Imperial College London

Decision support system to evaluate **VENT**ilation in **ARDS (DeVENT)**

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1. Study Management Group

ROLE	NAME	ADDRESS/CONTACT DETAILS
Chief Investigator	**Dr Brijesh Patel** Imperial College London, UK.	**Address**: Royal Brompton & Harefield NHS Foundation Trust (RB&HFT); Royal Brompton Hospital (RBH), Adult ICU; Sydney Street, London SW3 6NP **Email**: brijesh.patel@imperial.ac.uk
Co-Investigators	**Professor Stephen Rees**	**Address:** Aalborg University, Denmark. Aalborg University, Denmark. Fredrik Bajers Vej 5, Aalborg 9229, Denmark **Email:** sr@hst.aau.dk
	Assoc. Prof Dan Karbing	**Address:** Aalborg University, Denmark. Fredrik Bajers Vej 5, Aalborg 9229, Denmark **Email:** dank@hst.aau.dk
	Assoc. Prof Matthieu Jabaudon	**Address:** Université Clermont Auvergne, Rue Montalembert 58, Clermont Ferrand 63003, France **Email:** mjabaudon@chu-clermontferrand.fr
	Dr Raiko Blondonnet	**Address:** Université Clermont Auvergne, Rue Montalembert 58, Clermont Ferrand 63003, France **Email:** rblondonnet@chu-clermontferrand.fr
	Assoc. Prof Peter Schellengowski	**Address:** Medical University of Vienna, Department of Medicine I, Waehringer Guertel 18-20, A-1090 Vienna, Austria **Email:** peter.schellongowski@meduniwien.ac.at
	Professor Thomas Staudinger	**Address:** Medical University of Vienna, Department of Medicine I, Waehringer Guertel 18-20, A-1090 Vienna, Austria **Email:** thomas.staudinger@meduniwien.ac.at
	Professor Masao Takata	**Address:** Imperial College London, UK Chelsea and Westminister Hospital, 369 Fulham Road, Chelsea SW10 9NH **Email:** m.takata@imperial.ac.uk
	Professor Ian Adcock	**Address:** Imperial College London, UK National Heart and Lung Insititue, Guy Scadding building, Dovehouse Street, London, SW3 6LY

		Email: ian.adcock@imperial.ac.uk
	Professor Danny McAuley	**Address:** Centre for Experimental Medicine, Queen's University Belfast, 2017, University Road, Belfast, BT7 1NN, Northern Ireland, United Kingdom. **Email:** d.f.mcauley@qub.ac.uk
Industry partners	**Mr Jorgen Hansen** CEO, Mermaid A/C **Dr Nooshin Barmanis** CMO, Mermaid A/C	**Address:** Hedelund 1, Norresundby 9400, Denmark **Email:** jh@mermaidcare.com **Email**: nb@mermaidcare.com
Clinical Trials Unit	**Imperial Clinical Trials Unit (ICTU)**	**Address:** Imperial Clinical Trials Unit, Stadium House, 68 Wood Lane, London, W12 7RH
Senior Statistician	**Dr Emanuela Falaschetti**	**Address:** Imperial Clinical Trials Unit, Stadium House, 68 Wood Lane, London, W12 7RH **Email:** e.falaschetti@imperial.ac.uk
Study Statistician	**Nicholas Johnson**	**Email:** nicholas.johnson@imperial.ac.uk
Trial Managers/ Research Co-ordinators	**Dr Sharon Mumby**, Imperial College London, UK. **Ms Natalie Dormand**, Royal Brompton & Harefield NHS Foundation Trust	**Address:** National Heart and Lung Insititue, Guy Scadding building, Dovehouse Street, London, SW3 6LY **Email:** s.mumby@imperial.ac.uk **Address**: Royal Brompton & Harefield NHS Foundation Trust (RB&HFT); Royal Brompton Hospital (RBH), Adult ICU; Sydney Street, London SW3 6NP N.Dormand@rbht.nhs.uk deventstudy@imperial.ac.uk
ICTU Operations Manager	**Mary Cross** **Dr. Ana Boshoff**	**Address:** Imperial Clinical Trials Unit, Stadium House, 68 Wood Lane, London, W12 7RH **Email:** m.cross@imperial.ac.uk

For general queries, supply of study documentation, and collection of data, please contact:

Study Manager: Dr Sharon Mumby

Address: National Heart and Lung Institute, Guy Scadding building, Dovehouse Street, London, SW3 6LY

Tel: 0207 594 7955 E-mail: s.mumby@imperial.ac.uk

Fax: N/A Web address: N/A

Clinical Queries: Clinical queries should be directed to DeVENTstudy@imperial.ac.uk who will direct the query to the appropriate person.

Sponsor: Imperial College London is the main research Sponsor for this study. For further information regarding the sponsorship conditions, please contact the Head of Regulatory Compliance at:

Joint Research Compliance Office
Imperial College London and Imperial College Healthcare NHS Trust
Room 215, Level 2, Medical School Building
Norfolk Place
London, W2 1PG
Tel: 0207 594 9459/ 0207 594 1862
http://www3.imperial.ac.uk/clinicalresearchgovernanceoffice

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Address: 1049 Bruxelles/Brussel, Belgique/Belgie
Telephone: +32 22991111

This protocol describes the DeVENT study and provides information about procedures for entering participants. Every care was taken in its drafting, but corrections or amendments may be necessary. These will be circulated to investigators in the study. Problems relating to this study should be referred, in the first instance, to the Chief Investigator.

This study will adhere to the principles outlined in the International Conference on Harmonisation Good Clinical Practice (ICH GCP) and UK Policy Frame Work for Health and Social Care Rresearch guidelines. It will be conducted in compliance with the protocol, the Data Protection Act 2018 and other regulatory requirements as appropriate.

2. Glossary of Abbreviations

Abbreviation / Acronym	Full Wording
ABG	Arterial Blood Gas
AE	Adverse Event
ALPE	Automatic Lung Parameter Estimation
APACHE II	Acute Physiology and Chronic Health Evaluation Score II
APMIC	Anaesthesia, Pain Medicine and Intensive Care
APRV	Airway Pressure Release Ventilation
ARDS	Acute Respiratory Distress Syndrome
BAL	Bronchoalveolar lavage
CI	Chief Investigator
CO_2	Carbon Dioxide
CONSORT	Consolidated Standards of Reporting Trials
COVID-19	Novel Coronavirus Disease 2019
CRF/eCRF	Case Report Form/Electronic Case Report Form
CTU	Clinical Trials Unit
DMEC	Data Monitoring and Ethics Committee
DNAR	Do Not Attempt Resuscitation
ECMO	Extracorporeal Membrane Oxygenation
$ECCO_2R$	ExtraCorporeal Carbon Dioxide Removal
EQ-5D-5L	EuroQoL-5 Dimension Questionnaire (5 level version)
EELV	End-Expiratory lung Volume
$FE'CO_2$	End-tidal CO_2 fraction
FiO_2	Fraction of Inspired Oxygen
GCP	Good Clinical Practice
HADS	Hospital Anxiety and Depression Score
HRA	Health Research Authority
HRQoL	Health Related Quality of Life
ICF	Informed Consent Form
ICH	International Council on Harmonisation
ICTU	Imperial Clinical Trials Unit
ICU	Intensive Care Unit
IRAS	Integrated Research Application System
MHRA	Medicines and Healthcare products Regulatory Agency
MOCA	The Montreal Cognitive Assessment
MREC	Multi-centre Research Ethics Committee
NHS	National Health Service
NIHR	National Institute for Health Research
NIV	Non Invasive Ventilation
NMBD	Neuromuscular Blocking Drugs
$PaCO_2$	Partial Pressure of Carbon Dioxide in arterial blood
PaO_2	Partial Pressure of Oxygen in arterial blood
PBW	Predicted Body Weight
PEEP	Positive End Expiratory Pressure
P/F ratio	PaO_2/FiO_2 ratio
PI	Principal Investigator
PIS	Patient Information Sheet
PPI	Patient and Public Involvement

Pplat	Plateau Pressure
PTSD	Post Traumatic Stress Disorder
PTSS 14	Post Traumatic Stress Syndrome Questionnaire
RALE	Radiographic Assessment of Lung Oedema
REC	Research Ethics Committee
RR	Respiratory Rate
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SAPS II	Simplified Acute Physiology Score
SBT	Spontaneous Breathing Trial
SGRQ	St George's Respiratory Questionnaire
SOFA	Sequential Organ Failure Assessment
SOPs	Standard Operating Procedures
SpO_2	Oxygen Saturation
SRM	Study Reference Manual
TAPSE	Tricuspid Annular Plane Systolic Excursion
TIDIeR	Template for intervention description and replication
TMF	Trial Master File
TMG	Trial Management Group
TSC	Trial Steering Committee
VCO_2	Carbon Dioxide production
VILI	Ventilator Induced Lung Injury
VO_2	Oxygen Consumption
Vt	Tidal Volume

Keywords

ARDS, Mechanical ventilation, Artificial intelligence, Clinical decision support, Biomarkers, Phenotyping, Extra-Corporeal Membrane Oxygenation (ECMO), COVID-19

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4. Study Summary

TITLE	**De**cision support system to evaluate **VENT**ilation in ARDS (DeVENT study)
DESIGN	Multi-centre Randomised Controlled Trial Multi-centre prospective longitudinal observational and exploratory study
AIMS	To evaluate whether an open-loop physiologic model-based decision support system (Beacon Caresystem) reduces driving pressure during mechanical ventilation in patients with ARDS. To perform a cross-sectional study to characterize cohorts of subjects with ARDS in terms of clinical features, physiological measurements and non-invasive measurement of biomarkers (including those in BAL and blood) To perform a longitudinal study in ARDS cohorts, repeating the measurements made during the cross-sectional study. To use the measurements made as part of the cross sectional and longitudinal studies to develop phenotypic handprints for adults with ARDS.
POPULATION	Adult patients diagnosed with the Acute Respiratory Distress Syndrome (ARDS) undergoing mechanical ventilation in ICU.
SAMPLE SIZE	110 patients with ARDS
ELIGIBILITY	Adult patients mechanically ventilated in ICU with ARDS as defined by the 2012 Berlin definition of ARDS.
INCLUSION CRITERIA	• Invasive mechanical ventilation. • A known clinical insult with new worsening respiratory symptoms • Chest radiograph with bilateral infiltrates consistent with evidence of pulmonary oedema but not fully explained by cardiac failure. • Hypoxaemia as defined by PaO_2/FiO_2 of ≤ 300mmHg (or ≤ 40kPa) (pre-ECMO PaO_2/FiO_2 will be used should patient be placed on extracorporeal support).
EXCLUSION CRITERIA	• Age < 18 years old. • The absence of an arterial catheter for blood sampling at study start. • Consent declined. • Over 7 days of mechanical ventilation. • Treatment withdrawal imminent within 24 hours. • DNAR (Do Not Attempt Resuscitation) order in place • Severe chronic respiratory disease requiring domiciliary ventilation and/or home oxygen therapy (except for sleep disordered breathing) • Veno-Arterial ECMO • Head trauma or other conditions where intra-cranial pressure may be elevated and tight regulation of arterial CO_2 level is paramount

DURATION	Total duration of intensive care (all sites) with up to one-year follow-up (in selected sites).
RCT PRIMARY OUTCOME	To assess the average driving pressure delivered by the mechanical ventilator over the period of time when ARDS ventilation management is advised by the Beacon Caresystem as compared to standard care.
RCT SECONDARY OUTCOMES	• Daily average calculated delivered pressure over time, for periods of spontaneous breathing. • Daily average calculated mechanical power over time. • Daily average calculated oxygenation index over time. • Daily average ventilatory ratio over time. • Incidence and duration of proning events and pre- and post- respiratory physiology. • Ventilator free days at 28 days. • Composite endpoint including any cause of death at 28 days and days free of mechanical ventilation within 28 days among survivors • Time from control mode to support mode. • Proportion of breaths dysyncronous with the ventilator • Number of changes in ventilator settings per day. • % of time in control mode ventilation. • % of time in support mode ventilation. • Total duration of mechanical ventilation. • Changes in tidal volume over time. • Changes in Positive End Expiratory Pressure (PEEP) setting over time. • Timing, incidence and duration of neuromuscular blockade • Mortality at 28 days, 6 months and 1 year • Organ failure free days in the first 28 days, assessed using the sequential organ failure assessment (SOFA) score and/or delta SOFA • Ventilation related complications e.g. pneumothorax and/or pneumomediastinum • Device malfunction event rate • Number of times the advice from the Beacon system is followed through the duration of the study.
EXPLORATORY PHYSIOLOGICAL MEASUREMENTS	• Daily average physiological status defined as daily averages of measured values of oxygenation (SpO_2), end-tidal CO_2 fraction ($FE'CO_2$), metabolism (VO_2, VCO_2), ventilation (respiratory rate, tidal volume, anatomical dead space), pulmonary mechanics (mean airway pressure, respiratory system compliance), ventilator settings, PaO_2/FiO_2, shunt fraction, and end-expiratory lung volume over time as continuously measured by the Beacon system.
EXPLORATORY IMAGING, FUNCTIONAL AND LONG TERM MEASUREMENTS	• ICU/hospital/follow-up skeletal/respiratory muscle ultrasound • ICU/hospital/follow-up imaging and lung function including Radiographic Assessment of Lung Oedema (RALE) score over time. • Sf-36 Health Related Quality of life and EQ-5D-5L (patient and carers) • St George's Respiratory Questionnaire (SGRQ) • Cognitive Status Questionnaire e.g. PTSS-14; Hospital Anxiety and Depression Scale (HAD5); The Montreal Cognitive Assessment (MoCA) BLIND

- Return to work rates e.g. W&SAS (patient and carers)
- 6-minute walk test

EXPLORATORY BIOLOGICAL MEASUREMENTS

- Bronchoalveolar lavage, brushings, urine and whole blood (cellular and soluble components) for genomic, transcriptomic, proteomic, lipidomic, and metabolomic handprints.
- Specific analyses may include but are not limited:
    - Systemic inflammatory and cell death responses
    - Pulmonary inflammatory and cell death responses
    - Pulmonary and systemic epithelial and endothelial markers of function and injury
    - Bronchoalveolar lavage, whole blood, and leukocyte microvesicles
    - Cell specific analyses including using flow cytometry, cell culture and immunochemistry.

5. Introduction

Background

The Acute Respiratory Distress Syndrome (ARDS) occurs in response to a variety of insults, such as trauma, pneumonia (including COVID-19) and severe sepsis, which results in alveolar oedema formation secondary to alveolar-capillary barrier dysfunction (1,2). The majority of the lung volume in ARDS shows bilateral dependent consolidation with a small volume (also known as the 'baby' lung due to its smaller volume) being left for actual ventilation. Mechanical ventilation is often required to provide adequate gas exchange and although it is life-saving in this setting, it is also now known to contribute to the morbidity and mortality in the condition. The consolidated lung has blood flow but no ventilation. In contrast, the ventilators delivers high pressures and volumes cause regional over distension of the 'baby' lung. This induces further inflammation and pulmonary oedema in the injured lung known as ventilator-induced lung injury (VILI). Decompartmentalisation of alveolar inflammation can induce systemic inflammation leading to multi-organ failure and death. The Berlin Definition classified patients with ARDS into 3 independent categories – mild, moderate and severe – according to severity of hypoxaemia. Increased severity grade was associated with increased mortality (3). The recent LUNG SAFE study showed that ARDS represented 10.4% of total ICU admissions and was present in 23.4% of all mechanically ventilated patients (4). There is no current therapy for ARDS besides supportive management in intensive care and mortality remains 40%.

A landmark study in 2000, the ARMA trial, showed that a lung protective ventilation strategy using tidal volumes (Vt) of 6 mls/kg (versus 12 mls/kg) and a maximum end-inspiratory Plateau Pressure (Pplat) ≤ 30cmH_2O decreased mortality from 40% to 31% (5). Other adjunctive interventions (which essentially reduce the VILI component of ARDS) have also been shown to improve mortality in ARDS and these include application of neuromuscular blockade to prevent patient-ventilator asynchrony (6); prone position to improve ventilation-perfusion matching within the lung (7); and open-lung ventilation strategies to reduce the opening and closing of lung units which can cause injury known as atelectrauma (8). When patients do not respond to these measures and show refractory hypoxaemia, they often require extra-corporeal support to facilitate oxygenation and prevention of VILI. Extra-corporeal membrane oxygenation (or ECMO), is the attachment of a patient to an artificial membrane lung. In brief, this is performed by placing a large peripheral venous drainage cannula (percutaneously) to drain blood from the patient and this blood is pumped through an artificial membrane lung (outside of the body, hence, extra-corporeal) to oxygenate the blood. This oxygenated blood is subsequently returned to the patient reversing the hypoxaemia and enabling lung rest by reducing the support required from conventional mechanical ventilation. ECMO has recently been shown to improve survival in severe refractory ARDS (9,10). Once patients' lungs repair, ECMO is removed but the patient remains on mechanical ventilation and remains susceptible to VILI and further episodes of lung failure.

The kinetics of progression and resolution of individuals with ARDS remains uncertain. The Berlin definition data showed progression of ARDS over seven days with 29% of patients progressing from mild to moderate and 13% from moderate to severe. A secondary analysis of the Lung SAFE study shows that only 24% of ARDS patients resolved within 48 hours whereas 76% persisted to fulfil ARDS diagnostic Berlin criteria after 48 hours of intitial ARDS diagnosis (11). Those which resolved, had a higher PaO_2/FiO_2 ratio, reduced multi-organ failure (with a lower Sequential Organ Failure Assessment (SOFA) score) and a mortality of 31%. In comparison, those patients which had persistent ARDS at day 2 had an overall hospital mortality of 41% but this mortality increased with severity of disease, from 36% with mild, to 39% with moderate and 57% with severe ARDS. In a multivariate analysis, pneumonia was a risk factor

for persisting ARDS. Other factors measured on day 1 significantly associated with persistent ARDS were lower PaO_2/FiO_2 ratio, higher PIP, higher non-respiratory SOFA score, and higher tidal volume.

Rationale for Study

Clinical impact. The definition of ARDS is based upon changes in PaO_2/FiO_2 ratio which does not differentiate the physiological causality of hypoxaemia i.e. a) insufficient overall ventilation; b) shunting of blood through unventilated vascular beds; c) ventilation/perfusion (VQ) inequality; or d) diffusion limitation. Given that PaO_2/FiO_2 ratio is not independent of FiO_2, that is many combinations of shunt and VQ inequality can produce similar ratios at a given FiO_2. Hence, each patient with ARDS is likely to have differing combinations of hypoxaemic causalities, each of varying impacts dependent on aetiology, progression of disease over time, and severity. Hence, current ARDS therapy is not personalised to the respiratory physiology of the patient in real time. Furthermore, each intervention / manoeuvre / type of ventilatory strategy impacts the various causalities of hypoxaemia to different extents. For instance, patients with severe ARDS may undergo prone position but a positive effect can be due to a combination of the first three causalities (a-c above). Understanding the extent of each causalty and tailoring interventions to individual physiology could enable harmonisation of clinical care and potentially avoid or guide more invasive clinical interventions such as ECMO. ECMO is implemented for two main indications: 1. refractory hypoxaemia, and 2. to facilitate reduction in VILI by ultra-protective ventilation. However, ECMO support although life-saving carries significant risk and is often applied in extremis (with worse outcomes) (9,10). Understanding the underlying physiological cause for hypoxaemia could enable a more personalised, standardised and scientifically applied management process for ARDS.

Case for personalised ventilation. Despite 20 years of clinical trial data showing significant improvements in ARDS mortality through lung protective ventilation via low tidal volume ventilation (5), limitation of inspiratory pressures (12), conservative fluid management (13), open lung ventilation (8), and prone position (7), there remains a gap in the personalised application at the bedside. Needham et al showed 69% of ventilator settings are non-adherent to lung protective ventilation strategies (14). A recent study has shown that unpersonalised recruitment of the lung utilising high pressures leads to harm (15). A machine learning analysis of the data from this study showed that this negative impact was greater in a proportion of patients with consolidated lung with pneumonia (likely to be non-recruitable) (16). In addition, a ventilator driving pressure of $>16cmH_20$ is associated with a significant increase in mortality (12). In this study, Amato and colleagues showed a strong association between driving pressure and survival even though all the ventilator settings that were used were lung-protective. Importantly, the protective effects of higher PEEP were noted only when there were associated decreases in ΔP. Hence, the pressures set on the ventilator should be determined by the diseased lungs' pressure-volume relationship which is often unknown or difficult to determine. Knowledge of extent of recruitable lung could improve the ventilator driving pressure. Hence, personalised management demands the application of mechanical ventilation according to the physiological state of the diseased lung at that time. Hence, there is significant rationale for the development of point-of-care clinical decision support systems which help personalise ventilatory strategy according to the current physiology.

Case for understanding physiological trajectory and response. In parallel, the prospective, longitudinal analysis of physiological trajectory, and physiological responsiveness to adjunctive manoeuvres (e.g. prone position, recruitment manoeuvre, fluid balance) during ARDS is also of key importance. Such a study if embedded in a randomised clinical trial would enable robust data to discover the timely prediction of deterioration and to discern the optimal time for the

application of more invasive interventions such as ECMO. At present there is no clinically validated lung physiology monitor to longitudinally assess breath by breath respiratory physiology in ARDS.

Point-of-care measurement of respiratory physiology. The Beacon Care system (17,18) is a model-based bedside decision support system using mathematical models tuned to the individual patient's physiology to advise on appropriate ventilator settings. Personalised approaches using individual patient description may be particularly advantageous in complex patients, including those who are difficult to mechanically ventilate and wean, in particular ARDS. The core of the system is a set of physiological models including pulmonary gas exchange, acid-base chemistry, lung mechanics, and respiratory drive (18).

The Beacon Caresystem tunes these models to the individual patient such that they describe accurately current measurements of lung physiology to base further clinical decisions and monitor lung health in critical care. Once tuned, the models are used by the system to simulate the effects of changing ventilator settings. The results of these simulations are then used to calculate the clinical benefit of changing ventilator settings by balancing the competing goals of mechanical ventilation. For example, an increased inspiratory volume will reduce an acidosis of the blood while detrimentally increasing lung pressure. Appropriate ventilator settings therefore imply a balance between the clinical preferred value of pH weighted against the preferred value of lung pressure. A number of these balances exist, and the system weighs these, calculating a total score for the patient for any possible ventilation strategy. The system then calculates advice as to changes in ventilator settings so to as improve this score.

The Beacon Care system includes a number of physiological models, each of which have been validated separately, and as part for the Beacon Care system. Mathematical models of pulmonary gas exchange have been shown to describe patients during and following surgery (19)(20)(21), in the ICU (22-24), and have been validated against the experimental reference technique for measuring gas exchange (25)(26). Mathematical models of acid-base have been shown to accurately simulate changes in CO_2, O_2 and strong acid in blood (27), as well as the mixing of blood from different sources (28). Models of respiratory drive have been shown to accurately simulate the effects of changes in support ventilation (29). The Beacon Caresystem has been shown in 4-8 hour periods to reduce levels of inspired oxygen, tidal volume, and pressure support, without detrimental effects (30) and while protecting the respiratory muscles (31).

Beacon Caresystem's functionality as an "open loop" system. This means that the advice provided by the system is presented to the clinician. The ventilator settings are then changed by the clinician, and the patient's physiological response to these changes is automatically used by the system to re-tune the models and repeat the process of generating new advice. Patients with severe lung abnormalities such as acute respiratory distress syndrome (ARDS), which often result in small, stiff lungs, are often in control ventilation mode with little or no spontaneous breathing. For these patients, the clinician often increases PEEP to try to recruit units of the lung which are collapsed. This can be difficult, as increasing PEEP may result in elevated lung pressure and hence an increased the risk of lung injury, incomplete expiration and air trapping, and haemodynamic compromise, especially in those with heart failure. The Beacon Caresystem will advise the clinician to optimise PEEP according the measured physiology at that time and hence, will enable the clinician to determine if the patient is a responder or non-responder to the PEEP manoeuvre. PEEP optimisation should enable best ventilation according to personalised press-volume assessments with potential reductions in driving pressure. Importantly, risk is mitigated by the fact that the clinician can always override the advice given.

Purpose of study. To compare mechanical ventilation in ARDS patients following advice from the Beacon Caresystem to that of standard routine care to investigate whether use of the system results in a better application of PEEP and driving pressure across all severities and phases of ARDS. In addition, the Beacon Caresystem records breath by breath physiological data including pressure, flow and gas waveforms and hence, we will utilise all raw data collected by the Beacon Caresystem to physiologically characterise the progression and resolution phases of ARDS (figure 1). In parallel to the RCT, biological samples will be taken to enable a combined physiological and biological phenotyping of ARDS. Finally, exploratory measures for long term ICU outcomes and radiological indices will also be examined.

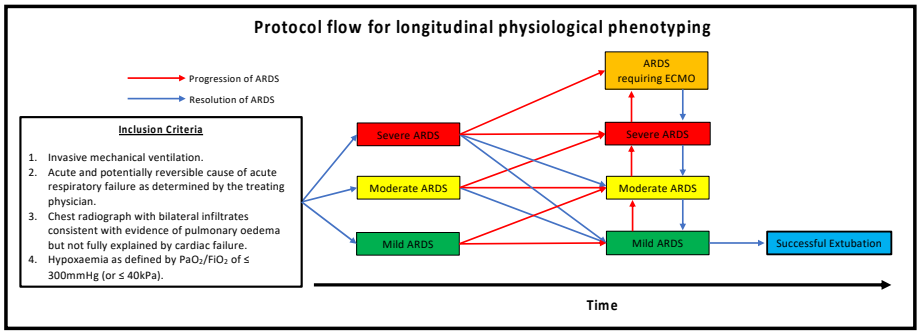


Figure 1: Progression and resolution of ARDS and flow for physiological phenotyping utilising Beacon Caresystem (32).

COVID-19 specific aspects. Critical cares across the world have admitted numerous mechanically ventilated patients with COVID-19 pneumonia. ARDS secondary to COVID-19 has been thought to present with a different respiratory physiology and trajectory as compared to non-COVID19 induced ARDS. We will include a sub-analysis to test the Beacon Caresystem in the ventilatory management of patients specifically admitted with COVID19-induced ARDS but also allow a deeper physiological understanding of COVID19-induced ARDS. In addition, this will include a comparison with those not effected by COVID-19 or mixed, for instance, respiratory compliance, dead space, shunt fraction. Both would enable mapping of trajectory and application of personalised therapies through physiological enrichment. Finally, a beneficial effect from the Beacon Caresystem with its immediate application to facilitate the local and remote management of large numbers of ventilated patients (as seen during this pandemic), could change the outcome of mechanically ventilated patients during the course of this and future pandemics.

6. Study Objectives

RCT Primary objectives and outcome (in all sites):
Objective: To assess the average driving pressure delivered by the mechanical ventilator over the period of time when ARDS ventilation management is advised by the Beacon Caresystem as compared to standard care.

Driving pressure will be measured once a day, using end inspiratory and expiratory pauses. Respiratory pressures at the end of inspiratory (Pplat) and expiratory (PEEP) pauses are know to approximate average pressure in the alveoli at these points, such that their difference, Pplat-

PEEP, is the correct measure of of driving pressure applied to the lungs. This measurement will only be performed in breaths where no spontaneous breathing activity occurs. In addition to the measurement of driving pressure performed twice daily, surrogate measurements of driving pressure will be obtained continuously by approximating Pplat with peak inspiratory pressure (Ppeak), and PEEP with PEEP values set on the ventilator (PEEPset).

Outcome: The overall final analysis will be performed as the average driving pressure per unit time. However, given the nature of ICU management (transfer, disconnection, nebulisation etc), the driving pressure calculation will only involve periods when the Beacon Caresystem is operating and attached successfully to the patient.

RCT Secondary objectives/outcomes (in all sites):
Objective: In mechanically ventilated patients with ARDS we will determine the effects of the Beacon Caresystem compared to standard care on the outcomes listed below.

1. Daily average calculated delivered pressure over time, for periods of spontaneous breathing.
2. Daily average calculated mechanical power over time.
3. Daily average calculated oxygenation index over time.
4. Daily average ventilatory ratio over time (33).
5. Incidence and duration of proning events and pre- and post- respiratory physiology.
6. Ventilator free days at 28 days.
7. Composite endpoint including any cause of death at 28 days and days free of mechanical ventilation within 28 days among survivors
8. Time from control mode to support mode.
9. Proportion of breaths dysyncronous with the ventilator.
10. Number of changes in ventilator settings per day.
11. % of time in control mode ventilation.
12. % of time in support mode ventilation.
13. Total duration of mechanical ventilation.
14. Changes in tidal volume over time.
15. Changes in PEEP setting over time.
16. Timing, incidence and duration of neuromuscular blockade
17. Mortality at 28 days, 6 months and 1 year
18. Organ failure free days in the first 28 days, assessed using the sequential organ failure assessment (SOFA) score and/or delta SOFA
19. Ventilation related complications e.g. pneumothorax and/or pneumomediastinum
20. Device malfunction event rate
21. Device related adverse event rate
22. Number of times the advice from the Beacon system is followed through the duration of the study.
23. Daily Radiographic Assessment of Lung Oedema (RALES score over time).

Exploratory outcome measures (in sites which have local ethical approval):

See appendix 3 for details.

7. Study Description

As illustrated in the consort diagram, figure 2, this is a 2 year multi-centre international randomised, controlled, allocation concealed, open, pragmatic clinical trial which will enrol 110 patients with ARDS (according to Berlin definition) with a PaO_2/FiO_2 of ≤ 300mmHg (or ≤ 40kPa). Patients will be randomised to either have the Beacon Caresystem attached with advice

activated (N=55) or standard care with the Beacon Caresystem attached with advice inactive (N=55). The study will also use the Beacon Caresystem to longitudinally physiologically phenotype patients with ARDS.

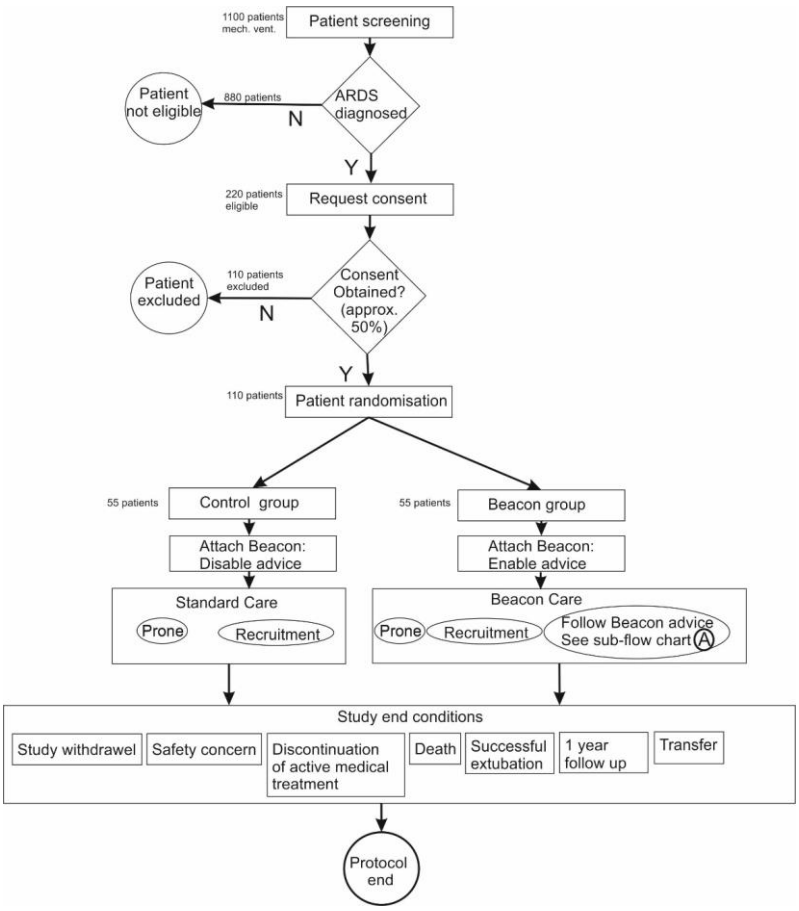


Figure 2 – Consort diagram. For the Beacon advice sub-flow chart see Figure 3.

8. Trial Methods

Pre-registration evaluations
Patients will only be assessed on the inclusion and exclusion criteria detailed below. This will require a history and examination. An arterial blood gas (ABG) sample and chest x-ray will be needed but would be collected as part of routine clinical care.

Inclusion Criteria

- Invasive mechanical ventilation.

- A known clinical insult with new worsening of respiratory symptoms
- Chest radiograph with bilateral infiltrates consistent with evidence of pulmonary oedema but not fully explained by cardiac failure.
- Hypoxaemia as defined by PaO_2/FiO_2 of ≤ 300mmHg (or ≤ 40kPa) (pre-ECMO PaO_2/FiO_2 will be used should patient be placed on extracorporeal support).

Exclusion Criteria

- Age < 18 years old.
- The absence of an arterial catheter for blood sampling at study start.
- Consent declined.
- Over 7 days of mechanical ventilation.
- Treatment withdrawal imminent within 24 hours.
- DNAR (Do Not Attempt Resuscitation) order in place
- Severe chronic respiratory disease requiring domiciliary ventilation and/or home oxygen therapy (except for sleep disordered breathing)
- Veno-Arterial ECMO
- Head trauma or other conditions where intra-cranial pressure may be elevated and tight regulation of arterial CO_2 level is paramount

Patients are potentially eligible for co-enrolment in other studies, this will be decided on a case by case basis in keeping with UK guidelines for critical care research. Imperial Clinical Trials Unit (ICTU) should be informed if co-enrolment is being considered. Co-enrolment with any studies should be documented in the CRF alongside the study identifiers.

Withdrawal criteria

Each participant has the right to withdraw study at any time. In addition, the investigator may discontinue a participant from the study at any time if the investigator considers it necessary for any reason including:

- Ineligibility (either arising during the study or retrospective having been overlooked at screening)
- Significant protocol deviation
- Significant non-compliance with treatment regimen or study requirements
- An adverse event which results in inability to continue to comply with study procedures
- Disease progression which results in inability to continue to comply with study procedures
- Consent withdrawn

However, to maintain integrity of the randomized trial, all information collected up to that time will still be used and analyzed as part of the study.

The reason for withdrawal will be recorded in the eCRF and medical records.

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 stabilized.

9. Study Interventions

Intervention Description

Table 1: Trial intervention in "TIDieR" format

TIDieR item number	Item descriptor	Item
1	Brief name	Beacon Caresystem
2	Why	Beacon Caresystem enables improved ventilation and closer monitoring of respiratory failure
3	What materials	Beacon Caresystem and consumables
4	What procedures	The Beacon Caresystem will be attached to each arm of the study with advice being enabled in the intervention arm and disbled in the standard care arm.
5	Who provides	An appropriately trained clinician/nurse/respiratory therapist with the required competencies to understand the Beacon Caresystem.
6	How	Continuous bedside care.
7	Where	Participating adult ICUs.
8	When and how much	Commence within 7 days of diagnosis of ARDS until the patient is extubated from mechanical ventilation.
9	Tailoring	The device is used until the patient is extubated from mechanical ventilation or is transferred to another centre (outside of trial). The duration of this may vary between patients.
10	How well	The utilisation of the Beacon Caresystem advice will be measured and also the differences in ventilation parameters.

The system will be attached to all eligible patients but depending on the randomisation will be started in either "control group" mode, with ventilator advice deactivated, or "intervention group" mode with ventilator advice activated. The study manual will provide detailed information regarding the attachment, set up, initiation and management of the Beacon Caresystem device. Software updates for the device will be performed as new software becomes available. Of note, these updates are not a change in the algorithm which decides on advice.

All aspects of intensive care and disease therapies will be according to standard critical care guidelines to that centre and country. The Beacon Caresystem will be attached to the patient on screening. When the Beacon Caresystem presents an advice, it can be one of five types (see figure 3):

Arterial Blood Gas / Automatic Lung Parameter Estimation: Beacon advises on the need for arterial blood gas (ABG) or the need to measure pulmonary gas exchange. Beacon continuously monitors whether the physiological models of the system are able to describe current measurements. If not, the system advises the user to either take an ABG or to measure pulmonary gas exchange in a procedure known as the automatic lung parameter estimation (ALPE) procedure. ALPE consists of two changes in inspired oxygen fraction (FiO_2) and return to baseline, a procedure which is guided by the system and takes approximately 5-10 min. These measurements are expected to be performed by the attending nurse. Care wil be taken in perfoming this procedure to allow for an increase in FiO_2 of 20% or greater, necessary for stable estimation of End-Expiratory lung Volume (EELV). Two to three minutes after the system is first started the system will always advise on taking an ABG. ABG values are entered manually into the system. The bedside caregiver can enter an ABG or initiate an ALPE at any time. Following

measurement, the flow returns to point A at the start of the flow. As described above, ALPE measurements will be part of prone and recruitment manoeuvres.

Ventilator advice: When Beacon advises on changing ventilator settings these are modified and the flow returns to point A at the start of the flow.

Bounds advice: The Beacon system's advice can be constrained so as to only recommend changes in ventilator settings within clinically defined bounds. These bounds will be set by the attending physician during the ward round. For instance, particular attention can be paid to the bounds associated with the setting of PEEP in patients with cardiogenic shock. In rare cases, ventilator advice from Beacon may be outside the clinically defined advice bounds of the system, and Beacon will notify the user accordingly. In this case the nurse confers with the attending physician to confirm that it is acceptable to change the bounds. If so, the bounds are changed and the flow returns to point A at the start of the flow. If it is not acceptable to change bounds the nurse and attending physician will agree on a time period to wait before again consulting Beacon advice to change bounds.

Mode/Anaesthesia advice: On occasion, during the management of the individual patient, it will be necessary to change the mode of ventilation between control mode, where the patient has little spontaneous breathing activity, and support mode, where the patient triggers the start of breaths spontaneously and is supported by the ventilator. When the patient is ventilated in a controlled ventilation mode, Beacon monitors the breathing efforts of the patient, and when measured minute ventilation or respiratory frequency differ significantly from ventilator settings, the system indicates to the user that it may be advisable to change to support ventilation mode. When the patient is ventilated in a support ventilation mode, Beacon calculates arterial pH value, and when this is below 7.25 the system indicates to the user that it may be advisable to change to control ventilation mode, or that the patient may require reduction of anaesthesia. As changing mode or anaesthesia depends not only on mechanical ventilation but also on other clinical factors, the attending nurse confers with the attending clinician to confirm that a mode change is advisable. If so, the mode is changed and the flow returns to point A at the start of the flow. If it is not acceptable to change mode the nurse and attending physician will agree on a time period to wait before again consulting Beacon advice to change mode/anaesthesia.

Spontaneous breathing test (SBT) advice: At the end of successful ventilator management it is necessary to extubate the patient. Beacon monitors the level of support provided to the patient and the rapid shallow breathing index, and when these have reached defined limits (as preset by the physician) it advises the user that an SBT has been passed. As the decision to extubate depends on many factors other than mechanical ventilation, the Beacon system provides a report illustrating the results of the SBT and a checklist of other clinical extubation criteria. The nurse completes the checklist and if all criteria are passed confers with the attending physician as to whether extubation is agreed. If so, "extubation agreed" is noted in the CRF and the protocol returns to the main protocol flow. If it is not acceptable to extubate the nurse and attending physician will agree on a time period to wait before again consulting Beacon advice to change mode/anaesthesia.

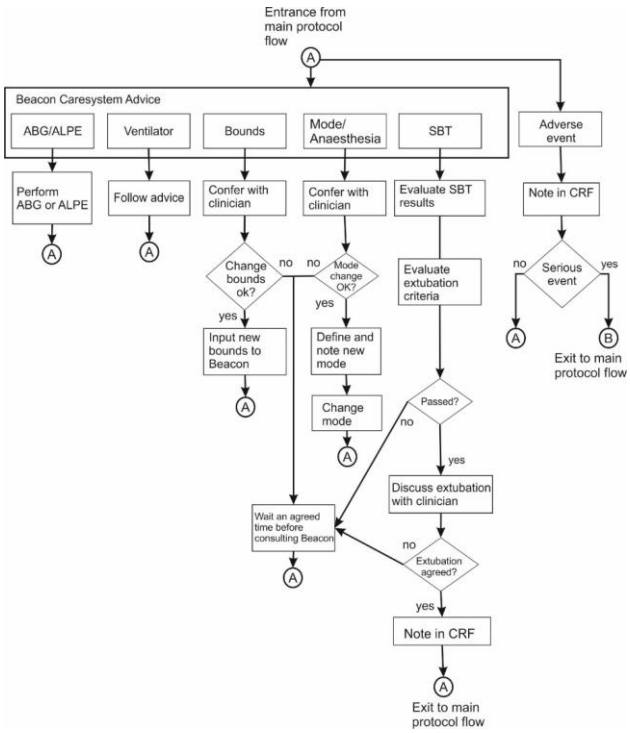


Figure 3 – Beacon advice sub-flow chart.

Intervention Group

Once enrolled into the study and randomized to intervention, the Beacon will provide advice and parameters such as changes in ventilation, shunt fraction, end-expiratory lung volume (EELV) etc to the treating clinician. Should the patient go onto a mode not supported by the Beacon Caresystem (e.g. Airway Pressure Release Ventilation (APRV)) or onto ECMO, the Beacon Caresystem advice will be paused. Once a supported mode is re-established the Beacon advice will be activated. The Beacon will remain on the patient for as long as the patient stays in the study centre, is successfully extubated (i.e. not requiring non-invasive ventilation or nasal high flow oxygenation for >24 hours), attains trachemask for >24 hours, or passes away.

In addition to when the Beacon provides ventilatory advice, standard clinical procedure will be performed either to place the patient in prone position, or perform recruitment manoeuvres (figure 4). For each of these procedures, the automatic lung parameter estimation (ALPE) procedure will be performed prior to, during and subsequent to the start and end of the procedure (figure 4). However, due the nature of ICU processes in some centres looking after COVID-19 patients, this may not be possible. The definition of an ALPE procedure is described below. For change in position to prone or supine, an ALPE will be peformed not more that 30 minutes prior to position change and 30 to 60 minutes subsequent, for patients both on intervention and control arms. At both these time points inspiratory and expiratory pauses will also be performed so as to determine accurate driving pressure before and after the manoeuvre, for both control

and intervention arms. During periods of prone or supine will not incur extra ALPE measurements unless requested by the system for patients on the intervention arm of the protocol. For recruitment manouevres, an ALPE will be peformed not more that 30 minutes prior to and 30 to 60 minutes following the end of the recruitment manoeuvre. As recruitment manoeuvres can be performed by a variety of techniques clinical judgement will be used to assess the end of a manoeuvre, but with this period defined to incorporate either incremental or decremental PEEP changes. During the period of recruitment, including PEEP adjustment, the protocol will not incur extra ALPE measurements unless requested by the system on the intervention arm alone. Several Beacon screens will be used to monitor patient changes caused by these manoeuvres, available only in the intervention arm, as illustrated by figures A1-A3 in appendix 1.

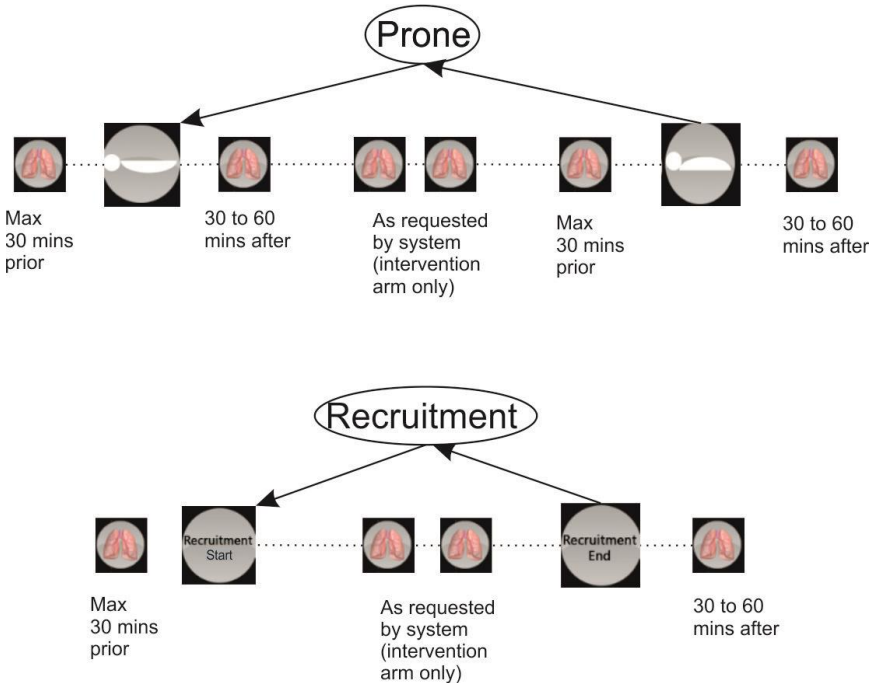


Figure 4 – Prone position and recruitment manoeuvre flow, including intermittent ALPE procedures.

In addition, an ALPE procedure will be perfomed routinely, once or twice a day as convenient, ideally on clinical shift change with at least 8 hours duration between these routine ALPE measurements. These will be performed at the same time as the inspiratory and expiratory pauses performed so as to determine accurate driving pressure as described in section 6. Additional ALPE measurements will be performed as requested by the system or on request of the clinician for the intervention arm only.

Control Group

For this group, mechanical ventilation is managed according to standard care at the local centre. On randomisation to the Standard Care group, a computer communication cable will be connected from the ventilator to the Beacon Caresystem by a trained bedside nurse and/or physician and/or a member of the research team. Data communication is only in one direction, from the ventilator to the Beacon Caresystem. The Beacon Caresystem will then be powered on. In this group Beacon advice will be disabled, with the system being used solely for data collection including changes in ventilation. Research team members will not advise on mode of ventilation or type of respiratory interventions for patients randomised to this arm of the study. Physiological variables captured in this arm of the study will mirror the intervention arm. The Beacon will remain on the patient for as long as the patient stays in the study centre, is successfully extubated (i.e. not requiring non-invasive ventilation or nasal high flow oxygenation for >24 hours), attains trachemask for >24 hours, or passes away.

Prone and recruitment manoeuvres will be performed as for figure 3 of the intervention arm according to standard clinical practice but including the ALPE procedures as described in the figures. The Beacon screens visualising the results (Figures A1-A3, appendix 1) will not be available for patients in the control arm. This strategy will allow for comparison of physiological status between control and intervention arms, but will not risk modifying care in the control arm.

In addition, an ALPE procedure will be perfomed routinely, once or twice a day as convenient ideally on clinical shift change with at least 8 hours duration between these routine ALPE measurements. These will be performed at the same time as the inspiratory and expiratory pauses performed so as to determine accurate driving pressure as described in section 6. As for prone and recruitment manoeuvres Beacon screens visualising the ALPE results (Figures A1-A3, appendix 1) will not be available for patients in the control arm.

Description of intervention and control arms in patients during ECMO

Patients which have been randomised on ECMO or placed on ECMO post-randomisation will be attached to the Beacon Caresystem but the system will only be activated to give advice during periods when the ECMO sweep gas is off. During such periods, the interventions described above as per control and intervention arms will be followed. For instance, once or twice daily routine ALPE procedures will be performed with at least 8 hours duration between these routine ALPE measurements. In addition, an ALPE procedure will also be performed as soon as possible after sweep has been switched off and advice will be activated in the intervention arm. However, the ALPE will not lead to advice or be shown in both control or intervention arms as advice will not be on when ECMO gas sweep is on.

Protocol end

Both arms of the study the protocol ends with either:

- the patient's legal representative requests withdrawal from the study
- there is a safety concern about the therapy such that withdrawal is mandated
- discontinuation of active medical treatment occurs
- the patient dies; is successfully extubated; achieves 1 year follow up; or patient is transferred to a non-study site.

Patient transfer is considered to be prior to or following successful extubation. Successful extubation is defined as ≥24 hours of unassisted spontaneous breathing after extubation.

Unassisted breathing is without the support of supplementary pressure (NIV) or gas flow (high-flow oxygen therapy). All decisions following extubation, including those relating to non-invasive ventilation (NIV) and re-intubation will be at the discretion of the attending physician according to standard care. In addition, and for both arms of the study, the decision to perform tracheostomy, including the timing and type of tracheostomy will be at the discretion of attending physician according to standard care. For both arms of the study, duration of mechanical ventilation will be defined as per latest evidence, regardless of the presence of tracheostomy. For those patients transferred to another institution the research team will attempt to find the length of ventilation, ICU stay and hospital stay. These transferred patients may also be requested to attend follow-up clinic. Patients may also be contacted over the telephone, or by email or post telephoned for follow up information if they are unable to attend follow-up clinic.

Following cessation of therapy, the Beacon caresystem will be cleaned according to the local hospital's Infection Control Policy and in accordance with manufacturer's instructions.

10. Assessments and Follow-up

Clinical data will be collected during trial participants stay in the ICU up to successful liberation from mechanical ventilation after randomisation. For routinely collected clinical data, the health record will be the source document and for study specific clinical measurements the CRF will be the source document.

Beacon Caresystem will be automatically attaining data for mechanical ventilation in both arms of the study on a daily basis when attached.

Day 0 (baseline):
Day 0 is 24 hours prior to randomisation. If more than one value is available for this 24-hour period, the value closest but prior to the time of randomisation will be recorded. Day 0 (baseline) data collected will include but is not limited to:

- Patient demographics (including but not limited to date of birth, gender, measured height, predicated body weight)
- Date/time of consent and randomisation
- Date and time of hospital and ICU admission
- Assessment of functional status including co-morbidities
- Smoking history and status
- Alcohol intake
- Admission diagnoses
- Timing of ARDS diagnosis and aetiology
- Date/time of onset of mechanical ventilation
- Use and duration of non-invasive ventilation / nasal high flow prior to intubation
- Date and time of worst PaO_2/FiO_2 ratio
- Acute Physiology and Chronic Health Evaluation score (APACHE II)
- Determinants of Sequential Organ Failure Assessment (SOFA) score
- Ventilation parameters including but not limited to: Mode of ventilation, minute volume, Respiratory Rate (RR), mean airway pressure, peak inspiratory pressure, plateau pressure, PEEP; I:E ratio; compliance; resistance and measured values including but not limited to oxygenation (SpO_2), end-tidal CO_2 fraction ($FE'CO_2$).
- Arterial blood gas including but not limited to FiO_2, PaO_2, Partial Pressure of Carbon Dioxide in arterial blood ($PaCO_{2)}$, pH
- Prior use of adjunctive therapies including Neuromuscular Blocking Drugs (NMBD),

prone position, recruitment maneuvers
- Fluid balance – cumulative and daily up to day 0
- Vasopressor / Inotrope agent usage
- Diuretic usage and use of renal replacement therapy
- Laboratory results in last 24 hours.
- Microbiological results to date.
- Date/time of attachment of Beacon Caresystem

Note: In centres where patients are referred for ECMO support, randomization may occur after patient has been placed onto ECMO. In these cases, pre-ECMO data will be collected from the clinical referral form and/or the referral hospital.

Daily Data:
Day 1 is from the time of randomisation to the end of that calendar day. If more than one value is available for this period, the value closest but after the time of randomisation will be recorded. All other daily measurements will be recorded and collected between 6-10am or as close to this time as possible, unless otherwise stated in the CRF. Daily data will be collected to protocol end and will include but is not limited to:

- Ventilation parameters including but not limited to: Mode of ventilation, minute volume, RR, mean airway pressure, peak inspiratory pressure, plateau pressure, PEEP; I:E ratio; compliance; resistance and measured values including but not limited to oxygenation (SpO_2), end-tidal CO_2 fraction ($FE'CO_2$).
- Arterial blood gas including but not limited to FiO_2, PaO_2, $PaCO_2$, pH, BE, HCO_3^-
- Commencement or transfer for ECMO following randomization
- If patient is on ECMO, then ECMO parameters including but not limited to: ECMO rpm, blood flow, sweep flow, post-oxy, pre-oxy, ECMO 100% test.
- Use of adjunctive therapies including NMBD, prone position, recruitment maneuvers.
- Fluid balance – cumulative and daily.
- Vasopressor / Inotrope agent usage
- Diuretic usage and use of renal replacement therapy
- Microbiological results to date.
- Adverse events – clinically noted and device related (please see appendix 2 for a list of potential events).
- Daily average and breath by breath physiological status as continuously measured by the Beacon Caresystem.
- ICU and pre-/post-ICU hospital lung imaging and function in relation to ARDS which includes but not limited to chest X-ray and CT imaging).

Day 1, 3, 7 and 14 (in sites with capability):
- Echocardiography and lung ultrasound parameters including but not limited to ventricular size and function and tricuspid annular plane systolic excursion (TAPSE), with established clinical protocols. (see appendix 3)

Day 1, 3, 7,10, and weekly thereafter (in sites with capability):

- Skeletal and respiratory muscle ultrasound (see appendix 3)

Day 1, 2, 3, 5, 7, 10, 14 and weekly thereafter:
- Determinants of SOFA score (as per SOP)

ICU discharge to 6 months (+/-1month) post ICU discharge (in sites with capability):

- Sf-36 Health Related Quality of life and EuroQoL-5 Dimension Questionnaire (5 level version)(EQ-5D-5L) (patient and carers)
- St George's Respiratory Questionnaire (SGRQ)
- Cognitive functional tests
    - mini Mental State examination
    - Post Traumatic Stress Syndrome Questionnaire (PTSS)-14
    - Hospital Anxiety and Depression Scale (HADS)
    - The Montreal Cognitive Assessment (MoCA) BLIND
- Return to work rates (W&SAS) (patient and carers)
- Primary and Secondary care utilisation
- 6-minute walk test
- Lung imaging and function in relation to ARDS (as per current clinical protocol i.e. if clinically indicated, which includes pulmonary function tests, CT imaging).
- Skeletal and respiratory muscle ultrasound (see appendix 3)

Up to 1 year (+/-2month) post ICU discharge (in sites with capability):

- Sf-36 Health Related Quality of life and EQ-5D-5L (patient and carers)
- St George's Respiratory Questionnaire (SGRQ)
- Cognitive functional tests
    - mini Mental State examination
    - PTSS-14
    - Hospital Anxiety and Depression Scale (HADS)
- Return to work rates (W&SAS) (patient and carers)
- 6-minute walk test
- Lung imaging and function in relation to ARDS (as per current clinical protocol i.e. if clinically indicated, which includes pulmonary function tests, CT imaging (including dual energy protocol).
- Skeletal and respiratory muscle ultrasound (see appendix 3)

The following data will also be collected:

- Date and time of any discontinuation of Beacon Caresystem and reason
- Date and time of any discontinuation of mechanical ventilation
- Date and time of critical care discharge
- Date and time of hospital discharge
- Date and time of death
- Dates and times of neuromuscular blockade
- Dates and times of prone position
- Dates and times of recruitment manouevres
- Dates and times of ECMO or ExtraCorporeal Carbon Dioxide Removal ($ECCO_2R$) support

Discharge from critical care is defined as first discharge to a medical ward in the hospital or another hospital; a transfer between ICUs is not considered a discharge from critical care. Hospital discharge is the first date that the patient is discharged to home/ community, a transfer between hospitals is not considered as a hospital discharge.

Unassisted breathing i.e. no ventilatory support is defined as: extubated with supplemental oxygen, or room air, or open T-tube breathing, or tracheostomy mask breathing, or CPAP ≤ 5 cm H_2O without pressure support for a calendar day. Patients receiving pressure support via

non-invasive ventilation will be defined as receiving ventilatory support (except for those with sleep disordered breathing).

Ventilator free days (VFDs) to day 28 are defined as the number of days from the time of initiating unassisted breathing to day 28 after randomisation, assuming survival for at least two consecutive calendar days after initiating unassisted breathing and continued unassisted breathing to day 28. If a patient returns to assisted breathing and subsequently achieves unassisted breathing to day 28, VFDs will be counted from the end of the last period of assisted breathing to day 28. A period of assisted breathing lasting less than 24 hours and for the purpose of a surgical procedure will not count against the VFD calculation. If a patient was receiving assisted breathing at day 27 or dies prior to day 28, VFDs will be zero. Patients transferred to another hospital or other health care facility will be followed to day 28 to assess this endpoint.

For each patient, data will be collected describing demographics (sex, age, weight, height), ICU admission (date of admission, APACHE II, Simplified Acute Physiology Score (SAPS II) score, primary diagnosis, secondary diagnosis, reason for admission, reason for intubation), ARDS diagnosis (time of diagnosis, mild or moderate ARDS, criteria, cause of ARDS). Daily disease status will be recorded (Sequential organ failure assessment (SOFA) score, heart rate, arterial blood pressure, PaO_2/FIO_2 ratio, administered levels of sedation and neuromuscular blockade). Timing and results of SBT, extubation, NIV, reintubation and tracheostomy will be noted in the CRF for calculation of primary and secondary effect parameters. Number of arterial blood gas samples and changes in levels of administered sedation and neuromuscular blockade will be captured dynamically and then analysed accordingly.

Data collection from NHS Digital
We may also request data from NHS Digital. NHS Digital is part of the Department of Health. We would like to know whether patients had further health problems after their enrolment in this study. In order to do this, we will send their NHS number, date of birth and post-code to NHS Digital. NHS Digital can then provide us with details of historical and future hospital records, current health status or if they have died or not. These data will be supplied by NHS Digital on behalf of the Office of National Statistics. We will collect data from NHS Digital for the 1 year the patient is enrolled in the study.

11. Schedule of assessments

Table 1 lists all of the assessments and indicates with an ‘x’ at which visits the assessments are performed. Patients should be seen for all visits on the designated day, or as close to it as possible – the visit window/tolerance for each visit is given below at the table

Table 1: Schedule of assessments

	Days post randomisation										
	Baseline (0)*	Daily data**	1	2	3	5	7	10	14 (and weekly thereafter)	Discharge to 6 months (+/- 2 months)	1 year (+/- 2 months)
Consent	X										
Inclusion/Exclusion criteria	X										
Demographic data	X										
Date/time of consent and randomisation	X										
Date and time of Hospital and ICU admission	X										
Assessment of functional status including co-morbidities (inc concomitant medication)	X										
Smoking history and status	X										
Alcohol intake	X										
Admission diagnoses	X										
Timing of ARDS diagnosis and aetiology	X										
Date/time onsent of mechanical ventilation	X										
Use and duration of non-invasive ventilation / nasal high flow prior to intubation	X										
Date and time of worst PaO_2/FiO_2 ratio	X										
APACHE II	X										
Determinants of Sequential Organ Failure Assessment (SOFA) score	X	X	X	X	X	X	X	X	X		
Ventilation parameters including but not limited to: Mode of ventilation, minute volume, RR, mean airway pressure, peak inspiratory pressure, plateau pressure, PEEP; I:E ratio; compliance; resistance defined as daily averages of measured values including but not limited to oxygenation (SpO_2), end-tidal CO_2 fraction ($FE'CO_2$)	X	X									
Arterial blood gas including but not limited to FiO_2, PaO_2, $PaCO_2$, pH	X	X									
Prior use of adjunctive therapies including NMBD, prone position, recruitment maneuvers	X	X									
Fluid balance – cumulative and daily	X	X									
Vasopressor / Inotropic agent usage	X	X									
Diuretic usage and use of renal replacement therapy	X	X									
Laboratory results in last 24 hours	X	X									
Microbiological results to date	X	X									

Date/time of attachment of Beacon Caresystem	X									
Commencement or transfer for ECMO following randomization		X								
If patient is on ECMO, then ECMO parameters including but not limited to: ECMO rpm, blood flow, sweep flow, post-oxy, pre-oxy, ECMO 100% test		X								
Daily average physiological status defined as daily averages of measured values including but not limited to oxygenation (SpO_2), end-tidal CO_2 fraction ($FE'CO_2$), and PaO_2/FiO_2		X								
Daily average physiological status as continuously measured by the Beacon Caresystem		X								
ICU and pre-/post-ICU hospital lung imaging and function in relation to ARDS which includes but not limited to chest X-ray and CT imaging).		X								
Echocardiography and lung ultrasound parameters including but not limited to ventricular size and function and tricuspid annular plane systolic excursion (TAPSE), with established clinical protocols.			X		X		X		X		
Skeletal and respiratory muscle ultrasound (in sites with capability)			X		X	X	X	X	X	X	X
Adverse events		X								
Is patient fit for extubation and reason for non-extubation (if spontaneous breathing criteria are passed or positive evaluation performed by clinician		X								
Sf-36 Health Related Quality of life and EQ-5D-5L (patient and carers)									X	X
SGRQ									X	X
Cognitive functional tests mini Mental State examination PTSS-14 Hospital Anxiety and Depression Scale (HADS)									X	X
Return to work rates (W&SAS) (patient and carers)									X	X
Primary and Secondary care utilisation									X	
6 minute walk-test									X	X
Contact with NHS Digital if required										X
Lung imaging and function in relation to ARDS (as per current clinical protocol i.e. if clinically indicated,		X							X	X

which includes pulmonary function tests, CT imaging (including dual energy protocol)										
Date and time of any discontinuation of Beacon Caresystem and reason										X
Date and time of any discontinuation of mechanical ventilation										X
Date and time of critical care discharge										X
Date and time of hospital discharge										X
Date and time of death										X
Dates and times of neuromuscular blockade										X
Dates and times of prone position										X
Dates and times of recruitment maneuvers										X
Dates and times of ECMO or $ECCO_2R$ support										X

Sample collection:

	Days post randomisation						
Samples ^	Baseline (Day 0)*/#	1-3	5-7	9-11	13-15 (and weekly thereafter)	Discharge to 6 months (+/- 2 months)	1 year (+/- 2 months)
Blood	X	X	X	X	X	X	X
Bronchoscopy (only sedated and ventilated) with bronchoalveolar lavage (BAL) – COVID-19 postiive	Only performed when clinically relevant						
Bronchoscopy (only sedated and ventilated) with bronchoalveolar lavage (BAL) – COVID-19 negative	X		X		X		
Bronchoscopy when on ECMO	X		X		X		
Urine	X	X	X	X	X	X	X

*24 hours before randomisation. If more than one value is available for this 24-hour period, the value closest but prior to the time of randomisation will be recorded
** Day 1 is from the time of randomisation to the end of that calendar day. If more than one value is available for this period, the value closest but after the time of randomisation will be recorded. All other daily measurements will be recorded and collected between 6-10am or as close to this time as possible, unless otherwise stated in the CRF.

A sample may be taken prior to commencing ECMO. This will likely be prior to consent but after screening. *If the patient is not enrolled into the study then this sample will be discarded. This is to overcome the logistics of delayed sampling, and in particular, to examine the pro-thrombotic nature of COVID-19 and the effect of ECMO.*

^ The day of sampling may fall on weekends / holidays when staff are not available. If this does occur, samples/scans will be taken/performed on the day prior/next available day. This will be recorded on the CRF and also on the sample accountability log, along with the day the samples were taken (e.g. day 8 instead of day 7)

12. Safety Reporting

It is recognised that the patient population in the ICU will experience a number of common aberrations in physiological values, laboratory values, signs and symptoms due to the severity of their underlying disease and the impact of standard therapies. These will not necessarily constitute an AE unless they require significant intervention, lead to discontinuation of intervention or are considered to be of concern in the investigator's clinical judgement.

Clinical outcomes from ARDS are exempt from adverse event reporting, unless the investigator deems the event to be related to the use of the device. The following events will be considered clinical outcomes.

- Death related to ARDS and ensuing multi-organ failure
- Neurological insult e.g. intracranial bleeding
- Cardiovascular failure, including the need for vasopressors / inotropes
- Hepatic failure
- Renal failure, including the need for renal replacement therapy
- Haematological / Coagulation failure, including thrombocytopaenia

Adverse Event (AE)
Any untoward medical occurrence in a patient or clinical study subject and which does not necessarily have a causal relationship with this treatment (i.e. any unfavourable or unintended change in the structure (signs), function (symptoms), or chemistry (lab data) in a subject to whom a treatment/study procedure has been administered, including occurrences unrelated to that product/procedure/device).

1. Severity of Adverse Events

Mild:	Awareness of event but easily tolerated
Moderate:	Discomfort enough to cause some interference with usual activity
Severe:	Inability to carry out usual activity

2. Causality of Adverse Events

Unrelated:	No evidence of any causal relationship
Unlikely:	There is little evidence to suggest there is a causal relationship (e.g. the event did not occur within a reasonable time after administration of the trial medication). There is another reasonable explanation for the event (e.g. the patient's clinical condition, other concomitant treatment).
Possible:	There is some evidence to suggest a causal relationship (e.g. because the event occurs within a reasonable time after administration of the trial medication). However, the influence of other factors may have contributed to the event (e.g. the patient's clinical condition, other concomitant treatments).
Probable:	There is evidence to suggest a causal relationship and the influence of other factors is unlikely.
Definite:	There is clear evidence to suggest a causal relationship and other possible contributing factors can be ruled out.

Adverse Device Effects (ADE)
ADE is an untoward and unintended response to a medical device.

The phrase "responses to a medical device" means that a causal relationship between the device under investigation 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 device qualifies as a device effect. This also includes any event resulting from insufficiencies or inadequacies in the instruction for use or deployment of the device and includes any event that is a result of a user error.

Serious Adverse Device Effect (SADE)
An untoward occurrence that:
• Results in death; or Is life-threatening (places the subject, in the view of the Investigator, at immediate risk of death)
• Requires hospitalization or prolongation of existing hospitalization (hospitalisation is defined as an inpatient admission, regardless of length of stay; even if it is a precautionary measure for observation; including hospitalisation for an elective procedure, for a pre-existing condition)
• Results in persistent or significant disability or incapacity (substantial disruption of one's ability to conduct normal life functions)
• Consists of a congenital anomaly or birth defect (in offspring of subjects or their parents taking the study drug regardless of time of diagnosis)
• Is otherwise considered medically significant by the investigator.
Important medical events that may not be immediately life-threatening or result in death or hospitalisation but may jeopardise the subject or may require intervention to prevent one of the outcomes listed in the definition of serious will also be considered serious.

Serious Adverse Device Effects (SADE)
A serious adverse device effect (SADE) is any untoward medical occurrence seen in a patient that can be attributed wholly or partly to the device which resulted in any of the characteristics or led to characteristics of a serious adverse event.
SADE is also any event that may have led to these consequences if suitable action had not been taken or intervention had not been made or if a circumstance has been less opportune. All cases judged by either the reporting medically qualified professional or the sponsor.

Unanticipated Adverse Device Effect (UADE)
Any serious adverse device effect on health or safety or any life-threatening problem or death caused by, or associated with a device, if that effect, problem, or death was not previously identified in nature, severity or degree of incidence in the investigational plan or application (including a supplementary plan or application), or any other unanticipated serious problem associated with a device that related to the rights, safety or welfare of the subject.

Unanticipated Serious Adverse Events (SAE)
Any untoward and unexpected medical occurrence or effect that:
- Results in death.
- Is life-threatening – refers to an event in which the subject 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.
- Requires hospitalisation, or prolongation of existing inpatients' hospitalisation.
- Results in persistent or significant disability or incapacity.
- Is a congenital anomaly or birth defect.
- Is otherwise considered medically significant by the investigator.

Life-threatening" in the definition of "serious" refers to an event in which the subject 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.

** "Hospitalisation" means any unexpected admission to a hospital department. It does not usually apply to scheduled admissions that were planned before study inclusion or visits to casualty (without admission).

Medical judgement should be exercised in deciding whether an AE is serious in other situations. Important AEs that are not immediately life-threatening or do not result in death or hospitalisation but may jeopardise the subject or may require intervention to prevent one of the other outcomes listed in the definition above, should also be considered serious.

Adverse Event recording

AEs will be recorded from the time of consent in the adverse event section of the relevant Case Report Form. All clearly related signs, symptoms, and abnormal diagnostic procedures results should be recorded in the source document using the event terms and grading given in the relevant CRF/eCRF pages.

For the purposes of the study, AEs will be followed up according to local practice until the event has stabilised or resolved, or the Follow-up Visit, whichever is the sooner. SAEs will be recorded throughout the study

Reporting of SAEs

Reporting of all SAEs (exept common ICU related events as in **appendix 2**), occurring during the study must be performed as detailed in SAE reporting instructions. If the investigator becomes aware of safety information that appears to be related to the trial, involving a subject who participated in the study, even after an individual subject has completed the study, this should be reported to the Sponsor. It is recognised that the patient population in the ICU will experience a number of common aberrations in laboratory values, signs and symptoms due to the severity of their underlying disease and the impact of standard therapies. These will not necessarily constitute an AE unless they require significant intervention, or are considered to be of concern in the investigator's clinical judgement.

All SAEs will be reviewed by the Chief Investigator or a designated medically qualified representative to confirm expectedness and causality.

Reporting of SAEs and review by the CI will be via the trial data collection system (CRF/eCRF)

(i) Related SAEs

Related: resulted from administration of any of the research procedures

(ii) Unexpected SAEs

Unexpected: type of event is not listed in the protocol as an expected occurrence

(iii) Reporting of SAEs that are related and unexpected

SAEs that are *related and unexpected*, SADEs and USADEs should be notified to the relevant REC and the Sponsor within 15 days of the Chief Investigator becoming aware of the event.

In addition, all SAE/SADE/UADEs should be reported to the manufacturer of the device at the same time.
Follow up of patients who have experienced a related and unexpected SAE should continue until recovery is complete or the condition has stabilised. Reports for related and unexpected SAEs should be unblinded prior to submission if required by national requirements.

Contact details for reporting SAEs are as follows:

Joint Research Compliance Office
Imperial College London and Imperial College Healthcare NHS Trust
E-mail: jrco@imperial.ac.uk

Chief Investigator
Dr. Brijesh Patel
Division of Anaesthesia, Pain Medicine and Intensive Care (APMIC),
Department of Surgery and Cancer, Faculty of Medicine,
Imperial College London, Royal Brompton Hospital campus.
Adult ICU, Royal Brompton Hospital,
Sydney Street, London. SW3 6NP

Annual reporting of Serious Adverse Events
Annual Progress reports will be submitted to the Sponsor and the Ethics Committee in accordance with local requirements. The Annual Progress Report will detail all SAEs recorded

Reporting urgent safety measures
If any urgent safety measures are taken the CI/Sponsor shall immediately and in any event no later than 3 days from the date the measures are taken, give written notice to the relevant REC of the measures taken and the circumstances giving rise to those measures.

13. Statistics and data analysis

Sample size and recruitment

The required sample size for the primary outcome is 110 patients. 55 patients per group will allow to detect a difference of 3cmH_2O in driving pressure between the groups with 90% power and a two sided alpha of 0.05 assuming a control group driving pressure of 15 cmH_2O with a standard deviation of 2.5 cmH_2O and including a 40% dropout. We have used data from the MIMIC dataset (as published in Serpo Neto et al (34)) for the estimation of the driving pressure. In view of the longitudinal analysis, loss to follow up has taken account of an average mortality of 34% and a 6% drop out. . To account for any potential increase in mortality rate amongst the COVID-19 cohort of patients, the DMEC is to review the loss to follow up rate and recommend an increase in recruitment if necessary

Statistical analysis plan

The primary outcome of driving pressure during ventilation and the other repeated measurements outcomes will be analysed using mixed model, including total ventilation time and stratification variables in the model. Categorical data will be presented as number and percentage and comparisons between the two groups done using the chi-squared or Fishers exact test and logistic regression will be used to adjust for important covariates. Continuous

variables will be checked to determine whether they are normally distributed or not and presented as mean (SD) or median (range) and appropriate transformation will be considered for non normally distributed data. Comparisons of numeric data will be done using the 2-sample independent t test or the Wilcoxon rank-sum test. Analysis of covariance will also be used adjusting for other covariates where appropriate. Time-to-event outcomes (e.g. successful extubation, first prone episode etc) will be analysed by Cox regression (proportional hazards regression) and reported as hazard ratios with 95% CI. Patients will be classified as having extubated or not and this variable will be analysed between the 2 groups using the log-rank test with the accompanying Kaplan-Meier curves. A per protocol and intention-to-treat basis analysis will used. All statistical tests will be 2-sided and significance set at $p < 0.05$. Detailed analysis methods will be documented in the study's Statistical Analysis Plan (SAP).

Any deviations from the statistical analysis plan will be dealt with in accordance with Imperial Clinical Trial Unit's statistical Standard Operating Procedures.

Randomisation

Patients will be randomly allocated to one of two groups, i.e. the Standard Care group or the Beacon group. Randomisation will be stratified by site; ECMO/non ECMO; and Covid/non-Covid. Patients will be centrally allocated to an arm of the study from a master randomisation list created by the study statistician, stratified by ECMO and COVID status to control for different patient severity across parts of the year. Given the unblinded nature of this device study, allocation concealment will be maintained through random size block allocation of patients.

Interim analysis

There will be no formal interim analysis in view of the short recruitment window of the study. Adverse event analysis will be performed after 10 patients have been randomised in each site.

A closed report will be carried out by the study statistician for the independent DMEC meeting. This report will primarily cover quality of data collection and study safety parameters but may also include primary and secondary endpoint data if requested.

Missing data

Every effort will be made to minimise missing baseline and outcome data in this trial. Patient ICU data from electronic patient records (EPR) will also be used to complement missing data. The level and pattern of the missing data in the baseline variables and outcomes will be established by forming appropriate tables and the likely causes of any missing data will be investigated. This information will be used to determine whether the level and type of missing data has the potential to introduce bias into the analysis results for the proposed statistical methods, or substantially reduce the precision of estimates related to treatment effects. If necessary, these issues will be dealt with using multiple imputation or Bayesian methods for missing data as appropriate. Detailed methodology for dealing with missing data will be documented in the Statistical Analysis Plan (SAP).

Other statistical considerations

Subgroup analyses will be performed including the interaction term (treatment group by subgroup) in the model and estimates and 95% confidence intervals will be reported. Primary and exploratory subgroups are listed below in an attempt to reduce the risk for erroneous conclusions due to false positive and false negative findings.

Primary subgroup analysis:

1. Baseline respiratory system compliance in quintiles (as per Murray score) at randomization (and pre-ECMO respiratory system compliance if randomised post-ECMO)
2. ECMO and non-ECMO at randomisation
3. Duration of ventilation prior to randomisation

Exploratory subgroup analysis:

1. Murray Score on randomisation (or pre-ECMO if randomised post-ECMO).
2. Hyper- and hypo-inflammatory ARDS endotypes
3. Focal versus non-focal ARDS
4. Specific cohorts of admission diagnoses e.g. viral, bacterial, non-infective; COVID-19 versus non-COVID-19

Data and all appropriate documentation will be stored for a minimum of 20 years after the completion of the study.

14. Regulatory,ethical and legal considerations

Each co-ordinator in each country will take responsibility for the following activities within their country:

1. Quality assurance and quality management (overseen by the sponsor)
2. To ensure compliance with the study protocol and SOPs
3. To ensure compliance with any national guidelines or regulations
4. To assist in the application for ethics approval in their country
5. To ensure personnel are suitably trained and qualified to perform the study procedures
6. To ensure compliance with the protocol regarding handling of samples and data
7. To evaluate safety and to ensure serious adverse events (SAEs) are reported as per the protocol and legislation
8. To present study reports to the national authorities / Ethics Committees as required
9. To ensure Clinical Investigation Agreements and any local approvals are in place at each centre in their country
10. To provide indemnity for participating centres for their country where required
11. To liaise with the overall DeVENT project sponsor (Imperial College London)

Overall Ethical Considerations

There is a major unmet need for improved treatment for patients with ARDS. This study will provide an understanding as to the clinical benefit of a system for generating advice aiming at aiding the clinician to optimize mechanical ventilator settings during ARDS. Mechanical ventilator treatment includes both patients who are heavily sedated and unable to give informed consent and those less severely ill who are able to give consent. For unconscious patients, advice will be obtained from next of kin or treating physician. For the patient studied here, appropriate mechanical ventilation – the goal of the system – is well known to be beneficial. As appropriate mechanical ventilation is necessary in these patients who are typically most difficult to manage due to the severity of lung disease, then evaluation of the Beacon Care system in these patients is essential and may be beneficial to the individuals included in the study. It is expected that patients in the Beacon randomization group will show improved personalised delivery of ventilation and monitoring of lung physiology. Patients in the standard care group, will receive care at the level normally applied at the hospital. The Beacon Caresystem© may

advise on the settings of the ventilator connected to the patient. The system does not automatically change the settings on the ventilator and it only advises the nurse and doctor. It is always up to the doctor to actually make these changes and the chances that incorrect advice is provided and implemented are minimal.

The previous section details the risks associated with the study, which are minor in comparison to the potential benefits, indicating that the study is ethically justifiable.

In addition, to develop physiological handprints which will enable improved clinical understanding which will be used to determine clinical progression and efficacy of interventions, is considered to be ethically justified. The sampling and imaging procedures (see appendix 3) which will be used in the study have all been carried out safely in subjects with ARDS and in most cases are part of routine clinical practice. Most procedures are non-invasive. The most invasive procedure, bronchoscopy, has been used extensively in subjects with ARDS to assess lung inflammation and infection. In patients suspected for or positive for COVID-19 positive we will only perform bronchoscopy in those who are on ECMO to avoid aerosolization and conduct all procedures in accordance to recommendations from local infection control / health & safety protocols and Public Health England. Subjects may decline from enrolling in any part of this study without precluding them from enrolment in the main study.
Risk is low from biological sampling –samples are taken alongside routine clinical blood samples using the same vascular lines that have already been connected to your body. Bronchoscopy is a standard procedure performed on ICU. In keeping with standard recommendations, patients who are receiving more than 80% inspired oxygen or have a high positive end expiratory pressure (i.e. >8cm H_2O) will not undergo bronchoscopy and BAL. Bronchoscopy will also only be undertaken if the ICU consultant has no concerns regarding safety of the procedure. The risk for bronchoscopy is much less when a patient is on ECMO.
In light of recent public health emergency planning with respect to COVID-19, patients with a spectrum of emerging and unknown pathogens will likely be enrolled. Hence, there is a high likelihood that data and biological samples are prospectively and systematically collected and shared rapidly in view of the emergent requirement for disease understanding. Hence, we may share this data with clinical, academic and public health partners as described later prior to the end of the clinical trial (appendix 3).

Ethics approvals.
Initial Approval: Prior to enrolment of subjects. The trial will require research and ethical (REC) and Health Research Authority (HRA) approval from all countries. We will apply separately for ethical approval to a multi-centre research ethics committee (MREC) flagged for trials involving patients without capacity. The ethics application made by the Chief Investigator will cover all collaborating sites in the UK. The application to the REC and the relevant NHS R&D offices will be made through the Integrated Research Application System (IRAS). Each EU partner will apply for ethics under its own national / institutional framework.

Approval of Amendments: Proposed amendments to the protocol and aforementioned documents must be submitted to the REC and HRA for approval as instructed by the Sponsor. Amendments requiring REC approval may be implemented only after a copy of the REC's approval letter has been obtained.

Amendments that are intended to eliminate an apparent immediate hazard to subjects may be implemented prior to receiving Sponsor or REC approval, refer to urgent safety measures. However, in this case, approval must be obtained as soon as possible after implementation.

Annual Progress Reports will be submitted to the Research Ethics Committee (REC) and the Sponsor in accordance with local / national requirements. The Annual Progress Report will also detail all SAEs recorded.

The Sponsor will ensure that the study protocol, Patient Information Sheet (PIS), Informed Consent Form (ICF), GP letter and submitted supporting documents have been approved by the Health Research Authority (HRA) which includes Research Ethics Committee (REC) approval if applicable, prior to any patient recruitment taking place. The protocol and all agreed substantial protocol amendments, will be documented and submitted for HRA approval prior to implementation. All non-UK sites will have documents converted to the host language through official translators.

Before site(s) can enrol patients into the study confirmation of capacity and capability must be issued by the institution hosting the trial. It is the responsibility of the PI at each site to ensure that all subsequent amendments gain the necessary approvals by the participating site. This does not affect the individual clinician's responsibility to take immediate action if thought necessary to protect the health and interest of individual patients.

Within 90 days after the end of the study, the CI will ensure that the REC is notified that the study has finished. If the study is terminated prematurely, those reports will be made within 15 days after the end of the study.

The CI will supply a final summary report of the clinical study to the REC and the Sponsor in parallel within one year after the end of the study.

The Investigator will ensure that this study is conducted in accordance with the 7th revision of the 1964 principles of the Declaration of Helsinki.

The study fulfils the rules of the Helsinki Declaration. The study protocol is sent to the Ethical committees of The Health Research Authority (UK), IRAS reference number 266521.

The Investigator will ensure that this study is conducted in full conformity with the UK Framework for Health and Social Care Research, principles of Good Clinical Practice (GCP) (ICH GCP E6 guidelines) and any other relevant regulatory requirements.

The trial protocol was prepared in compliance with the SPIRIT 2013 statement (40).

Non-Compliance and Serious Breaches: All protocol deviations and protocol violations will be reported via the eCRF/CRF and reviewed by the Chief Investigator and reported to the ICTU QA manager on a monthly basis. Protocol violations will be reported to the Sponsor.
An assessment of whether the protocol deviation/violation constitutes a serious breach will be made.

A serious breach is defined as:
A breach of the conditions and principles of GCP in connection with a trial or the trial protocol, which is likely to affect to a significant degree:
The safety or physical or mental integrity of the UK trial subjects; or
The overall scientific value of the trial

The Sponsor will be notified within 24 hours of identifying a likely Serious Breach. If a decision is made that the incident constitutes a Serious Breach, this will be reported to the REC within 7 days of becoming aware of the serious breach.

Device regulations. This is an academic study of a marketed medical device for which there is a labeled indication. As the trial will be employing a medical device for a purpose for which it has approval, and the device has a CE mark, approval from the Medicines and Healthcare products Regulatory Agency (MHRA) will not be required. DeVENT study is not a Clinical Study of an Investigational Medicinal Product, and thus is not governed by the Medicines for Human Use (Clinical Trials) Regulations 2004.

Biobanking. Biological samples including but not limited to blood, urine, broncho-alveolar lavage/brushings will be stored in a biobank for future analysis. All analyses undertaken will relate to furthering the understanding of ARDS. These samples will be identified only by a numerical identifier and results from these tests including genetic information will not be stored in the case notes or given to the subject, their family or doctors involved with their care. The samples will be stored in an approved secure facility. Only approved researchers will be able to access the samples. The sample labels will contain no subject identifiable information. The movement and storage of samples will be carried out in accordance with the Human Tissue Act and respective national regulations. Further details are provided in Appendix 3.

Consent.
Consent to enter the study must be sought from each participant only after a full explanation has been given, an information leaflet offered and time allowed for consideration. Signed participant consent should be obtained. The right of the participant to refuse to participate without giving reasons must be respected. In most cases it will not be possible to gain prospective consent for the patient at the time of enrollment. The nature of the study's population is such that patients are critically ill and often unconscious and, in many cases, will not be able to grant consent themselves. As the Beacon Caresystem device takes an open loop approach with the decision to change the ventilator settings ultimately lying with the clinical team, there is minimal risk in participation into the study. Hence, given the emergent nature of the study situation the Beacon Caresystem (with the advice turned off) will be attached to and samples collected. Given the urgent nature of COVID-19 and the process of ECMO, a similar sample of blood may be taken prior to starting ECMO (T0) and hence, often prior to discussion with personal nominee, at the discretion of the clinical team, prior to consent/advice below. If they are not enrolled into the study then this sample will be discarded. No analysis of data or samples will occur until consent/advice as below is obtained. This has been discussed with our PPI representative who is fully supportive of this process.

Personal legal representative advice. Due to the acute care trial setting and the vulnerability of the patients' population, a patient information sheet will be provided and advice sought from a third party acting as a consultee; in most cases this person will be a personal consultee, who is someone who knows the person lacking capacity and is able to advise the researcher about that person's wishes and feelings in relation to the project and whether they should participate in the research. This person must be interested in the welfare of the patient in a personal capacity, not in a professional capacity or for remuneration and will mostly likely be a relative, partner, legal power of attorney, or close friend. Written advice will be documented via the personal consultee declaration form and stored in both the medical notes and the site file. However, where the personal consultee is not available on site, the researcher may contact the personal consultee via telephone and seek verbal advice. The researcher will talk the consultee through the patient information sheet and send a copy via email or in the mail. The verbal agreement will be recorded in the telephone consultee declaration form. The telephone consultee declaration form will be signed by a second member of staff who has witnessed the telephone advice. This witness may be a member of the research team or site medical staff. A copy of the telephone consultee declaration form will be placed in the medical notes and the site file. In such cases,

where a telephone consultation occurs, a written personal consultee declaration form will be obtained as soon as possible.

Professional legal representative advice. Where no Personal Consultee is available, the researcher will nominate a professional person (independent of the study) to assist in determining the participation of a person who lacks capacity. The nominated professional consultee is someone who will be appointed by the researcher to advise the researcher about the person's (who lacks capacity) wishes and feelings in relation to the project and whether they should participate in the research. In the event a Personal Consultee cannot be identified the appointed Nominated Consultee will not be involved in either the research project or the patient's clinical care and will be completely independent of both. In the event that a personal consultee is identified after the nominated professional consultee advice has been obtained, the above process for personal consultee declaration will be followed and all advice forms will be filled as detailed previously.

Retrospective patient consent. If a surviving patient regains competency, we will approach the patient to obtain their consent to continue in the study. If the patient refuses consent or prefers to withdraw during this ICU stay the intervention will be stopped but the regular/expected medical care will still be provided. We will ask the patient if we can use their existing hospital data. Without their consent, no additional information about the patient will be collected for the purposes of the study. However, to maintain integrity of the randomized trial, all information collected up to that time will still be used and analyzed as part of the study.

A copy of the signed Informed Consent Form (ICF) along with a copy of the most recent approved Patient Information Sheet (PIS) will be given to the study participant. The original signed consent form will be retained at the study site (one filed in the medical notes and one field in the Investigator Site Master File (ISF)). A copy of the consent form will also be given to the patient. If new safety information results in significant changes to the risk–benefit assessment, the consent form will be reviewed and updated if necessary. All subjects, including those already being treated, will be informed of the new information, given a copy of the revised consent form and asked to re-consent if they choose to continue in the study.

Contact with General Practitioner
It is the investigator's responsibility to inform the subject's General Practitioner (where applicable – this will not be required for the healthy volunteers) by letter that the subject is taking part in the study provided the subject agrees to this, and information to this effect is included in the Subject Information Sheet and Informed Consent. A copy of the letter should be filed in the Investigator Site File.

Subject Confidentiality

The investigator must ensure that the subject's confidentiality is maintained. On the CRF or other documents submitted to the Sponsors, subjects will be identified by a subject ID number only. Documents that are not submitted to the Sponsor (e.g., signed informed consent form) should be kept in a strictly confidential file by the investigator.

The investigator shall permit direct access to subjects' records and source document for the purposes of monitoring, auditing, or inspection by the Sponsor, authorised representatives of the Sponsor, NHS, Regulatory Authorities and RECs.

Insurance and Indemnity
Imperial College London holds negligent harm and non-negligent harm insurance policies which apply to this study. Mermaid A/C holds standard Indemnity and insurance for the device. Each

individual clinical site will ensure independent indemnity and insurance for the device used in their host institution.

Trial Registration

The study will be registered on a trial database in accordance with requirements of the International Committee of Medical Journal Editors (ICMJE) regulations.

Data Protection and Patient Confidentiality
The investigators and study site staff will comply with the requirements of the Data Protection Act 2018 concerning the collection, storage, processing and disclosure of personal information and will uphold the Act's core principles.

End of Trial
The end of the trial will occur when the final participant has completed the last follow up visit and all study data have been captured on the study database.

Study Documentation and Data Storage
The investigator must retain essential documents until notified by the Sponsor, and for at least ten years after study completion. Subject files and other source data (including copies of protocols, CRFs, original reports of test results, correspondence, records of informed consent, and other documents pertaining to the conduct of the study) must be retained. Documents should be stored in such a way that they can be accessed/data retrieved at a later date. Consideration should be given to security and environmental risks.

No study document will be destroyed without prior written agreement between the Sponsor and the investigator. Should the investigator wish to assign the study records to another party or move them to another location, written agreement must be obtained from the Sponsor.

Sponsor
Imperial College London will act as the main Sponsor for this study. Delegated responsibilities will be assigned to the clinical sites taking part in this study.

Funding
This study is funded by the European Commision Horizon 2020. The grant co-ordinator for this study is Mermaid A/C, Denmark. The consortium partners are Imperial College London (alongside Royal Brompton & Harefield NHS Foundation Trust as a clinical collaborator), Aalborg University, Medical University Vienna, and CHU-Clermont Ferrand. All payments are through the European Commission and no payments are made independent of this funding. There will be no payments made to participants in the study.

15. Data management and quality assurance

Confidentiality. Source documents are original documents, data, and records from which participants' CRF data are obtained. These include, but are not limited to, hospital records (from which medical history and previous and concurrent medication may be summarised into the CRF), clinical and office charts, laboratory and pharmacy records, diaries, radiographs, and correspondence.

All data will be handled in accordance with the Data Protection Act 2018, NHS Caldecott Principles, The Research Governance Framework for Health and Social Care, 2nd Edition (2017), and the condition of the REC approval. The Case Report Forms (CRFs) will not bear the

subject's name or other personal identifiable data. A study Identification Number (ID), will be used for identification.

CRF entries will be considered source data if the CRF is the site of the original recording (e.g., there is no other written or electronic record of data). In this case, the CRF will be used as the source document.

In addition, anonymised data will be collected from the Beacon Caresystem and stored on a secure server within each clinical site. A secure ftp data transfer of these data will be made to a secure server at Aalborg University, Denmark, to allow data analysis by scientific partners. Aalborg University will receive the data in accordance with site agreement, and will assume the responsibility of Data Processor for the shared copy of the data in order to process it for the purpose of this project. Further linked-anonymised data sharing will be enabled with Imperial College London for sub-studies. All documents will be stored safely in confidential conditions. On all study-specific documents, other than the signed personal/professional consultee advice forms, the participant will be referred to by the study participant number/code, not by name.

Data collection. The principle means for data collection will be through electronic data capture through the internet on the SMART Trial database by each individual study site. Each participant will be allocated a unique Participant Study Number at trial entry, and this will be used to identify him or her on the CRF for the duration of the trial. Data will be collected from the time of trial entry until hospital discharge. Trial data will be entered onto a CRF and processed electronically as per ICTU Standard Operating Procedures (SOPs) and the study specific Data Management Plan. Data queries will be raised electronically. Data will be collected in a pseudo anonymous form on the Beacon Caresystem (measurements by the mechanical ventilator and measurements by Beacon sensors of respiration, gas exchange, lung mechanics, metabolism and entered arterial blood gas results). This breath by breath raw data collected on the Beacon Caresystem will be securely transferred, stored and processed at Aalborg university. Both eCRF and the Beacon Caresystem will contain only coded reference to each subject.

All additional research patient data will be completed in an electronic Case Report Form (eCRF) which will be configured within the ICCA database (electronic patient record) used in each of the intensive care units under standard operating procedures.

All patient consent/assent forms will be signed, copied and scanned with a hard copy saved for each patient.

Data will be collected from the device after each patient by research team and with the assistance from clinical engineering support to ensure each patient's data is fully saved on a secure cloud database. The volume of data (breath by breath recording) means that it cannot be recorded on any CRF and University of Aalborg will generate an automatic report per patient. Data will be entered in the CRF in cases of adverse events related and not related to mechanical ventilation.

Data will be managed according to the NHS Act 2006, the Health and Social Care Act 2012, the Data Protection Act 2018, and the Human Rights Act 1998 and the study will be conducted according to UK code of Good Clinical practice (GCP) for research.

Data analysis. Data analysis will be performed through a collaboration between relevant scientific partners including Imperial College London and University of Aalborg. Additional post-hoc analyses not covered within this protocol in addition to the development of other collaborations then further amendments will be made to the trial protocol.

Archiving. All trial documentation, including that held at participating sites and the trial coordinating centre, will be archived for a minimum of 10 years following the end of the study.

16. Study Management

The day-to-day management of the study will be co-ordinated through Imperial College Clinical Trials Unit.

Committees involved in the study

A Trial Management Group (TMG) will be convened including the Chief Investigator, co-investigators and key collaborators, trial statistician and trial manager. The TMG will be responsible for day-to-day conduct of the trial and operational issues. Details of membership, responsibilities and frequency of meetings will be defined in separate terms of Reference

A Trial Steering Committee (TSC) will be convened including as a minimum an independent Chair, independent clinician, the Chief Investigator and Trial Manager. The role of the TSC is to provide overall supervision of trial conduct and progress. Details of membership, responsibilities and frequency of meetings will be defined in a separate Charter.

The Data Monitoring and ethics Committee (DMEC) will be comprised of at least 2 independent clinicians, one with experience in clinical trials, and an independent statistician. One of the independent clinicians will have experience in the regulatory aspects of clinical trials involving medical devices. The role of the DMEC will include: monitoring the data and making recommendations to the TSC on whether there are any ethical or safety reasons why the trial should not continue; considering the need for any interim analysis; advising the TSC regarding the release of data and/or information; considering data emerging from other related studies. The DMEC will continually assess both safety and efficacy data on a regular basis with additional meetings can be convened if the event of any safety concerns. The DMEC should be independent of both the Investigators and the funder/Sponsor and should be the only body that has access to unblinded data. At least two independent members of the DMEC should convene to make the committee quorate.

If funding is required above the level originally requested, the independent DMEC may be asked by the CI, TSC, Sponsor or Funder to provide advice and, where appropriate, information on the data gathered to date in a way that will not compromise the trial.

The study will be monitored periodically by trial monitors to assess the progress of the study, verify adherence to the protocol, ICH GCP E6 guidelines and other national/international requirements and to review the completeness, accuracy and consistency of the data
Monitoring procedures and requirements will be documented in a Monitoring Plan, in accordance with the risk assessment.

Risk Assessment
A study-specific risk assessment will be performed prior to the start of the study to assign a risk category of 'low', 'medium' or 'high' to the trial. Risk assessment will be carried out by the ICTU QA Manager in collaboration with the Study Manager and the result will be used to guide the monitoring plan. The risk assessment will consider all aspects of the study and will be updated as required during the course of the study.

Quality Control and Quality Assurance

Quality Control will be performed according to ICTU internal procedures. The study may be audited by a Quality Assurance representative of the Sponsor and/or ICTU. All necessary data and documents will be made available for inspection.

The study may be subject to inspection and audit by regulatory bodies to ensure adherence to GCP and the NHS Research Governance Framework for Health and Social Care (2nd Edition).

Peer review
The trial has undergone peer review as part of the funding application to the EC Horizon 2020. The trial has also been reviewed by senior members of ICTU as part of the Collaborations process. The protocol has been reviewed by intensive care, ARDS and ECMO experts.

Patient and Public Involvement
PPI representatives were involved in giving feedback on the the design of the research and the management of the research. PPI representatives have provided feedback on the PIS/Informed Consent Form (ICF) prior to ethics submission and their comments have been taken into consideration. Upon request, patients involved in the trial will be provided with a lay summary of the principal study findings. The most significant results will be communicated to the public through press releases. Patient and public involvement (PPI) representatives were involved in the design, management, undertaking of the Urgent Public Health badged DeVENT study. The aim of the DeVENT study is to phenotype patients with the Acute Respiratory Distress Syndrome (ARDS) and the PPI meetings highlighted the importance of understanding the biology of ARDS in order to find better treatments. Covid-19 is a cause of ARDS and prior to UPH badging PPI representatives were consulted and supported the amendment to the study protocol to help understand the biology of Covid19-induced ARDS. Given the acute and life- threatening nature of Covid-19 induced ARDS, many patients and their relatives, will place a high value on studies investigating reasons for increased susceptibility which potentially will reduce mortality and/or substantial morbidity. Our PPI representative Ms Yosien Burke who has had personal experience of the major impact that severe respiratory failure can have on someone's life, will play an active part in the TSC, participating in the regular meetings. She will make the research findings more accessible and comprehensible to patients, the public and the media, as appropriate. Finally, advice from PPI representatives for blood sampling prior to personal nominee approval has been sought and given the negligible risk but high benefit during this pandemic and future research, they have been highly supportive.

Publication Policy
Information concerning the study, patent applications, processes, scientific data or other pertinent information is confidential and remains the property of the Sponsor. The investigator may use this information for the purposes of the study only.

It is understood by the investigator that the Sponsor will use information developed in this clinical study and, therefore, may disclose it as required to other clinical investigators. In order to allow the use of the information derived from this clinical study, the investigator understands that he/she has an obligation to provide complete test results and all data developed during this study to the Sponsor.

Verbal or written discussion of results prior to study completion and full reporting should only be undertaken with written consent from the Sponsor.

Therefore all information obtained as a result of the study will be regarded as CONFIDENTIAL, at least until appropriate analysis and review by the investigator(s) are completed.

Any request by site investigators or other collaborators to access the study dataset must be formally reviewed by the TSC.

The results may be published or presented by the investigator(s), but the Sponsor will be given the opportunity to review and comment on any such results for up to 1 month before any presentations or publications are produced.

A Clinical Study Report summarising the study results will be prepared and submitted to the REC within a year of the end of study.

The study will be reported in accordance with the Consolidated Standards of Reporting Trials (CONSORT) guidelines and the Template for Intervention Description and Replication (TIDieR) checklist and guide (35,36).

We plan to publish our trial protocol and statistical analysis plan to ensure transparency in our methodology. The study findings will be presented at national and international meetings with abstracts on-line. Presentation at these meetings will ensure that results and any implications quickly reach all of the intensive care community. This will be facilitated by our investigator group which includes individuals in executive positions in the UK and European Society of Intensive Care Medicine as well as ECMOnet and EuroELSO committees. In accordance with the open access policies proposed by the NIHR we aim to publish the clinical findings of the trial in high quality peer-reviewed open access (via Pubmed) journals. This will secure a searchable compendium of these publications and make the results readily accessible to the public, health care professionals and scientists.

We will actively promote the findings of the study to journal editors and critical care opinion leaders to ensure the findings are widely disseminated (e.g. through editorials and conference presentations) and are included in future guidelines. Due to limited resources, it will be not be possible to provide each patient with a personal copy of the results of the trial. However, upon request, patients involved in the trial will be provided with a lay summary of the principal study findings. The most significant results will be communicated to the public through press releases.

Authorship Policy. Authorship will be determined according to the internationally agreed criteria for authorship (www.icmje.org). Authorship of parallel studies initiated outside of the Trial Management Group will be according to the individuals involved in the project but must acknowledge the contribution of the Trial Management Group and the Study Coordination Centre.

17. Appendix 1 – Beacon screens for monitoring ARDS interventions

Figures A1-A3 illustrate the Beacon screens for monitoring the effects of manoeuvres. The system allows toggling between the view of periodic physiological status (figure A1) and continuously measured clinical variables (figure A2-A3). Figures A2 and A3 show two different views following vertical scrolling to visualise different measurements.

Symbols indicating recruitment start and end, prone and supine positioning and ECMO start are marked, with these having been clicked by the user as part of data entry during initiation and termination of these activities.

Figure A1 – Monitoring of patient's physiological state describing manoeuvres.

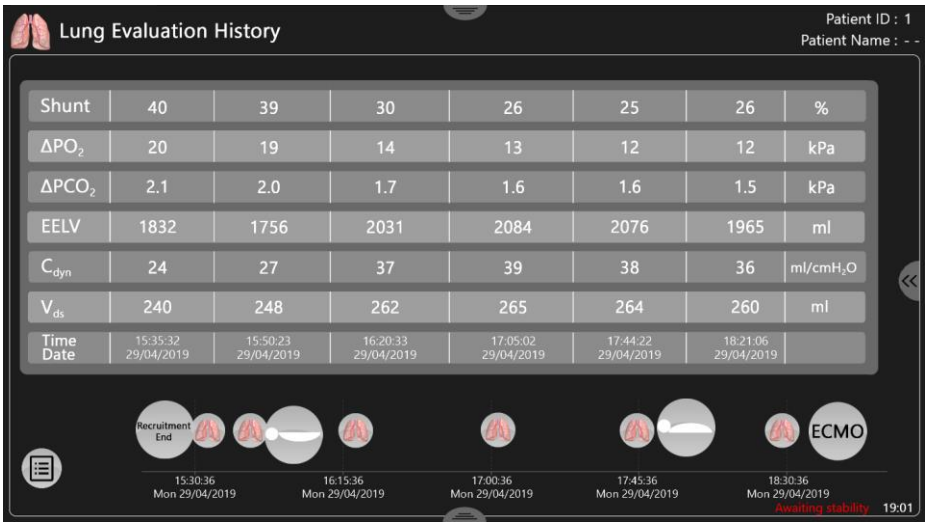
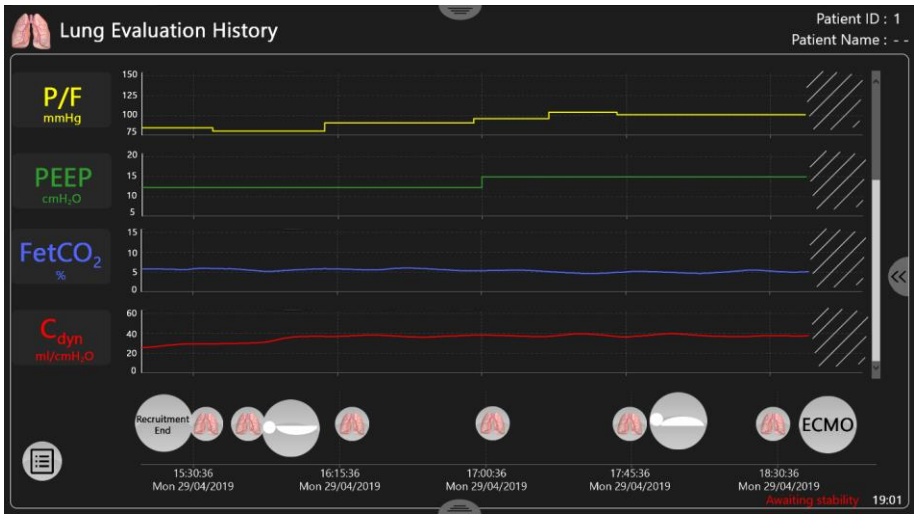


Figure A2 – Monitoring of patient's clinical state describing manoeuvres.

Figure A3 – Monitoring of patient's clinical state describing manoeuvres.



18. Appendix 2 – List of expected adverse events during study

The following list considers whether there is an adverse event or not taking into account the patient population and clinical requirements in ITU.

Expected ICU related complications:

- Hypotension
- Hypertension
- Bradycardia
- Tachycardia
- Desaturation
- Arrythmia
- Re-intubation
- Death related to ARDS and ensuing multi-organ failure
- Neurological insult e.g. intracranial bleeding
- Cardiovascular failure, including the need for vasopressors / inotropes
- Hepatic failure
- Renal failure, including the need for renal replacement therapy
- Haematological / Coagulation failure, including thrombocytopaenia
- Cardiac arrest
- Death

These will only be reported if the treating clinician associates this to the device. This includes any reaction or adverse event that the investigator has concerns about based on previous experience and the patient population. Additionally, any Beacon device errors that are expected as per the device literature will not be considered an adverse event.

The following will be recorded for complications related to mechanical ventilation and device-malfunction for the secondary outcome measure:

1. Device malfunction for >6 hours.
2. Desaturation post change to mehcnical ventilation settings.
3. Barotrauma (pneumothorax, pneumomediastinum etc)
4. Re-intubation
5. ECMO / ECCO2R initiation post-randomisation
6. Tracheostomy
7. Death

Imperial College London

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19. Appendix 3 – Exploratory studies

The pathophysiological and pathobiological processes involved in the progression and resolution of ARDS are poorly understood and there is no current method of predicting trajectory of ARDS. However, the DeVENT study offers a unique opportunity to longitudinally characterise the clinical, physiological, radiological, and biological progression and resolution of ARDS to enable an understanding of disease trajectory. This is currently very important in light of the current COVID-19 pandemic as most ARDS patients is secondary to COVID-19 infection.

Aims:
To investigate the clinical, physiological, radiological, and biological mechanisms which characterise the progression and resolution of ARDS (and COVID-19).

Population:
All patients recruited to the DeVENT Study in centres that are capable and have the regulatory approvals to attain relevant samples.

Study assessments:

Biological Sampling

- **Blood sampling** at (T1) baseline (i.e. on randomisation), and between days 1-3 (T2), 5 -7 (T3), 9-11 (T4), and 13-15 (T5) and weekly (T6, etc) thereafter when in ICU. Blood samples will be taken at subsequent follow-up clinics. Given the urgent nature of COVID-19, a similar sample of blood may be taken prior to starting ECMO (T0) and hence, often prior to discussion with personal nominee, at the discretion of the clinical team. If they are not enrolled into the study then this sample will be discarded.

- **Bronchoscopic sampling** (only if ventilated), with bronchoalveolar lavage (BAL) and deep bronchial brushes, will only be performed if clinically relevant. If patient is in addition on ECMO, patients will be sampled at baseline (T1BAL) and between days 5-7 (T2BAL), and 13-15 (T3BAL) and weekly (T4BAL, etc) thereafter when in ICU. Bronchial brushing maybe performed in some patients. If the patient undergoes a bronchoscopy for clinical purposes, samples will be taken for research purposes dependent on the time of sampling.

- **Urine sampling** (if available) at baseline (T1U) (i.e. on randomisation) and days 1-3 (T2U), 5-7 (T3U), 9-11 (T4U), and weekly (T5U, etc) thereafter.

Excess blood, urine and bronchoscopy samples taken by the clinical team for clinical purposes at the same time-points above may be stored and processed in a similar manner and be utilised for research purposes in order to reduce sampling at any time-points above.

The day of sampling may fall on weekends / holidays when staff are not available. If this does occur, samples/scans will be taken/performed on the day prior/next available day. This will be recorded on the CRF and also on the sample accountability log, along with the day the samples were taken (e.g. day 8 instead of day 7). Blood and urine sampling will be collected by trained study staff and processed according to standardised procedures (37,38).

Additional blood samples (40ml) may be taken at various time-points for leukocyte isolation. Given the uncertain nature of time of insult, Bronchoscopy and BAL will be undertaken where possible, and processed as previously described (38,39). Participants will be closely monitored

during and after bronchoscopy and BAL. A sample will be sent for microbiological analysis. Some of the following analyses may ALSO be performed in patient and human volunteer samples. From our extensive specialist ICU experience, the expected adverse events associated with bronchoscopy procedures include reversible desaturation and minor contact bleeding.

Biological Analyses

Transcriptomic, lipidomic, proteomic and metabolomic techniques may be used on samples such as blood, urine and bronchial brushings to develop clinically useful phenotype handprints. Analyses will be performed to allow intelligent patient and experimental model selection, and identify appropriate samples (for example DNA, RNA, proteins, cells, tissues, blood) for use in the high-dimensional analyses. BAL inflammatory markers (for example cytokines and chemokines measured by ELISA, multiplex sandwich immunoassays, high performance liquid chromatography and meso-scale discovery technology). Breath inflammatory and metabolic markers (including exhaled nitric oxide and metabolomic analysis of volatile organic compounds in exhaled air and metabolites in exhaled breath condensate). Lipid inflammatory mediators may be assessed through the analysis of BAL, serum, plasma and urine biomarkers which may include but not be limited to the measurement of thromboxane B2, prostaglandin E metabolite and 15-epi-lipoxin A4.

To assess **systemic inflammatory and cell death responses**, we may measure plasma and serum inflammatory and cell death response biomarkers which may include but are not limited to measurement of plasma CRP, inflammatory mediators (including but not limited to TNFα, IL1β, IL6, IL8, MLKL, RIPk1/3), proteases and antiproteases, adhesion and activation molecule expression (including but not limited to sICAM1), NETs, coagulation factors (including but not limited to thrombin-antithrombin complex, tissue factor, protein C, thrombomodulin and plasminogen activator inhibitor1), cleaved and whole cytokeratin 16, and Receptor for Advanced Glycation End-products (RAGE) ligands will be undertaken, Specific extracellular vesicle and cellular populations within the blood and BAL (using but not limited to cytospins and flow cytometry) for identification of transcriptome changes within these populations may be carried out.

Pulmonary inflammatory and cell death responses will be assessed via BAL biomarkers which may include but are not limited to the measurement of cytokines (including but not limited to TNFα, FasL, IL1β, IL6, IL8), proteases and antiproteases, coagulation factors (including but not limited to thrombin-antithrombin complex, tissue factor, protein C, thrombomodulin and plasminogen activator inhibitor), and RAGE ligands will be undertaken. Identification of specific cellular populations within the BAL (using but not limited to cytospins, flow cytometry, ELISpot assays, in vitro cell expansion) will also be undertaken. Intracellular signalling activity in the alveolar space which may include but not limited to the measurement of BAL total and phosphorylated p38, ERK and JNK MAPKs and STAT -1/-3 from cellular extracts will be measured. Activated and total IκBα and β may be measured in cytoplasmic extracts and NFκβ and AP-1 in nuclear extracts. These investigations will inform further assessment of the influence of clinically relevant causes of weaning failure (e.g. severity of lung pathology, ventilator-induced lung injury and ventilator associated pneumonia).

Pulmonary and systemic epithelial and endothelial function and injury may be investigated by testing plasma, serum and BAL biomarkers which may include but are not be limited to measurement of RAGE, cleaved and whole cytokeratin 16, angiopoeitin I/II, surfactant protein-

D, von Willebrand Factor, pro-collagen peptide-3 as well as total protein, plasma albumin, α2-macroglobulin, and protein permeability (albumin:α2-macroglobulin ratio) will be undertaken. Urinary albumin/creatinine ratio will also be measured.

Samples from subjects may also be tested on primary cultures of fresh human endothelia, epithelia, neutrophils, monocytes, macrophages and skeletal muscle cells as well as mesenchymal stromal cells to determine surrogate markers of inflammation which may include but not be limited to the measurement of activation (shape change, CD11b surface expression, superoxide release), adhesion and transmigration, cytokine release and matrix metalloproteinase production, rate of apoptosis and their ability to phagocytose. Cells may be isolated from samples for subsequent analysis of cell death and inflammatory pathway activation using a variety of techniques including but not limited to RNA sequencing and flow cytometry.

Microvesicles may be isolated from blood and BAL to study the alveolar and systemic microvesicle release, content and function, which may include but not be limited to the measurement of inflammatory mediator release and cell death. Microvesicles may be co-cultured with human cell lines and primary cell cultures in the presence of BAL and serum/plasma from the same patient to determine the effect on their functional properties (cytokine release, phagocytosis, polarization markers expression). Urine micrvovesicles may undergo similar analyses for assessment of renal physiology and dysfunction.

Circulating cells as well as their respective microvesicles may be isolated from blood. Cells may be stimulated (such as monocytes) or matured for 5-7 days to produce monocyte-derived macrophages (MDMs) and stimulated to identify mechanisms which modulate inflammatory responses in these cells. Furthermore, trophic infection may be examined in circulating cells by Flow Assisted Cell Sorting.

Immunothrombotic analyses are particularly relevant to COVID-19 given the significant pro-thrombitic nature of this disease. Samples will be utilised for phenotyping ARDS secondary to COVID-19 versus non-COVID-19. Levels of circulating cytokines and vascular dysfunction will be measured as described previously alongside markers of haemostasis (which may include but are not be limited von Willebrand factors (antigen and activity), factor VIII, protein C, protein S, ADAMTS 13, and antithrombin levels) to determine clinical immunothrombotic phenotypes. In addition, we will measure key fibrinolytic parameters involved in the breakdown of clot (which may include but are not be limited fibrinogen and D dimer levels, plasminogen, PAI-1, tPA, soluble thrombomodulin and urokinase levels to determine fibrinolytic capacity and activity). Importantly, ECMO can modulate these coagulation measures and hence, pre-ECMO blood sampling is of paramount importance. Given the low risk of sampling and the high importance to discovering novel therapies to treat COVID-19, this has been added to the sampling regime, and will take place prior to personal nominee advice.

Physiological measurements
Daily average physiological status defined as daily averages of measured values of oxygenation (SpO_2), end-tidal CO_2 fraction ($FE'CO_2$), metabolism (VO_2, VCO_2), ventilation (respiratory rate, tidal volume, anatomical dead space), pulmonary mechanics (mean airway pressure, respiratory system compliance), ventilator settings, PaO_2/FiO_2, shunt fraction, and end-expiratory lung volume over time as continuously measured by the Beacon system.

ICU/hospital cardiac, lung and skeletal/respiratory muscle assessments

a) Echocardiography and lung ultrasound parameters including but not limited to ventricular size and function and tricuspid annular plane systolic excursion (TAPSE), with

established clinical protocols.

b) Ultrasound images of the rectus femoris, parasternal muscle and diaphragm will be taken at baseline and on days 1, 3, 7 10, 14 and weekly thereafter, with a final image point on the day of ICU discharge or transfer (or within 24hr of discharge).
c) If able, parasternal and diaphragm imaging will be performed on the first day of a spontaneous ventilation mode.
d) If able, parasternal and diaphragm imaging will be performed during a spontaneous breathing trial (SBT), or when the physician has identified someone as suitable for extubation.
e) If able, parasternal and diaphragm imaging will be performed 24-hours after extubation.
f) Follow-up ultrasound imaging at outpatient follow-up clinics are unchanged and will take place up to 6 and between 6-12 months after ICU discharge.
g) If two time points coincide or are separated by 1 day (i.e. SBT imaging falling on day 7, or first day of spontaneous mode ventilation falling on day 6 etc), then a repeat set of images will not be taken the following day. Rectus femoris imaging time-point will also be adjusted accordingly to avoid repeated disruption to the patient.

ICU/hospital radiological assessments

a) RALE score may be assessed.
b) Axial thoracic CT scans may be assessed for relative proportions of normal lung, ground-glass opacity and lung consolidation and scored as previously described (40) to give a total lung parenchyma score (TLS).
c) Axial thoracic CT scans may be assessed for focal and non-focal patterns of ARDS as previously described (41).
d) Axial thoracic-abdominal CT scans may be assessed for skeletal and respiratory muscle cross-sectional area.

Functional and long term outcome measures

Variables which impact long-term patient related outcome will be measured in a longitudinal manner:

1. ICU/hospital/follow-up skeletal/respiratory/cardiac muscle ultrasound.
2. ICU/hospital/follow-up imaging (X-ray, CT, ultrasound) and lung function in relation to ARDS (as per usual clinical practice).
3. Sf-36 Health Related Quality of life and EQ-5D-5L (patient and carers) (6 month and 1 year after randomization)
4. St George's Respiratory Questionnaire (SGRQ) (1 year after randomization)
5. Cognitive Status Questionnaire e.g. mini Mental State examination; PTSS-14; Hospital Anxiety and Depression Scale (HADS) (1 year after randomization)
6. Return to work rates e.g. W&SAS (patient and carers) (6 month and 1 year after randomization)
7. 6-minute walk test (6 month and 1 year after randomization)

Bio- and image- banking procedures: The scope is to cover all human samples and associated data in the study. The Patient Informed Consent also covers many of the details described here. The types of samples acquired in this study are described above, and includes samples of peripheral blood, urine, bronchial lavage, and bronchial brushes. These samples will be processed from fresh into different formats, for storage at different temperatures. All sample

management (acquisition, processing, storage, shipment, analysis, disposal) throughout the study will be in accordance with:

- EU and relevant national legal and ethical standards, (including, any national research governance requirements and self regulation). The investigators in the project will provide the Management and Ethics Board with a summary of their applicable national or institutional rules regarding Biobank Activities, as well as changes national legal requirements related to Biobank Activities.
- the procedures detailed in the Study Reference Manual (SRM)

The SRM will be provided to all participating centres. All samples will be managed only by fully trained and qualified research personnel.

Images will be stored in the Royal Brompton & Harefield NHS Foundation Trust servers as these images may contain useful information for clinical management of the patient. Images will be performed or analysed in a blinded manner to ensure allocation concealment. If images are transferred outside hospital servers, they will be pseudoanonymised using the study number.

Coding of samples and data: Special precautions will be taken to ensure the study is carried out with a high degree of confidentially. All study data, images, and samples related to the subject will be coded. Each subject will be allocated a code number at the time consent is given. The code will be used to identify him/her and associated data and results, without having to use his/her name, medical record number, or other common identifiers. The coding of all information resulting from the subject's participation in the study is to ensure that the results are kept confidential by keeping the subject's identity and results separate. Each sample will have a sample identifier. Only the coded information will leave the investigator site. No information will be stored on the sample labels that may be used to identify the subject. The subject code together with the sample identifier ensures each sample is uniquely identified.

Only the clinical investigator at each site will have access to the code key with which it is possible to connect personal data to the individual participant. These data are available for review by the sponsor monitoring the study, regulatory authorities and independent ethics committees. The purpose of these reviews is to assure the proper conduct of the study.

For the blood sample for genetic analysis extra precautions will be taken to ensure confidentiality. The sample will be labelled with the same code that is given to the subject in the study. As an added level of security, the DNA when it is extracted from the blood sample and the results of any research on the DNA will also receive a second code number. A file linking the first and second codes will be kept in a secure place with restricted access. If the subject changes his/her mind about participating in the genetic research, this link will allow the sample to be located and destroyed.

Sample and image data storage: Samples taken for each subject will either be sent for immediate analysis, local to the investigator site, to a specialised analysis centre, or processed further and stored at the investigator site, in the local storage facilities before dispatch to, and storage in facilities at Imperial College London.

All samples and image data will be stored securely, with access restricted to approved staff, until required for analysis. The Designated Individual at Imperial College London will be accountable to the Human Tissue Authority for compliance with the Human Tissue Act, the local Person Designated will be responsible for the samples.

All storage facilities will have their own local contingency and disaster/recovery plans. The investigator, for each investigator site, will be the local custodian. He/she will be, accountable for the safe-keeping of the samples and associated data, unless otherwise specified by law. The location of each sample and image will be recorded and tracked throughout its life cycle to maintain a chain- of-custody, in accordance with the SRM. At the end of the storage time any remaining samples and images will be destroyed and their disposal recorded, unless otherwise required to be anonymised by local ethics.

As new scientific data become available we will be able to use this resource of stored samples and images to investigate if this new data is relevant pending additional ethical approval. Samples and images will be stored for up to 20 years. No staff at any storage facilities or facilities outside clinical work areas will have information that directly identifies any subject.

Analysis and Access to samples/images: All analyses are intended to help understand pulmonary, multi-organ, and systemic inflammation associated with ARDS (and COVID-19). Not all of the analyses will be carried out on the samples/images straight away. Until then samples/images will be retained at the sites of sampling or they will be transferred to the research facilities within Imperial College London. When analyses are scheduled to be carried out will depend on when methods are available and sufficient samples/images are available for an analysis. This means that some of the samples/images that are taken in the study and left over samples/images from the research described may be stored for future analysis. Samples/images remaining from any analysis will be returned to Imperial College London or others as appropriate, to enable fair access, by others.

The samples may be used by any of the partners (academic and industry) in this study and may be made available to third parties (on behalf of the sponsor and CI), in accordance with the governance procedures of the DeVENT study for Biobanking, and ethical and legal requirements.

Access to samples is regulated by the Scientific Board consisting of Dr Brijesh Patel, Dr Sharon Mumby, Prof Masao Takata, and Prof Ian Adcock (all of Imperial College London). Investigators, including other third parties relevant to all partners of DeVENT can apply for access to stored study samples and/or data in the study database, based on strictly defined research questions formulated and worked out according to the DeVENT Science and Writing Plan. After endorsement by the Scientific Board the primary responsible investigator for a particular research question will be allowed access to the required, pre-defined sample numbers and amount of material in the biobank. Release of samples from the biobank will require a letter of transfer. Samples may require expedited transport in view of public health emergencies (e.g. covid-19, SARS, MERS-CoV etc) and other emerging pathogens. Hence, samples will be safely stored in appropriate containment level facilities at the respective university and clinical labopratories (e.g. Royal Brompton Hospital) or transferred for specialised analysis with collaborative partners. Access to samples and data will be monitored by the Imperial College London biobank sample tracking system. Tracking samples' life cycle after release from the biobank will be the responsibility of the investigator receiving them.

The informed consent of the donor should cover the use of the human samples for the purpose of the intended research use. However, national regulation or institution policy of an investigator may require that the research requires the prior written approval of an ethics or other qualified committee based on a written research plan. The investigators shall adhere to such requirements and to the extent applicable, will not use any human samples for research use without such prior written approval.

Rights of the Subject: If a subject changes his/her mind about participating in the research, the code and link to his/her identity will enable their samples to be located and destroyed, if he/she wishes, so they cannot be used for further research. However, if the samples have been analysed the sponsors are not obliged to destroy the results and can continue to use the data from those samples. Deciding to withdraw will have no impact on the treatment and care for the subject. The data will be handled in accordance with the relevant Data Protection Laws. The special precautions of coding data (describe above) control access to the data by only those who can break the code, thus preserving your identity and data associated with you. Subjects have the right to request information on their data and a copy provided to them and to request and inaccuracies to be corrected. Each subject will be able to see the general results published from the study, but will not be able to identify their individual results. Where there is any clinically relevant information or unexpected findings from analysis of a subject's samples in the study the subject will be given the opportunity to decide whether he/she wishes to be made aware of the information and the potential impact on him/her in advance of participating in the study. Any information of this nature will, with the subject's permission, be shared with the relevant doctor involved in his/her care. If results are relevant to a subject's health appropriate counselling will be provided, in accordance with local requirements.

Statistics: Statistical power calculation of the number of samples needed will be carried out as part of all experimental designs by a bioinformatics and systems biology work package. Statistical power analysis of the experimental (omics and targeted) datasets is measured as the probability of obtaining statistical significance when true biological differences exist between the compared groups of samples (1 - β; true positive rate). The analysis will be done with the support of bioinformaticians at Imperial College London's Data Science Institute.

Analysis of Descriptive Data. Data will be reported as proportions for categorical variables. For quantitative variables that are normally distributed means ± standard deviations (SD) will be reported. Non normally distributed data will be log transformed to report geometric means with their 95% confidence intervals. In the situation when the transformation does not improve the skewness of the data, then such data will be reported as medians with the interquartile range.

Parametric tests will be used if the data is normally distributed or logarithmically transformed. If the data is not normally distributed non-parametric tests will be used. Analyses will be performed using univariate and multivariate analyses to characterise relationships with physiological/clinical parameters with biological measurements. Comparative analysis of variance between groups (independent samples) for continuous data will be performed using the Student's t test for normally distributed data and the Mann Whitney U test for non-normally distributed data. A comparison of proportions between groups will be performed using the Pearson Chi^2 test.

Generation of phenotype handprint will be overseen by members of the Imperial College London bioinformatics and systems biology group. Classifiers and predictors will be developed based on univariate and multivariate statistical analyses and clustering of omics data, network and pathway modelling (association through protein-protein interaction curated databases), simulation and visualization with graphical interfaces, for the generation of fingerprints (differential expression signatures), and handprint biomarkers (qualitative network state representations amenable to simulation) predictive of disease progression and resolution, and response to interventions in ARDS patients and models, and will support the design and analysis of validation experiments. Based upon the integration of data collected from severe ARDS patients, classifiers and predictors will be developed. This will form the basis of the initial phenotype handprint. Given the complexity of the data involved, the Data Science Institute and

the Artificial Intelligence Network at Imperial College London will be contracted to collate and analyse the data.

20. Appendix 4 – Healthy volunteer recruitment

In addition to patients enrolled on the DeVENT study (as per appendix 3), healthy human volunteer paired blood and urine samples will be taken as part of this study at Imperial College London, so as to have a control comparison group for the biological analyses mentioned as per appendix 3.

We aim to recruit up to 100 healthy volunteers only at Imperial College London. Healthy volunteers will be consented. All volunteers will be provided with a separate participant information sheet (PIS), suffer from no chronic or inter-current illness and will not have had blood take in the previous 7 days. and a signed consent form will be kept. All healthy participants must be ≥18-years old and be able to provide informed consent for themselves. Volunteers may be asked about Covid-19 symptoms and be tested for the virus to ensure robust scientific evaluation of results.

Up to 60mls of blood may be taken using a needle inserted into the hand or arm. 120mls in total will be taken over a period of 4 weeks from each individual healthy volunteer. Urine samples will also be collected at the same time. Blood may be collected regularly from the same volunteer donor and a record of donations & the total collected will be maintained. The total (including donations elsewhere) will not exceed 500ml in a 6 month period.

Inclusion Criteria

- 18 years or older
- Able to consent
- Have mental capacity

Exclusion Criteria

- Blood borne viruses: HIV, Hep B, Hep C
- Blood taken in the last 7 days
- Under doctor for investigation
- Haematological disease
- Currently suffers from infection
- Needle phobia
- Problems with veins / vessels
- Refusal

Leucocyte cones from NHS blood and transplant

To reduce the number of volunteers required we will also request leucocyte cones from NHS transplant and blood in order to establish laboratory technique to perform laboratory tests for participants. Up to 2 leucocyte cones a week will be ordered.

Expected healthy volunteer-related adverse events
The following AEs that could be reasonably expected to be associated with venepuncture procedure:

- Haematomas and ecchymoses around venepuncture site
- Minor discomfort
- Infection

21. References

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22. SIGNATURE PAGE 1 (Chief Investigator)

The signature below constitutes approval of this protocol by the signatory and provides the necessary assurances that this study will be conducted according to all stipulations of the protocol including all statements regarding confidentiality.

Study Title: Decision support system to evaluate VENTilation in ARDS (DeVENT Study)

Protocol Number: 19IC5421

Signed: _____

Name of Chief Investigator DR BRIJESH PATEL
Title

Date: 29/05/2020

Imperial College London

23. SIGNATURE PAGE 2 (Sponsor)

The signatures below constitute approval of this protocol by the signatory.

Study Title: Study title

Protocol Number: Protocol number

Signed: Cheuk Fung Wong Digitally signed by Cheuk Fung Wong Date: 2020.06.01 11:56:10 +01'00'

Name of Sponsor's Representative
Title
Sponsor name

Date: _____

Imperial College London

24. SIGNATURE PAGE 3 (Statistician)

The signatures below constitute approval of this protocol by the signatory.

Study Title: Study title

Protocol Number: Protocol number

Signed: Emanuela Falaschetti Digitally signed by Emanuela Falaschetti Date: 2020.05.28 10:09:51 +01'00'

Name of Statistician
Title
Organisation/Company

Date: _____

Imperial College London

25. SIGNATURE PAGE 4 (Principal investigator)

The signature of the below constitutes agreement of this protocol by the signatory and provides the necessary assurance that this study will be conducted at his/her investigational site according to all stipulations of the protocol including all statements regarding confidentiality.

Study Title: Decision support system to evaluate VENTilation in ARDS (DeVENT Study)

Protocol Number: 19IC5421

Address of Institution: _Royal Brompton and Harefield NHS Foundation Trust

_____Sydney Street, London SW3 6NP_

Signed: _____

Print Name and Title: Dr Brijesh Patel

Date: 29/05/2020