with COVID-19 pneumonia and respiratory failure often present with very marked hypoxaemia, with features that are different from other respiratory pathologies. First, it occurs relatively early in the course of the illness, sometimes without a major deterioration in lung compliance or respiratory mechanics (Marini & Gattinoni, 2020). This is distinct form classical ARDS, in which lung compliance is reduced. Second, it is often accompanied by relatively mild perception of breathlessness, leading to the widespread description of ‘happy hypoxia’ in patients with COVID-19 pneumonia (Tobin et al, 2020). Third, it is commonly associated with excessive ‘shunting’ of blood through diseased areas of lung, a problem that is usually prevented by the ability of lung blood vessels to vasoconstrict during hypoxia (‘hypoxic pulmonary vasoconstriction’, HPV), diverting blood flow away from diseased lung to healthy lung elsewhere (Dorrington & Talbot, 2004; Marshall et al, 1994).

These clinical observations have led many leading scientists to conclude that loss of HPV is an important pathophysiological feature of COVID-19 pneumonia. Marini & Gattinoni, for example, have reported that the: “*key issue in this early stage is disrupted vasoregulation, where the pulmonary vasoconstriction that normally occurs in response to hypoxia fails to occur because of an endothelial assault that mismatches perfusion to ventilation and may result in profound hypoxemia*” (Marini & Gattinoni, 2020). There is also emerging pathological and epidemiological evidence in support of this hypothesis. For example, direct infection of endothelial cells lining lung blood vessels (which are known to control the intensity of HPV) has been reported (Varga et al, 2020; Ackermann et al, 2020), and imaging studies have revealed unusually dilated pulmonary arteries, suggestive of a failure of HPV (Lang et al, 2020; Caruso et al, 2020; Santmarina et al. 2020). An important role for blood vessels in the pathophysiology of COVID-19 is also in keeping with the identification of vascular disease (e.g. hypertension) as an important predisposing factor for severe COVID-19 (Grasselli et al. 2020; Wiersinga et al, 2020).

**5.3 Almitrine bimesylate**

5.3.1 Rationale for use of almitrine in COVID-19

Almitrine bismesylate was manufactured and marketed as *Vectarion* by the French pharmaceutical company Servier, and introduced into clinical practice in the early 1980s. It was used for >30 years as an oral formulation for the treatment of hypoxia in patieints with chronic obstructive pulmonary disease (COPD), and it remains licenced in France as an intravenous formulation, for the treatment of hypoxia in patients with severe acute respiratory distress syndrome (ARDS). In both settings, its therapeutic action relies in part upon its ability to selectively enhance HPV, thereby diverting blood away from hypoxic regions of lung and improving arterial oxygenation. Although helpful in a range of respiratory conditions, including COPD and ARDS, we would predict a greater therapeutic effect of enhancing HPV in COVID-19 pneumonia, given the apparent loss of HPV in this setting. Any increase in arterial oxygenation would in turn be expected to reduce the need for supplementary oxygen and other forms respiratory support in COVID-19 pneumonia, including invasive mechanical ventilation, the need for which is associated with adverse outcomes including significant mortality (Grasselli et al, 2020; Wiersinga et al, 2020).

As the only licenced drug known to enhance HPV, we believe that almitrine holds unqiue promise as a therapeutic tool in the management of COVID-19 pneumonia. This view is independently shared by other expert commentators. Archer et al, for example, wrote of almitrine that ‘*its ability to enhance HPV and augment carotid body function could be beneficial in COVID-19 pneumonia*’, and called for this to be studied in the setting of an approved clinical trial (Archer et al, 2020). Similarly, in reviewing two recent case series reporting the use of almitrine in patients with COVID-19 pneumonia, Bendjelid et al suggested that ‘*the key factor that could make almitrine administration of great importance in COVID-19 patients is its ability to avoid intubation and mechanical ventilation*’ (Bendjelid et al, 2020). The potential of almitrine was also recognised by LifeArc and its expert advisory panel, in the award of substantial competitive funding for this trial.

5.3.2 Preclinical/mechanistic data on almitrine

The precise cellular mechanisms of almitrine remain uncertain, but the evidence that it can enhance oxygen sensing in animal studies is longstanding and extensive. This occurs both in the carotid body, leading to the stimulation of breathing when oxygen levels are reduced (e.g. Pequignot et al, 1987, Lopez-Lopez et al, 1998) and in the blood vessels of the lung, leading to enhanced HPV. The latter effect was demonstrated in dogs in 1983 (Romaldini et al, 1983).

Studies in healthy lungs have also confirmed that almitrine enhances HPV in humans. The subtle mismatch of gas and blood flow (V/Q mismatch) present in healthy lungs of volunteers breathing air, for example, was shown by Mélot et al (1989) to be ameliorated by almitrine, and a more striking study was performed by Moutafis et al (2002) on anaesthetized patients receiving one-lung ventilation immediately before having thoracic surgery. In this setting, patients are subjected to an iatrogenic 25% ‘shunt’ flow through the lungs. This was reduced by almitrine to around 10%, representing a marked effect on HPV. In experiments of this kind, involving artificially ventilated patients, the stimulatory effect of almitrine on breathing is eliminated, so the effect of almitrine on HPV is revealed in isolation.

5.3.3 Clinical experience with oral almitrine in patients with COPD

The evidence for oral almitrine being effective in improving V/Q matching accumulated over several decades. In many studies in patients with chronic obstructive pulmonary disease (COPD) almitrine elevated arterial oxygen partial pressure (PaO2) over periods of months (Bakran et al, 1990) or years (Weitzenblum et al, 1991; Bardsley et al, 1991; Górecka et al, 2003). The elevation in PaO2 was out of proportion to the small fall in PaCO2, leading researchers to conclude that the improvement in gas exchange was to a large extent due to enhanced HPV rather than stimulation of breathing.

Important adverse effects of oral almitrine include peripheral neuropathy and weight loss. Specifically, in the 30 years after its licence was awarded, 2304 cases of peripheral neuropathy were reported, of which 93.7% were non-serious, and 795 cases of weight loss were reported, of which 90.8% were non-serious. In 2013, the oral formulation of almitrine was withdrawn from the EU market after a European Medications Agency (EMA) Pharmacovigilance Risk Assessment Committee (PRAC) report examined these adverse events and concluded that, in the modern era of COPD management, the modest clinical efficacy of almitrine did not outweigh the potential for adverse effects (<https://www.ema.europa.eu/en/medicines/human/referrals/almitrine-containing-medicines>). Of note, the mean duration of treatment prior to the onset of symptoms was 11 months for peripheral neuropathy and 5 months for weight loss. These adverse effects therefore seem unlikely during the 7-day administration of almitrine in the current trial, but if they do occur they will be recorded and reported as Adverse Events of Special Interest.

5.3.4 Clinical experience with intravenous almitrine in patients with ARDS

Intravenous almitrine has been used extensively in patients with ARDS being treated with mechanical ventilation, and studies in this setting have shown that almitrine can improve V/Q matching and oxygenation. In 1988, Reyes et al studied nine patients using the multiple inert gas elimination technique (MIGET) during an almitrine infusion lasting 30 minutes. The pulmonary shunt of ~30% was reduced to ~17% during the infusion, returning to a high value by 60 minutes after stopping the infusion. Similarly, brief studies by Prost et al (1991) and Jolliet et al (1997) showed similar results, the latter study noting that almitrine could usefully be combined with prone positioning and nitric oxide inhalation. The longer-term studies available are those by B’chir et al (1998) for up to 60 hours of almitrine infusion, and Esnault et al (2019) who studied patients on ECMO receiving almitrine infusion for up to three days.

The adverse effect profile for intravenous almitrine is summarised in the Summary of Product Characteristics (SmPC) and includes liver dysfunction, lactic acidosis, pulmonary hypertension and dyspnoea. These effects have generally been reported as reversible after stopping drug administration.

5.3.5 Clinical experience with intravenous almitrine in patients with COVID-19

An important consideration in designing a trial of almitrine in COVID-19 is whether there is sufficient residual capacity for HPV in the pulmonary circulation for this to be a viable therapauetic target. One possible reason for suspecting that this may not be the case is the potential for pulmonary vascular effects of other pathways activated by COVID-19. It has been suggested, for example, that changes of ACE2 expression or angiotensin II levels may contribute to pulmonary vascular dysregulation, independent of the effects of hypoxia (e.g. Seltzer, 2020, Santamarina et al, 2020). Alternativelty, redistribution of blood by almitrine may not be possible due to pulmonary emboli or in situ thromboses, which are reported to be common in COVID-19 (Ackerman et al, 2020; Bompard et al 2020; Leonard-Lorant et al 2020).

The issue of whether HPV can be enhanced by almitrine in COVID-19 despite possible contributions from other mechanisms of pulmonary dysregulation has to a large extent been addressed through several case series/case reports in which intravenous almitrine has been used in the routine clinical care of patients with COVID-19 pneumonia (Losser et al, 2020, Barthelemy et al, 2020, Huette et al, 2020, Cardinale et al, 2020; Caplan et al 2020). Of these reports, ~~three~~ four of the five showed that almitrine was effective at improving oxygenation in patients who are intubated and ventilated with severe COVID-19 (Losser et al, 2020, Barthelemy et al, 2020, Huette et al, 2020; Caplan et al 2020). In the fifth report, a very short (30 min) infusion of almitrine had no significant impact on oxygenation (Cardinale et al, 2020).

Of note, no serious adverse events related to almitrine were reported in these case series, and in one case report, a significant fall in pulmonary artery pressure was noted after starting almitrine in a patient with pulmonary hypertension and right ventricular failure secondary to COVID-19 (Huette et al, 2020).

5.3.6 Dosing and formulation of almitrine in the current trial

The effects of intravenous almitrine are the most relevant to patients with COVID-19 pneumonia. We therefore approached Servier to request a supply of this formulation, which is still licenced for clinical use in France. Unfortunately, we were informed that the product was no longer in production, and that no stock of product or Active Pharmaceutical Ingredient was available. Furthermore, Servier had no plans to resume production, and owing to the complexicity of the manufacturing process (in particular the lyophilisation step) the estimated time frame for manufacture of an intravenous formulation (>6 months) would likely prohibit use within the current pandemic.

For these reasons, coupled with the considerable practical advantages of oral medication for hospitalised patients outwith the ICU setting and the well-established pharmacokinetic profile of almitrine (which allows a clear calculation of oral versus intravenous dose equivalence), we elected to manufacture an oral formulation of almitrine for this trial. However, we have adopted an oral dosing strategy designed to mimic the plasma almitrine levels normally achieved with intravenous use.

*Loading dose*: Prior studies (Reyes et al, 1988; Prost et al, 1991; Esnault et al, 2019) used an intravenous infusion of either 0.25 mg/kg or 0.5 mg/kg of almitrine as a test dose in acute respiratory distress syndrome (ARDS), and then measured the response at 1 hr after the start of the infusion. Using the pharmacokinetic model of Stavchansky et al (1989a) and an oral bioavailability of 0.7 (Bromet & Singlas, 1984; Gordon, 1995), Fig. 1A illustrates that an intial 100 mg oral dose of almitrine should result in a very similar plasma level to that obtained with an intravenous test dose of 0.5 mg/kg.

*Ongoing dosing*: Although some prior studies (B’Chir et al, 1998; Esnault et al, 2019) have used higher rates, Servier suggest an infusion rate of 2 – 4 μg/kg/min for the management of severe ARDS. Using the pharmacokinetic model of Stavchansky et al (1989a), Fig. 1B illustrates that an infusion at 2 μg/kg/min fairly rapidly results in plasma levels above those at which a good response in oxygenation was observed with previous test doses and we have therefore selected this dose for use in the current trial. Fig. 1B also illustrates that a 100 mg loading dose of almitrine, followed by 50 mg 4 hourly, results in a plasma profile that reasonably mimics that of an infusion at 2 μg/kg/min. Of note, this is the same dose approved for use over 5 days in an ongoing French clinical trial of intravenous almitrine for the treatment of COVID-19.

*Maximum plasma levels*: In relation to maximum plasma levels, it is of note that even if the oral availability were 100%, simulation shows that the plasma profile remains well below that of Servier’s upper 4 μg/kg/min infusion rate (the profile follows an infusion rate of ~ 3 μg/kg/min). Furthermore, at 1 week, the predicted plasma concentration of almitrine is still below the median measured in COPD patients (~500 ng/ml) who received chronic treatment with almitrine at the lower of two dose regimens (50 mg twice daily - the higher dose regime was 100 mg twice daily; Stavchansky et al, 1989b).

The availability of detailed pharmacokinetic data and experience from several decades of use in human pathophysiological and clinical studies mean that the dose of almitrine associated with biological activity are well established. We have therefore not included multiple arms for dose comparison within this trial.

**A B**



**Fig 1.** Pharmacokinetic simulations for almitrine concentration against time using the model of Stavchansky et al (1989a) and an oral bioavailability of 0.7 (Bromet & Singlas, 1984; Gordon, 1995). Panel A compares an oral dose of 100 mg with an intravenous infusion of 0.5 mg/kg (also shown are values for an infusion of 2 μg/kg/min) over a period of 1 hour. Panel B compares the lower and upper intravenous infusion rates provided by Servier with an oral dosing regimen of 100 mg, followed by 50 mg 4 hourly, for a period of 1 week.

**5.4** **Risk benefit analysis**

5.4.1 Potential benefits of almitrine in COVID-19

The reason for studying the use of almitrine in patients with COVID-19 pneumonia is that it has the potential to reduce both mortality and long term complications.

Despite the availability of some other therapies (e.g. dexamethasone), the management of respiratory failure secondary to COVID-19 pneumonia remains primarily supportive. Such therapy, delivered as supplemental oxygen with or without mechanical ventilation, may allow a particular patient to recover, where they otherwise would not have survived. The maximum form of support available for any particular patient will depend on both on resource availability (e.g. ICU beds, ECMO beds) and an assessment of whether the patient can tolerate higher level treatment (e.g. mechanical ventilation). By augmenting oxygenation at the maximum level of support available to any particular patient, almitrine may reduce mortality.

In addition to any effects at the maximal level of respiratory support, almitrine may also reduce the requirement of patents for higher levels of respiratory support. Here, almitrine has the potential to reduce the short- and long-term complications associated with invasive mechanical ventilation. In the UK, the mortality of patients requiring mechanical ventilation for COVID-19 pneumonia has been high (>40%), and the length of stay in the intensive care unit (ICU) has been protracted (>28 days for 20% of admissions to ICU; Armstrong et al, 2020). The rates of inpatient complications are considerable in this patient group (Wang et al, 2020). Likewise, the rates of adverse events related to ECMO are high (Combes et al, 2020). Longer term adverse effects of critical illness on cognitive and functional status are also well documented, and often relate to prolonged intubation and mechanical ventilation *per se*, rather than the effects of the underlying illness (Rengel et al, 2019). By reducing the likelihood of progression to mechanical ventilation and/or ECMO, almitrine may reduce long term morbidity.

A substantially larger and longer clinical trial would be required to identify effects of almitrine on mortality or long term morbidity in patients with COVID-19. This would not be appropriate without first establishing an effect of almitrine on clinical outcomes in a smaller trial, and the focus of the proposed trial is therefore the effect of almitrine on the use of respiratory support over a seven-day period.

5.4.2 Potential risks of almitrine in COVID-19

Almitrine is an established drug with a known side effect profile that includes pulmonary hypertension, peripheral neuropathy and weight loss.

*Peripheral neuropathy*: As detailed above (section 5.3.3), a sensory neuropathy, predominantly in the lower limbs, has been reported as an adverse effect of long term administration of oral almitrine in patients with COPD (Gherardi et al 1985, Howard 1989). The mean duration of treatment prior to the onset of this effect is reported to be 11 months, and as such we do not expect this adverse effect to occur during this proposed trial. Nevertheless, we will monitor daily for new symptoms of neuropathy during the current trial, in patients for whom are able to answer questions. Where patients are unable to respond to questions, for example because they are sedated and/or mechanically ventilated, this will not be possible, as there is no clinically validated means of monitoring for early peripheral neuropathy. Of note, however, critical illness polyneuropathy is a common complication of ICU admission *per se* in this population (Latronico and Bolton, 2011), and it is possible that by reducing the need for mechanical ventilation, almitrine could reduces the incidence of peripheral neuropathy in patients with COVID-19.

*Weight loss*: As also detailed above (section 5.3.3), oral almitrine has been associated with weight loss. This is also typically seen after many months of treatment (mean duration of therapy prior to onset of symptoms 5 months), and therefore seems unlikely to occur in the proposed seven-day study. Monitoring of weight loss directly in the current study would be complicated by the practical difficulties of weighing patients receiving higher levels of respiratory support, and by the clinical observation that COVID-19 *per se* is associated with substantial weight loss. However, almitrine will only be given to hospitalised patients, and the nutritional status of all participants will therefore be assessed daily by the clinical team. Our approach for monitoring for weight loss will be daily liaison with the clinical team, to assess whether any weight loss is felt to be out of keeping with the severity of the underlying disease process. For patients in ICU, daily nutritional status will typically involve a specialist multi-disciplinary team including expert dieticians and physicians.

*Pulmonary hypertension*: The biological effect of almitrine is to enhance HPV. This has generally been associated with only a mild elevation of pulmonary artery pressure in patients with ARDS (Reyes et al, 1988; Prost et al 1991). Right ventricular dysfunction was recently reported in two patients on ECMO, given doses substantially higher than those recommended by the manufacturer (7.3±4.6 μg/kg/min, compared with the recommended 2-4 μg/kg/min; Esnault et al 2019). However, by alleviating hypoxaemia, itself a potent cause of pulmonary hypertension, almitrine may in some cases be expected to reduce pulmonary artery pressure. There are conflicting reports on the effects of COVID-19 itself on pulmonary haemodynamics, but in one large cohort of patients with moderate-severe COVID-19 outside the ICU, the incidence of pulmonary hypertension (12%) and right ventricular dysfunction (14.5%) was considerably lower than that reported in previous cohorts of patients with ARDS (Pagnesi et al, 2020), and to date, the use of almitrine has been reported in 89 patients with COVID-19, with no serious adverse events, including no reports of pulmonary hypertension or right ventricular dysfunction (Losser et al, 2020, Barthelemy et al, 2020, Huette et al, 2020, Cardinale et al, 2020; Caplan et al 2020). Indeed, in one patient with elevated pulmonary artery pressure and acute cor pulmonale due to COVID-19, almitrine was associated with an improvement in right ventricular function that was attributed in part to improved oxygenation (Heutte et al 2020).

5.4.3 Risk mitigation

In addition to the specific measures above, we are mitigating against adverse effects of almitrine in numerous ways. First, we are excluding patients who are felt to be particularly vulnerable to these effects (e.g. those with elevated pulmonary pressures or right ventricular dysfunction). Second, we are using an oral dose of almitrine equivalent to the lowest therapeutic dose of intravenous almitrine, according to the manufacturer’s recommendation. Third, the duration of our trial (seven days) is much shorter than the duration of therapy previously associated with peripheral neuropathy or weight loss (many months). Fourth, we are nonetheless monitoring daily for the development of these side effects (as detailed in section 9.6), and will only administer IMP to patients in hospital. Fifth, we will report all serious adverse reactions during the trial to an independent data safety monitoring committee with the power to pause or terminate the trial if the side effect burden is felt to be too great. Finally, all SARs will also be reported to the MHRA as SUSARs (see section 11).

5.4.4 Overall risk-benefit balance

In summary, the potential benefits of almitrine in patients with COVID-19 are considerable, and the risks of almitrine in this setting can be mitigated as above. In keeping with this, our proposal trial received strong support from the expert advisory panel of the funders LifeArc (headed by Professor Sir Stephen Holgate), and of note, a similar trial has recently been approved using intravenous almitrine in France.

# OBJECTIVES AND OUTCOME MEASURES

|  |  |  |
| --- | --- | --- |
| Objectives | Outcome Measures | Timepoint(s) |
| **Primary Objective**  To determine whether administration of almitrine bismesylate can ameliorate hypoxaemia in Covid-19 and augment the effectiveness of supplemental oxygen therapy and respiratory support. | \*\*Change in level of respiratory support over 7 days of treatment. Levels from COMET <https://www.comet-initiative.org/assets/downloads/COVID-19%20meta%20COS_Table%201_7th%20July%202020.pdf> | Baseline and days 1-7 following almitrine/placebo administration |
| **Secondary Objectives**  To measure the time to de-escalation of respiratory support (if it occurs).  To assess the impact of the oral almitrine on daily circulating almitrine levels.  To assess the impact of almitrine on mortality from COVID-19.  **Physiological sub-study:**  To understand the relationship between oral almitrine administration and arterial oxygenation.  To understand the relationship between oral almitrine administration and plasma almitrine levels. | Time to de-escalation of respiratory support (if it occurs).  Daily blood almitrine concentration.  Mortality at 30 days captured via medical records / phone follow up.  Time profile for change in PaO2/FiO2 over 4 hours post first administration of almitrine/placebo.  Time profile of blood almitrine concentration over 4 hours post first administration almitrine/placebo. | Baseline and days 1-7 following administration of almitrine/placebo.  Baseline and days 1-7 following administration of almitrine/placebo  30 days  During the 4hrs after first administration of almitrine/placebo  During 4 hours after first administration of almitrine/placebo. |

\*\* Levels of respiratory support

Level 0: No respiratory support

Level 1: Simple inspired oxygen therapy (e.g. via mask, nasal cannulae, Venturi mask)

Level 2: Non-invasive respiratory support involving continuous positive airway pressure (CPAP), high-flow nasal oxygen or bi-level non-invasive positive pressure ventilation (NIPPV)\*,

Level 3: Invasive respiratory support involving intubation and mechanical ventilation\*,

Level 4: Extracorporeal membrane oxygenation (ECMO)\*

Level 5: Dead

\*The target range for oxygenation set by the treating clinician will vary with ward/HDU/ICU/hospital setting. Typically, this would be 94-96% on wards and 90-92% in ICU. The aim is not to constrain clinical judgement in the various settings but to use a randomized trial design in which these differences are not relevant to the treatment (almitrine/placebo) allocated.

# TRIAL DESIGN

The study may be conducted during a public health emergency when there will be enormous pressure on hospital staff. The design has therefore been kept as simple as possible to require the least commitment from staff commensurate with addressing the key objectives.

This study design is a randomised, controlled trial of almitrine administration. The trial will be a study in 116 patients of the level of respiratory support over 7 days of a continuous course of oral almitrine/placebo. The participants will be receiving standard clinical care for COVID-19, and will be requiring respiratory support at a moderate to high level (see section 8.2) at the time of randomisation. Daily blood samples will be taken for lactate, liver function tests, and assays of almitrine and storage of serum/plasma for subsequent measurement of almitrine concentrations.

In sites with the necessary research capacity, there will be an optional physiological nested sub-study in 30 participants of the effect on arterial oxygenation over 4 hours of the first dose of almitrine/placebo. These participants will be receiving respiratory support in a setting in which they have *in situ* an arterial line (making it possible to take hourly arterial blood samples) and also in which the fraction of inspired oxygen will be measurable at the time of each arterial sample. The study design is for the use of almitrine in an oral formulation. The dosage has been calculated to be appropriate for reducing shunt flow in the lungs. It is based on published pharmacokinetics for enteral administration of almitrine as capsules and the details are given in 5.3.6.

# PARTICIPANT IDENTIFICATION

## 8.1 Trial Participants

116 in total (58 IMP, 58 placebo)

**8.2 Inclusion Criteria**

Participant is willing and able to give informed consent for participation in the trial.

* Hospitalised patients
* Male or female, aged 18 and above
* Clinically confident or proven COVID-19 disease\* who require respiratory support\*\* and who have not undergone significant de-escalation of respiratory support\*\*\* (i.e. are not in a recovery phase).
* Female participants of childbearing potential must be willing to use effective contraception for 2 weeks after final dose of IMP. Women will be advised to use a hormonal method, an intrauterine device (IUD) or intrauterine system (IUS), a barrier method or sexual abstinence, where the definition of sexual abstinence is;

- “True abstinence: When this is in line with the preferred and usual lifestyle of the subject.” [Periodic abstinence (e.g., calendar, ovulation, symptothermal, post-ovulation methods), declaration of abstinence for the duration of exposure to IMP, and withdrawal are not acceptable methods of contraception].

\* A clinically confident diagnosis is made where there is either swab positivity for COVID-19, or where the clinical presentation (including any of symptoms, clinical chemistry (e.g. raised D-dimer, raised CRP) and radiology (CXR, CT or ultrasound findings)) is consistent with likely Covid-19 infection. A pre-planned subgroup analysis will compare the primary outcome for those with swab positive and “clinically likely” disease.

\*\* At the time of recruitment, patients will be at least moderate oxygen therapy (>4 l/min O2 flow to mask or nasal cannulae; FiO2 > 0.3 for Venturi mask) to maintain pulse oximeter saturation, SpO2, in the target range set by the treating clinician. Other higher levels of oxygen support (including higher doses of oxygen, non-invasive respiratory support (continuous positive airway pressure (CPAP), high-flow nasal oxygen, or bi-level non-invasive positive pressure ventilation (NIPPV)) and invasive mechanical ventilation via an endotracheal tube can all be included, but patients are excluded if they have received >72 hours of invasive mechanical ventilation during their current illness.

\*\*\* De-escalation of respiratory support is defined as a significant reduction in respiratory support that maintains saturation within the treating physicians’ target range within 24 hours of inclusion to this study. A significant reduction is any change in mode of oxygen delivery (i.e. intubated to non-invasive ventilation, non-invasive ventilation to standard oxygen therapy, or reduction of standard “wall” oxygen of more than 3 litres / min). Changes less than this will not be considered to be significant.

**Additional Inclusion Criteria for the Physiological Sub-Study**

* Arterial line in place for clinical care
* Receiving either non-invasive respiratory support or invasive mechanical ventilation for which the inspired oxygen fraction can be measured.

## 8.3 Exclusion Criteria

* Female participant who is pregnant, lactating or planning pregnancy during the course of the trial(women of childbearing potential as determined by the clinician must have a negative urine pregnancy test)
* Pre-existing significant liver disease or a baseline AST or ALT which is >3x the upper limit of normal.
* A previously established diagnosis of right ventricular dysfunction that is clinically significant in the opinion of the treating physician.
* A previously established diagnosis of significant pulmonary hypertension defined as a resting systolic pulmonary artery pressure of >50 mmHg on right heart catheter or echocardiography.
* Received invasive mechanical ventilation for >72h during current illness, at the time of recruitment into the study
* In the clinicians’ view, expected to survive <24 hours
* Patients who, in the absence of Covid-19, would be unable to give informed consent.
* Hypersensitivity to almitrine
* Hyperlactataemia (lactate >2mM)

# TRIAL PROCEDURES (STUDY DESIGN)

For all participants the level of respiratory support will be assessed over a 7-day period by recording the level of support the patient is receiving daily. Daily blood samples will be taken. For lactate and liver function blood will be sent to the local NHS clinical lab. For assay of almitrine concentration, samples will be taken and these will be stored for later analysis. The daily volume of blood taken for the trial will not exceed 20 ml (other than for those in the physiological substudy, in whom the volume on the first day of the study will not exceed 30 ml).

In the physiological sub-study the effect on arterial oxygenation over 4 hours after the first dose of almitrine/placebo will be assessed using hourly arterial blood gases samples.

**9.1**  **Recruitment**

**Identification of participants:** Potential participants will be identified by the clinicians responsible for the patient’s standard care, they will pass details to the research team for formal eligibility assessment. If the potential participant is able, they will be asked by their routine care clinicians whether they agree to discuss the trial with the research team. If they agree, a member of the research team will then contact the patient.

At participating centres, all eligible participants (until the target number (30) is reached) will be offered entry into the physiological sub-study, which involves additional measurements of oxygenation during the first four hours after the first dose of IMP/placebo.

## 9.2 Screening and Eligibility Assessment

There is no maximum duration between screening and registration / randomisation. Specific screening procedures will not occur outside normal clinical practice – all patients with confirmed or suspected Covid-19 infection admitted to hospital will be potentially eligible for the study. They will first be identified by clinical teams and where possible, dependent upon capacity, approached for their interest in the study prior to eligibility.

Screening information will include all inclusion and exclusion criteria and can be obtained from the current clinical record / electronic patient record / electronic observation management tool. Information on past medical history and concomitant medications will be collected at baseline, as will information on current treatments for Covid-19 including oxygen therapy. If patients are unable to provide details of past medical history at baseline, details will be obtained from the clinical record and confirmed with the patient retrospectively, where possible. Co-enrolment in other clinical trials is permitted in this study (including Urgent Public Health studies), provided that in the view of the local Principal Investigator the intervention in any other clinical trial is not targeting the same physiological process as almitrine (i.e. the pulmonary vascular response to hypoxia). For patients who may be pregnant, a pregnancy test (e.g. urinary beta HCG assay) will be performed during the screening process, after obtaining written informed consent.If the patient has already had a pregnancy test performed clinically during their admission there will be no requirement for a further test.

## 9.3 Informed Consent

Patients capable of giving informed consent will be offered verbal and written information about the study and the opportunity to discuss their participation with a member of the study team. Given the acute nature of the illness and the intervention, it will be acceptable to shorten the usual 24 hours consideration time as long as the investigator is satisfied with patient understanding and the patient is satisfied. The patient will be asked to complete the latest approved version of the consent form. If the patient is capable of giving consent but is unable to read and/or sign the consent form, a witness can sign (in the presence of the patient) to confirm that informed consent was provided.

**Legal representative consent (relative/family member/independent treating physician)**

Should the patient lack capacity to give consent due to the severity of their medical condition (e.g. acute respiratory failure or the need for immediate ventilation), then consent may be obtained from a relative acting as the patient’s legally designated representative.

Where a relative to act as the legally designated representative is not immediately available, randomisation and consequent treatment will proceed with consent provided by a treating clinician (independent of the clinician seeking to enrol the patient) who will act as the legally designated representative.

In this event, the legal representative will complete the consent form, and this will be documented in the patient’s clinical notes.

Those patients who survive and regain capacity during their hospital admission will, be contacted by a member of the research team. That member will explain to the patient that they participated in this study after advice had been sought from the legal representative. Written confirmation will be sought at that time that the patient is willing for the data already collected to be used in the way set out in the patient information sheet (PIS). If the participant does not want any further data to be collected, they will be withdrawn from the study (see section 9.8). This modality of consent is standard in many intensive care studies and has been successfully used in other Covid-19 research (RECOVERY, REC Ref 20/EE/0101).

The participants original consent form(s) will be filed in the medical notes, a copy given to the participant or legal representative and a copy filed in the Investigator site file.

**9.4 Randomisation**

# Randomisation will take place once consent has been obtained, with a view to administering the drug / placebo as soon as possible/practical after consent has been obtained. Randomisation will be 1:1 between active medication and placebo.

# Patients will be randomized 1:1 using minimisation with a random element based on the following factors:

# Current level of respiratory support (three levels - 1. Simple mask/nasal cannula oxygen therapy 2. Non-invasive respiratory support (includes CPAP, NIV and high flow nasal oxygen) 3. Invasive mechanical ventilation).

# Sex (male versus female)

# Clinical Frailty Score (CFS, < / = 3 or >3) (please see <https://www.bgs.org.uk/sites/default/files/content/attachment/2018-07-05/rockwood_cfs.pdf>). For ease, the definition of CFS 3 and 4 are provided here

# CFS3 = People whose medical problems are well controlled, but are not regularly active beyond routine walking

# CFS4 = While not dependent on others for daily help, symptoms limit activities.

* Consented and Eligible for Sub-Study (Yes/No)

# Randomisation will be performed by the PI or appropriately trained delegated members of the site team using Sealed Envelope, a robust and reliable web-based randomisation software package.

# 

# 9.5 Blinding and code-breaking

Participants, treating physicians and the researchers involved in day to day trial management and outcome assessments will be blind to the treatment allocation. The IMP (almitrine/placebo) will be identical in appearance and will be prepared by a commercially licenced manufacturer (see section 10).

If emergency unblinding is necessary, then this will be supplied for a single participant and can be accessed using the online randomisation system. This is 24-hour service access, using the participants’ randomisation number, offering the investigator access to break the blinding codes in the requirement of emergency access. Investigators should refer to the trial specific procedures (TSP) for the emergency unblinding procedure. Non-emergency unblinding can be requested via the randomisation system and will require approval by the Chief Investigator. Unblinding of the intervention is only required if knowledge of the treatment received will materially alter immediate patient treatment, or in the event of a SUSAR.

## 9.6 Trial Visits/Data Collection

Participants will have a daily assessment by a member of the trial team, including the assessments indicated in Table 1, below. In addition to collecting study outcome data, these assessments will where possible screen for known side effects of almitrine, as follows:

*1) Peripheral neuropathy*: All patients who are able to communicate at baseline will be asked about the presence of standard symptoms of peripheral neuropathy, and will undergo a standard monofilament screening test for lower limb sensory neuropathy at that stage. Daily screening therafter will consist of standard screening questions for the development of symptoms, following in those with new symptoms by a repeat monofilament testing.

*2) Weight loss*: It will not be practical to undertake daily weights for many patients in the study, particularly those on higher levels of respiratory support. Therefore each participant’s clinical team will be asked on a daily basis whether they feel that the patient is losing weight in a manner out of keeping with their underlying disease process. In all hospitalised patients, clinical teams will routinely perform a daily review of nutrional status as part of clinical care, which may or may not include weighing the patient. In an ICU setting, this daily review typically involves a multi-disciplinary team including expert dieticians and physicians.

*3) Liver dysfunction and plasma lactate*: daily blood tests will be taken.

Table 1. Schedule for main study.

|  |  |  |  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
|  | Screening | Baseline | Day 1 | Day 2 | Day 3 | Day 4 | Day 5 | Day 6 | Day 7 | Discharge | 30-day  mortality |
| Consent | X |  |  |  |  |  |  |  |  |  |  |
| Age | X |  |  |  |  |  |  |  |  |  |  |
| Sex | X |  |  |  |  |  |  |  |  |  |  |
| BMI | X |  |  |  |  |  |  |  |  |  |  |
| Comorbidities | X |  |  |  |  |  |  |  |  |  |  |
| Date of onset of symptoms | X |  |  |  |  |  |  |  |  |  |  |
| Date of hospitalization | X |  |  |  |  |  |  |  |  |  |  |
| COVID-19 screening bloods | X |  |  |  |  |  |  |  |  |  |  |
| Confirmation of negative pregnancy test (where applicable) | X |  |  |  |  |  |  |  |  |  |  |
| Blood almitrine concentration (for storage) (while an inpatient) |  | X | X | X | X | X | X | X | X |  |  |
| Blood lactate concentration (while an inpatient) | X | X | X | X | X | X | X | X | X |  |  |
| Liver Function tests (while an inpatient) | X | X | X | X | X | X | X | X | X |  |  |
| Four-hourly IMP Administration |  |  | X | X | X | X | X | X | X |  |  |
| Level of Respiratory Support | X | X | X | X | X | X | X | X | X |  |  |
| IMP Compliance |  |  | X | X | X | X | X | X | X |  |  |
| Review of symptoms (including new neuropathy) |  | X | X | X | X | X | X | X | X |  |  |
| Monofilament testing of feet |  | X | X\*\* | X\*\* | X\*\* | X\*\* | X\*\* | X\*\* | X\*\* |  |  |
| Clinical assessment of nutritional status |  | X | X | X | X | X | X | X | X |  |  |
| AE/SAE recording (up to 48hrs post IMP) |  | X | X | X | X | X | X | X | X | X |  |
| Discharge outcome |  |  |  |  |  |  |  |  |  | X |  |
| Contraception Advice\* | X |  |  |  |  |  |  |  |  |  |  |
| Review of notes +/- call to patient |  |  |  |  |  |  |  |  |  |  | X |

\* Participants will be advised to use appropriate contraception for 2 weeks following last dose of trial medication.

# For participants discharged before day 7 they will receive a phone call at day 7 or 48 hours after their final dose, whichever is the longer.

\*\* Monofilament testing will be performed for comparison with baseline when new symptoms suggestive of neuropathy are reported (on direct questioning).

In addition, the following will also be collected (after the first dose of IMP only) for those participants taking part in the sub-study

Table 2. Schedule for sub-study

|  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- |
| **Physiological sub-study** | Baseline | 1hr post IMP | 2hrs post IMP | 3hrs post IMP | 4hrs post IMP |
| Consent | X |  |  |  |  |
| Confirmation of an arterial line in place prior to randomisation | X |  |  |  |  |
| Arterial blood gases (including lactate and inspired partial pressure of oxygen) | X | X | X | X | X |
| Blood almitrine concentration (for storage) (while an inpatient) | X | X | X | X | X |
| Inspired oxygen fraction measurements | X | X | X | X | X |

## 9.7 Sample Handling

In women of childbearing potential, a urine sample will be collected from participants as part of the screening process, for a point of care urinary pregnancy test (β-HCG assay). The sample will be discarded once the result has been documented.

Venous blood tests will be collected once a day from participants in the main study (seven in total). In addition, where not available from routine clinical care, a baseline sample may be taken for liver function and lactate concentrations. Measurement of lactate and liver function tests will be performed by the local NHS clinical laboratory at each site, according to local NHS procedures. Results will be reviewed by local investigators, but will also be available to the local clinical team. Participants taking part in the sub study will provide five extra blood samples (one immediately prior to the first dose of IMP, and four after this dose, at hourly intervals).

In addition, serum and plasma samples will be obtained by centrifugation of whole blood, according to the local safety procedures/regulations at the time of the study, and guided by a Trial Specific Procedure. Samples will be stored in local sites pending transfer to Oxford for trial-specific analyses including almitrine concentration, and also for long term storage under an HTA licence (where written consent for such storage has been given). Transfer of samples will occur in accordance with a TSP/SOP. Samples from patients who have not given consent for long term storage/use in future research will be destroyed within 12 months after the end of the study.

Samples sent to the clinical laboratory at each study site will include participant identifiable information. Samples transferred from study sites to Oxford may also include patient identifiable information (where samples are transferred from the clinical laboratory). Such samples will be transferred securely by a trusted commercial courier, a copy of the corresponding participant consent form will also be transferred, which will be retained in Oxford for as long as the sample is stored. Samples will be de-identified prior to storage in Oxford.

## 9.8 Early Discontinuation/Withdrawal of Participants

During the trial, a participant may choose to discontinue trial treatment at any time. This may happen for several reasons, including but not limited to:

* The occurrence of what the participant perceives as an intolerable adverse event
* Inability to comply with trial procedures
* Participant decision

Participants may choose to stop treatment and/or study assessments at any time, including those who regain capacity after being enrolled into the trial on the basis of consent from a legal representative. This is not necessarily considered to be a withdrawal of consent for follow up, but participants may also withdraw their consent for follow up at any time. In accordance with regulatory guidance, de-identified data that have already been collected and incorporated in the study database will continue to be used (any identifiable data will be destroyed). Similarly, data collected from samples that have already been analysed will remain in the trial database but withdrawing participants can choose to have unused samples destroyed if they wish.

For participants who lack capacity, if their legal representative withdraws consent for treatment or follow-up then these activities will cease, and any unused samples will be disposed of.

In addition, the Investigator may discontinue a participant from the trial treatment at any time if the Investigator considers it necessary for any reason including, but not limited to:

* Pregnancy
* Ineligibility (either arising during the trial or retrospectively having been overlooked at screening)
* Significant protocol deviation
* Significant non-compliance with treatment regimen or trial requirements
* An adverse event which requires discontinuation of the trial medication or results in inability to continue to comply with trial procedures, including:
  + Significant liver dysfunction (AST or ALT >3 x the upper limit of normal)
  + Elevation of plasma lactate concentration to >4 mmol/L
  + Weight loss that is in the view of the treating clinician out of keeping with the severity of the underlying disease process
  + Objective evidence of new peripheral neuropathy (based on monofilament testing)
* Disease progression which requires discontinuation of the trial medication or results in inability to continue to comply with trial procedures

The type of withdrawal and reason for withdrawal (if available) will be recorded in the CRF.

If the participant is withdrawn due to an adverse event, the Investigator will arrange for follow-up visits or telephone calls until the adverse event has resolved or stabilised.

If a participant is withdrawn from treatment due to pregnancy the pregnancy will be followed-up to outcome. See the Safety Reporting section below.

## 9.9 Definition of End of Trial

Final data collection for final participant.

# 10 TRIAL INTERVENTIONS

## 10.1 Investigational Medicinal Product(s) (IMP) Description

The trial treatment is almitrine bimesylate, which is known to enhance ventilation and pulmonary vasoconstriction during hypoxia, and which increases arterial oxygen partial pressure in patients with severe respiratory disease. It is licenced (in intravenous form) in a number of countries, but it is no longer being manufactured and has never been licenced in the United Kingdom. In this trial, we will arrange manufacture of almitrine capsules, which will be administered orally (or via NG tubes, where appropriate) and compared with placebo capsules.

MODEPHARMA will overseethe manufacture of the active and placebo drug product capsules, clinical trials packaging and labelling, final QP release, storage and distribution of the investigational medicinal product (IMPs) from the following companies.

Custom Pharmaceuticals LTD, Unit 2 Fairway Trading Estate, Moulsecoomb Way, Bright, East Sussex, BN4 4PB are responsible for the development and manufacture of Almitrine 50mg and placebo capsules.

Wasdell Packaging Ltd, Units 1,2, 3, 5, 5, 7 and 8 Euro Way Industrial Estate, Swindon, SN5 8TW are responsible forclinical trials packaging, labeling, final QP release and storage.

The active capsules will contain 50mg almitrine bismesylate and the matched placebo capsules will contain a suitable inert backfill.

The investigational products will be packaged in containers and labelled according to current EU Good Manufacturing Practice (GMP) guidelines. The label will fulfill GMP Annex 13 requirements and/or local regulatory requirements.

The active capsules will be placed on an ICH stability program which will run in parallel to the clinical trial.

The IMPs will be shipped directly from the final QP releasing site to the trial sites following site initiations.

Please refer to the Investigational Medicinal Product Dossier (IMPD) for more details about the manufacturing of the active and placebo IMPs

At randomisation participants will be randomised to receive Almitrine bismesylate capsules 2 x 50mgthen 50 mg 4 hourly for 7 days or matched placebo (see 5.3.6 for details of dosing calculations). In the case where patients cannot swallow the capsules, the capsules will be opened, the contents mixed with water and administered via an NG tube (according to local hospital procedures), this is usual practice within the ICU setting.

### 10.1.1. Blinding of IMPs

The IMP/placebo will be blinded to researchers and participants. Packs will be supplied with kit numbers which will inform the randomisation schedule described in section 9.5.

### 10.1.2. Storage of IMP

Once QP released, the IMP will be stored at the manufacturers site until it is shipped to the study sites. All IMP will be stored at 15-25oC. Shipments will be temperature controlled to recruiting sites. Once received at the hospital pharmacies the IMP will be stored at 15-25 oC.

### 10.1.3. Compliance with Trial Treatment

Compliance will be recorded within the participants medical records as standard and within the trial CRF. If a patient is discharged from hospital before the end of the 7-day course of treatment, the medication will be stopped at discharge.

### 10.1.4. Accountability of the Trial Treatment

IMP will be stored by pharmacy at each site. Pharmacy will be responsible for receiving the IMP and initial accountability checks. Each time an IMP is given to a participant there will be an authorised prescription and the pharmacy will dispense the IMP according to their procedures and update the accountability log. Any unused IMP should be returned to the pharmacy for accountability and destruction. In addition, any undispensed IMP will be destroyed at the end of the trial.

### 10.1.5. Concomitant Medication

Based on the SmPC for oral almitrine (now withdrawn, as above), there are no contra-indicated concomitant medications.

### 10.1.6. Post-trial Treatment

No trial treatment will be available post discharge. The treatment is only given for 7 days whilst an in-patient (IMP stopped if discharge occurs before 7 days).

## Other Treatments (non-IMPS)

There are no non-IMPs in this trial design.

## Other Interventions

There are no additional interventions in the trial design.

# SAFETY REPORTING

## Adverse Event Definitions

|  |  |
| --- | --- |
| Adverse Event (AE) | Any untoward medical occurrence in a participant to whom a medicinal product has been administered, including occurrences which are not necessarily caused by or related to that product. |
| Adverse Reaction (AR) | An untoward and unintended response in a participant to an investigational medicinal product which is related to any dose administered to that participant.  The phrase "response to an investigational medicinal product" means that a causal relationship between a trial medication and an AE is at least a reasonable possibility, i.e. the relationship cannot be ruled out.  All cases judged by either the reporting medically qualified professional or the Sponsor as having a reasonable suspected causal relationship to the trial medication qualify as adverse reactions. |
| Serious Adverse Event (SAE) | A serious adverse event is any untoward medical occurrence that:   * results in death * is life-threatening * requires inpatient hospitalisation or prolongation of existing hospitalisation * results in persistent or significant disability/incapacity * consists of a congenital anomaly or birth defect\*.   Other ‘important medical events’ may also be considered a serious adverse event when, based upon appropriate medical judgement, the event may jeopardise the participant and may require medical or surgical intervention to prevent one of the outcomes listed above.  NOTE: The term "life-threatening" in the definition of "serious" refers to an event in which the participant was at risk of death at the time of the event; it does not refer to an event which hypothetically might have caused death if it were more severe.  \*NOTE: Pregnancy is not, an SAE. In the event that a participant or his/her partner becomes pregnant whilst taking part in a clinical trial or during a stage where the foetus could have been exposed to the medicinal product (in the case of the active substance or one of its metabolites having a long half-life) the pregnancy should be followed up by the investigator until delivery for congenital abnormality or birth defect, at which point it would fall within the definition of “serious”. |
| Serious Adverse Reaction (SAR) | An adverse event that is both serious and, in the opinion of the reporting Investigator, believed with reasonable probability to be due to one of the trial treatments, based on the information provided. |
| Suspected Unexpected Serious Adverse Reaction (SUSAR) | A serious adverse reaction, the nature and severity of which is not consistent with the Reference Safety Information for the medicinal product in question set out:   * in the case of a product with a marketing authorisation, in the approved summary of product characteristics (SmPC) for that product * in the case of any other investigational medicinal product, in the approved investigator’s brochure (IB) relating to the trial in question. |

NB: to avoid confusion or misunderstanding of the difference between the terms “serious” and “severe”, the following note of clarification is provided: “Severe” is often used to describe intensity of a specific event, which may be of relatively minor medical significance. “Seriousness” is the regulatory definition supplied above.

## 11.2 Assessment of results outside of normal parameters as AEs and SAEs

Daily liver function tests will be conducted. A significant liver dysfunction is defined as an AST or ALT which is >3x the upper limit of normal. The treating clinicians will have the discretion to withdraw the participant from receiving further treatment/placebo if such a significant dysfunction is found. An elevation of lactate concentration to more than 4 mmol/L will be similarly regarded.

## 11.3 Assessment of Causality

The relationship of each adverse event to the trial medication must be determined by a medically qualified individual according to the following definitions:

**Unrelated** – Where an event is not considered to be related to the IMP / intervention

**Possibly Related** – although a relationship to the IMP / intervention cannot be completely ruled out, the nature of the event, the underlying disease, concomitant medication, or temporal relationship make other explanations possible.

**Probably Related** – the temporal relationship and absence of a more likely explanation suggest the event could be related to the IMP / intervention

**Definitely Related** – the known effects of the IMP, its therapeutic class or based on challenge testing suggests that the IMP / intervention is the most likely cause.

All SAEs labelled possibly, probably, or definitely related will be considered as related to the IMP.

## 11.4 Procedures for Reporting Adverse Events

To reflect the time period in which there is significantly elevated plasma almitrine levels, the safety reporting window is from first dose of IMP until 48 hours after the last dose of IMP administration.

If a patient is discharged from hospital before the end of the 7-day course of treatment, the medication will be stopped at discharge. The patient will then be contacted by phone 7 days after the first dose or 48 hours after the final dose of almitrine, whichever is the longer.

All related AEs (as judged to be related to the IMP by the medically qualified investigator) occurring during the safety window for the trial as defined above that are observed by the Investigator or reported by the participant, will be recorded on the trial CRF. All related AEs will be followed up until resolution or stabilisation.

For all Adverse Reactions, the following information will be reported on the CRF: description, date of onset and end date, severity, assessment of relatedness to trial medication, other suspect drug or device and action taken. The severity of events will be assessed on the following scale as being mild, moderate, or severe.

It will be left to the Investigator’s clinical judgment to decide whether an AE is of sufficient severity to require the participant’s removal from treatment. A participant may also voluntarily withdraw from treatment due to what he or she perceives as an intolerable AE. If either of these occurs, the participant must be given appropriate care under medical supervision until symptoms cease, or the condition becomes stable and will continue to be monitored for safety events until the end of the safety reporting window. For further information on withdrawal see section 9.8.

## 11.5 Reporting Procedures for Serious Adverse Events

Patients with moderate to severe COVID-19, particularly those within the ICU/HDU setting, are at high risk of SAEs related to their underlying disease and/or the expected complications of critical illness. Therefore, only SARs occurring within the safety reporting window and judged by a medically qualified investigator to be related to the IMP will be reported. SARs will be reported on the SAE Reporting Form to the ORTU immediately or within 24 hours of Site Study Team becoming aware of the event being defined as serious.

ORTU will perform an initial check of the report, request any additional information, and ensure it is reviewed by a nominated Medical Reviewer (including Expectedness Assessment). All SAE information must be recorded on an SAE form either by direct entry in the trial database or by completing a hard copy of the form which is scanned and emailed to ORTU respiratorytrialsunit@ouh.nhs.uk Additional and further requested information (follow-up or corrections to the original case) will be detailed on the clinical trial database or by using a new SAE Report Form and scanned/emailed to ORTU.

## 11.6 Reference Safety Information

As we are seeking to mimic the plasma almitrine levels typically observed with intravenous infusion of almitrine, the Reference Safety Information (RSI) for the trial will be the summary of product characteristics (SmPC) for injectable almitrine bismesylate (Vectarion Injectable lyophilizate). Reporting procedures are as per section **11.5** above.

In addition, oral almitrine has been associated with peripheral neuropathy and weight loss. To date, these effects have only been reported with longer term use, compared with the seven-day period of administration in the current trial. No current SmPC exists for oral almitrine, but as discussed in section 5.3.3, a comprehensive review of these side effects was undertaken in 2013 by the Pharmacovigilance Risk Assessment Committee (PRAC) of the European Medicines Agency (EMA; <https://www.ema.europa.eu/en/medicines/human/referrals/almitrine-containing-medicines>). Over 30 years, 2304 cases of peripheral neuropathy (144 of which were serious) and 795 cases of weight loss (73 of which were serious) were reported. The mean duration of treatment prior to the onset of symptoms was 11 months for peripheral neuropathy and 5 months for weight loss. These events will also be considered and reported as SARs.

**11.6.1 Expectedness**

No SARs are considered expected by the sponsor for the purpose of expedited reporting of SUSARs and identification of SUSARs in the “Cumulative summary tabulation of serious adverse reactions” in the DSUR for the IMP.

The expectedness of all SARs will be determined by an ORTU medical reviewer. For assessment of expectedness in the Development Safety Update Report, see section 11.8 below.

## 11.7 SUSAR Reporting

All SUSARs will be reported by ORTU to the relevant MHRA and to the REC and other parties as applicable. For fatal and life-threatening SUSARS, this will be done no later than 7 calendar days after the Sponsor or delegate is first aware of the reaction. Any additional relevant information will be reported within 8 calendar days of the initial report. All other SUSARs will be reported within 15 calendar days.

Treatment codes will be un-blinded for specific participants.

Principal Investigators will be informed of all SUSARs for the relevant IMP for all studies with the same Sponsor, whether or not the event occurred in the current trial.

## 11.8 Development Safety Update Reports

The CI will submit (in addition to the expedited reporting above) DSURs once a year throughout the clinical trial, or on request, to the Competent Authority (MHRA in the UK), Ethics Committee, HRA (where required), Host NHS Trust and Sponsor.

For assessment of SARs in the DSUR, the RSI that was approved at the start of the safety reporting period will be used. When there has been approved changes to the RSI by substantial amendment during the reporting period, the RSI used for the DSUR will differ to the RSI used to assess expectedness at the time of SAR occurrence for SARs which require expedited reporting.

# 12 STATISTICS AND ANALYSIS

## 12.1 Statistical Analysis Plan (SAP)

The statistical aspects of the study are summarised here with details fully described in a formal statistical analysis plan (SAP). The SAP will be finalised before any analysis takes place.

**Description of Statistical Methods**

The primary outcome is the level of respiratory support given over the seven days of treatment. The outcome will be assessed daily using an ordinal scale. The primary analysis of this outcome will be using a mixed effects ordinal logistic regression model. Results will be presented as a common odds ratio (from proportional odds model) over time. The primary time-point will be at 7 days. The model will include treatment arm and minimisation factors as covariates.

The same data will be additionally analysed using time-to-event approaches, by assessing both ‘time-to-escalation’ and ‘time-to-de-escalation’ by assessing changes in respiratory support with respect to the baseline level. These outcomes will be analysed using Cox Proportional Hazards models, again adjusting for treatment arm and minimisation factors. Results will be summarised with a hazard ratio, 95% confidence interval and associated p-value. We will also analyse time to all-cause mortality, and time to discharge, in the same fashion.

The primary outcome of the physiological substudy is whether there has been a clinically significant rise in oxygenation. In any patient, this is defined as an increase in PaO2/FiO2 of 2 kPa or more, which is a binary outcome. These outcomes will be analysed using a logistic regression model including treatment arm and minimisation factors (including baseline level of respiratory support) as covariates. The result will be presented as an adjusted odds ratio, along with a 95% confidence interval and associated p-value. As a sensitivity analysis we will also perform the same analysis without adjusting for baseline characteristics.

## 12.2 Sample Size Determination

The primary analysis of the primary outcome will use a mixed effects ordinal logistic regression model which accounts for the daily measurements on the ordinal scale up to 7 days post randomisation. However, there is little guidance on how best to estimate the sample size for this type of model. We therefore chose to estimate our sample size based on an ordinal logistic regression model which only includes the ordinal scale value at 7 days, knowing that this would be a conservative estimate and that the mixed effects model will be more powerful.

In order to calculate the required sample size we estimate that the proportion of control group patients in the different ordinal scale groups at 7 days will be as follows: 0) 20%; 1) 50%; 2) 20%; 3) 2%; 4) 2%; 5) 6%. These estimates were based upon published data from a recent clinical trial in hospitalised patients with COVID-19. (Cao et al, 2020).

Assuming 80% power and a 5% significance level, the following sample sizes are required (Whitehead 1993), based upon three plausible estimates of the odds ratio (2.5, 2.75, and 3):

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
| **Odds Ratio** | **Sample size required per group** | **Total sample size** | **Total sample size allowing for 5% LTFU** | **Total sample size allowing for 10% LTFU** |
| 2.5 | 67 | 134 | 142 | 149 |
| 2.75 | 55 | 110 | *116* | 122 |
| 3 | 46 | 92 | 97 | 102 |

Based on these numbers we will aim to recruit 116 patients in total.

As mentioned previously, we expect the mixed effects model to be considerably more powerful than the model which only uses the outcome at 7 days, and therefore we hope to be able to detect a much smaller treatment effect. A study which used simulations to estimate the power associated with mixed effects ordinal logistic regression models entitled ‘Sufficient Sample Size and Power in Multilevel Ordinal Logistic Regression Models’ (Ali et al, 2016) found that a 5 day study with a 5 category ordinal outcome would give more than 90% power to detect a difference when there are 50 patients per arm.

One of our key secondary outcome measures is de-escalation by 7 days. In order to detect a change from 50% in the control arm to 75% in the treatment arm (hazard ratio = 2), and assuming 80% power and a 5% significance level, we would require 60 patients per arm.

For the physiological substudy, conservatively assuming that 10% of control patients will show a clinically significant rise in oxygenation by 2 hours (expected to be 0%), and assuming 5% alpha and 80% power, recruiting 10 control and 20 treatment arm patients will allow us to detect a rate of 60% or greater in the treatment arm.

## 12.3 Analysis Populations

All analyses will be carried out the intention-to-treat (ITT) population, i.e. participants will be analysed according to the treatment arm they were assigned.

**12.4 Decision Points**

None

**12.5 Stopping Rules**

Given the relatively small size of the study we do not plan any pre-specified interim analysis and we have no specific early stopping criteria. However, the DSMC will meet regularly during the study and all serious adverse reactions will be brought to the attention of this committee. The DSMC will make the final decision about whether the trial should be stopped early.

## 12.6 The Level of Statistical Significance

## A 5% level of significance will be used for the primary outcomes

**12.7** **Procedure for Accounting for Missing, Unused, and Spurious Data**

The primary statistical analyses will be conducted with linear mixed-effects modelling, which is robust in relation to missing data.

**12.8 Procedures for Reporting any Deviation(s) from the Original Statistical Plan**

Any deviations from the statistical plan will be described in the final report

**12.9 Health Economics Analysis**

There is no planned HE analysis as part of this phase II study.

**13 DATA MANAGEMENT AND QUALITY ASSURANCE**

Personal details for each participant will be held securely at the study site in the form of a Case Report Form (CRF), along with a copy of the consent form and patient identification number. This will be stored in a locked filing cabinet in a room that is locked when unoccupied

De-identified electronic data will be stored (using only the patient identification number) on NHS and/or University computers. All analysis and presentation of results will be undertaken using de-identified data only. Data will be stored for at least 10 years.

The study may be monitored or audited in accordance with the current approved protocol, GCP, relevant regulations and standard operating procedures.

A separate Data Management Plan is stored in the Trial Master File.

# 1 Source Data

These will include hospital records (from which medical history and previous and concurrent medication may be summarised into the CRF), clinical charts, laboratory records. All documents will be stored safely in confidential conditions. On all trial-specific documents, other than the signed consent form, the participant will be referred to by the trial participant number/code, not by name.

## 13.2 Access to Data

Direct access will be granted to authorised representatives from the Sponsor, host institution and the regulatory authorities to permit trial-related monitoring, audits, and inspections.

## Data Recording and Record Keeping

Data will be entered onto a secure, validated, GCP-compliant electronic data management system. All staff performing data entry will be appropriately trained prior to access being granted. Access to the data management system is controlled by individual user accounts, and a full audit trail is kept of all modifications made to data. The study database will be hosted on a secure server with appropriate access controls and disaster recovery procedures. The database will be backed up at least daily.

Standard Operating Procedures (SOPs) and best practice in design of data collection instruments will be followed to ensure quality control. The processes for validation of study data will be detailed in the study RAAMP, data management plan, and other associated documents. The Chief Investigator and/or Principal Investigator will facilitate access to study records for the purpose of monitoring, audits, and regulatory inspections. Participants’ consent to this will be sought at the time of enrolment into the study.

Electronic trial data will be retained through an archiving service as per the sponsoring institute’s policy and regulatory requirements after termination of the trial. ORTU remains the owner of all data stored on the database in relation to this study.

# 14 QUALITY ASSURANCE PROCEDURES

## 14.1 Risk assessment

The trial will be conducted in accordance with the current approved protocol, GCP, relevant regulations and standard operating procedures. A risk assessment and monitoring plan will be prepared before the study opens and will be reviewed as necessary over the course of the trial to reflect significant changes to the protocol or outcomes of monitoring activities.

## 14.2 Monitoring

Appropriate monitoring will be performed according to the trial specific Monitoring Plan by CTRG. Data will be evaluated for compliance with the protocol and accuracy in relation to source documents as these are defined in the trial specific Monitoring Plan. Following written standard operating procedures, the monitors will verify that the clinical trial is conducted, and data are generated, documented, and reported in compliance with the protocol, GCP and the applicable regulatory requirements.

## 14.3 Trial committees

**14.3.1 Trial Management Group**

Trial Management Group will meet regularly throughout the trial to discuss the day to day management of the trial, a TMG charter will be written detailing all the requirements.

**14.3.2 Data Safety Monitoring Committee**

The Independent Data Management Committee will meet monthly throughout the trial and will review safety data. Further details will be specific in the DSMC charter.

**14.3.3 Trial Steering Committee**

# A TSC will be convened to keep oversight of the trial. A charter will be written explaining the role of the TSC and each of its members. All members are required to sign a declaration of their participation. The charter will define how often the committee will meet during the course of the study.

# 

# 15 PROTOCOL DEVIATIONS

A trial related deviation is a departure from the ethically approved trial protocol or other trial document or process (e.g. consent process or IMP administration) or from Good Clinical Practice (GCP) or any applicable regulatory requirements. Any deviations from the protocol will be documented in a protocol deviation form and filed in the trial master file.

# 16 SERIOUS BREACHES

The Medicines for Human Use (Clinical Trials) Regulations contain a requirement for the notification of "serious breaches" to the MHRA within 7 days of the Sponsor becoming aware of the breach.

A serious breach is defined as “A breach of GCP or the trial protocol which is likely to affect to a significant degree –

(a) the safety or physical or mental integrity of the subjects of the trial; or

(b) the scientific value of the trial”.

If a serious breach is suspected the Sponsor must be contacted within 1 working day. In collaboration with the CI the serious breach will be reviewed by the Sponsor and, if appropriate, the Sponsor will report it to the REC committee, Regulatory authority and the relevant NHS host organisation within seven calendar days.

# 17 ETHICAL AND REGULATORY CONSIDERATIONS

**17.1 Declaration of Helsinki**

The Investigator will ensure that this study is conducted in accordance with the principles of the Declaration of Helsinki.

**17.2 Guidelines for Good Clinical Practice**

The Chief Investigator will ensure that this study is conducted in accordance with relevant regulations and with Good Clinical Practice.

**17.3 Approvals**

The protocol, informed consent form, participant information sheet and any proposed advertising material will be submitted to an appropriate REC and host institutions for written approval. The CI will submit and, where necessary, obtain approval from the above parties for all substantial amendments to the original approved documents.

## 17.4 Other Ethical Considerations

None

**17.5 Reporting**

The CI shall submit an Annual Progress report to the REC Committee, host organisation and Sponsor. An End of Study notification and final report will also be submitted to the same parties.

## 17.6 Transparency in Research

Prior to the recruitment of the first participant, the trial will have been registered on a publicly accessible database.

Results will be uploaded to the European Clinical Trial (EudraCT) Database within 12 months of the end of trial declaration (6 months for paediatric trials\*) by the CI or their delegate.

Where the trial has been registered on multiple public platforms, the trial information will be kept up to date during the trial, and the CI or their delegate will upload results to all those public registries within 12 months of the end of the trial declaration.

**17.7 Participant Confidentiality**

The study staff will ensure that the anonymity of the participants is maintained. The participants will be identified only by a participant identification number on all study databases and documents other than the consent form and CRF. All documents will be stored securely and only accessible by study staff and authorised personnel. The study will comply with the General Data Protection Regulation (GDPR) and Data Protection Act 2018, which require data to be de-identified as soon as it is practical to do so.

**17.8 Expenses and Benefits**

Patients will not be reimbursed their involvement with this trial.

# 18 FINANCE AND INSURANCE

**18.1 Funding**

This study is funded by LifeArc.

**18.2 Insurance**

The University has a specialist insurance policy in place which would operate in the event of any participant suffering harm as a result of their involvement in the research (Newline Underwriting Management Ltd, at Lloyd’s of London). NHS indemnity operates in respect of the clinical treatment that is provided.

## 18.3 Contractual arrangements

Appropriate contractual arrangements will be put in place with all third parties.

# 19 PUBLICATION POLICY

The Investigators will be involved in the writing of manuscripts, abstracts, press releases and any other publications arising from the study. Authorship will be determined in accordance with the ICMJE guidelines and other contributors will be acknowledged. Participants who wish to be informed of the study result will be asked to provide an email address, to which a summary of the results will be sent once the study is complete.

# 20 DEVELOPMENT OF A NEW PRODUCT/ PROCESS FOR THE GENERATION OF INTELLECTUAL PROPERTY

Ownership of IP generated by employees of the University vests in the University. The University will ensure appropriate arrangements are in place as regards any new IP arising from the trial.

**21 ARCHIVING**

All trial documentation will be archived at Restore Datacare, ORTU’s archiving facility.

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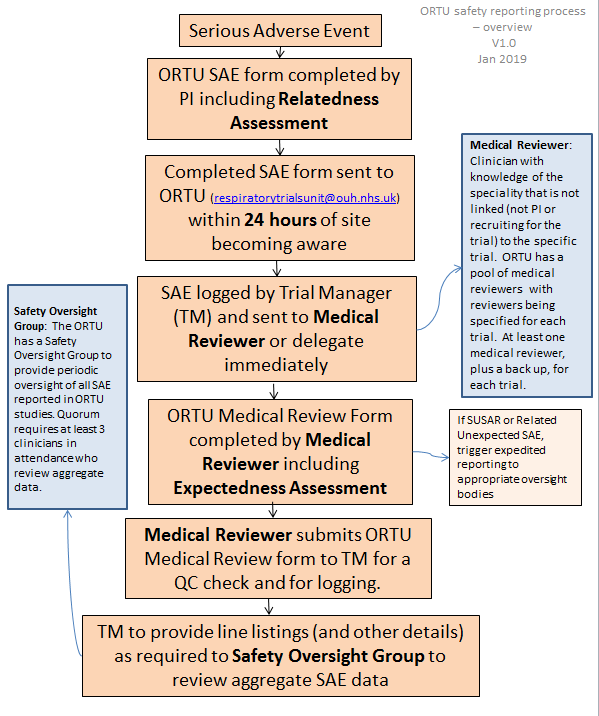
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**APPENDIX A: SAE REPORTING FLOW CHART**



# APPENDIX B: AMENDMENT HISTORY

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| --- | --- | --- | --- | --- |
| **Amendment No.** | **Protocol Version No.** | **Date issued** | **Author(s) of changes** | **Details of Changes made** |
|  |  |  |  |  |

List details of all protocol amendments here whenever a new version of the protocol is produced. This is not necessary prior to initial REC / MHRA / HRA submission.

Protocol amendments must be submitted to the Sponsor for approval prior to submission to the REC committee, HRA (where required) or MHRA.