OXYGENATE-Global Protocol Summary

Title	OXYGEN Acute Threshold Evaluation - Global trial: A multicentre randomized phase III trial of conservative versus liberal oxygen therapy in hospitalized patients on non-invasive respiratory support
Short Title	OXYGENATE-Global
Objective	To determine if conservative oxygen therapy versus liberal oxygen therapy reduces mortality at 28-days in hospitalized acute hypoxaemic respiratory failure (AHRF) patients who require non-invasive respiratory support. Secondary endpoints will assess if there is a reduction in oxygen consumption and cost effectiveness of conservative therapy.
Hypothesis	In hospitalized AHRF patients on non-invasive respiratory support, conservative oxygen therapy will reduce mortality at 28-days when compared with liberal oxygen therapy.
Design	Prospective multicentre, patient-centred phase III, parallel group randomized controlled trial.
Sample Size	5000 patients
Sites	OXYGENATE-Global will recruit across an established network of >50 hospital sites globally, including low- and middle- income countries (LMICs).
Population	Patients admitted to a participating institution with AHRF who require any type of non-invasive respiratory support (e.g. Non-Invasive Ventilation, High Flow Nasal Cannula (HFNC))

Eligibility Criteria	*Inclusion Criteria:* • Age ≥ 18 years • Deemed to be hypoxaemic (SpO_2 ≤88-90%) OR • Require non-invasive respiratory support to maintain SpO_2 ≥88-90%. 'Non-invasive' respiratory support includes HFNC (at any flow rate) and / or any method of non-invasive ventilation (CPAP, BiPAP, etc) • Within 16 hours of initiating non-invasive respiratory support • In an area of the hospital where continuous or intermittent (4-8 hours) patient monitoring is feasible by either pulse oximetry or Arterial Blood Gases (ABGs) *Exclusion Criteria:* • Invasive Mechanical Ventilation or extracorporeal life support is planned or anticipated on the day of screening or has previously been provided during this admission • Not for CPR (aggressive care) or deemed unlikely to survive past 24 hours (as determined by the clinical team) • Clinician deems the trial is not in the patient's best interests or a specific SpO_2 target is recommended (e.g. for COPD) • Known to be pregnant • Oxygen delivered during / immediately following sedation or anaesthesia • Known randomisation in this trial within the last 12 months

Strategies	*Conservative Oxygen Therapy* In this group, the FiO_2 is reduced to 0.21 (room air) while maintaining an SpO_2 ≥88% measured by peripheral pulse oximetry. The aim is to achieve the lowest FiO_2 as quickly as possible while maintaining an SpO_2 between 88-94%. *Liberal Oxygen Therapy* This group will follow standard / usual care at the clinician's discretion with no upper limits or specific measures for avoiding high FiO_2 or SpO_2. To minimize contamination this group will have a lower limit of SpO_2 ≥95%.
Outcomes	*Primary Outcome* All-cause mortality at 28-days, censored at hospital discharge. *Secondary Outcomes* • Oxygen consumption (total oxygen consumed censored at hospital discharge) • Healthcare costs with a health economic analysis conducted alongside the main trial • All-cause mortality at timepoints: - ICU discharge - Hospital discharge - 180-days • ICU and Hospital length of stay • Days alive and out of hospital at 90-days • Respiratory outcomes (duration, reinitiation, hypoxic episodes (SpO_2 <88%), progression to IMV, ECMO or death)

	• Organ support-free days at 28-days (respiratory, cardiovascular, renal) • Adverse and Serious Adverse Events • Health Related Quality of life assessed by EQ-5-D (180-days) in as many sites as feasible
Study Duration	The maximum patient follow-up is 6-months post-randomisation.