CLINICAL TRIAL PROTOCOL

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

(OXYGENATE-GLOBAL)

OXYGENATE-Global Protocol Version 1.0 Draft

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Contents

1. DOMAIN 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, 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. NIV, 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, RRT) • 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.

2. LAY DESCRIPTION

Oxygen is a life-saving treatment, commonly given to patients who have illnesses that affect their lungs. These illnesses include serious infections caused by bacteria and viruses that can damage the lungs. This damage causes lung failure where the lungs have stopped working and they don't have enough oxygen ('Hypoxaemic') to breathe normally. When this happens, the patient is admitted to hospital and needs to receive oxygen from a machine through their nose or a facemask. Traditionally, oxygen is given freely, with no limit to the amount of oxygen given to patients, but too much oxygen can also be harmful, is not usually needed by the patient, is expensive and sometimes difficult to access. This is particularly true in many parts of the world where patients do not have access to enough oxygen, the equipment or the staff needed to provide oxygen safely. This became obvious in low- and middle- income countries during the COVID-19 pandemic.

The OXYGENATE-Global trial will include adult patients who are admitted to hospital because they need help with their breathing. It will compare the use of a slightly lower amount of oxygen that is safe but avoids too much exposure with the use of higher levels of oxygen with no limits. The trial will find out if this lower amount of oxygen helps patients to get better faster and leave hospital sooner. It may reduce oxygen use, and the trial will also find out if this reduces healthcare costs and improves access to oxygen in all countries. This trial will be carried out around the world and is supported by the World Health Organization. Results will be important for patients both in Ireland who receive oxygen and in patients where there is limited oxygen available.

3. ABBREVIATIONS

To be added in finalised version

4. Version History

To be added in finalised version

5. OXYGENATE-Global Governance

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Block 6,
Clifton Karachi,
Pakistan.

Responsibilities

- First contact to regulatory authorities and ethical committees
- Submission of requested documents by authorities, ethical committees, after Sponsor approval of documents
- Correspond/communicate, prepare, sign and submit to applicable bodies for purpose related to the Study
- Submitting annual or bi-annual report to ethics committees, in accordance with applicable local requirements
- Make payment of fees associated to submitting documentation to the authorities referred to above, if applicable, after Sponsor approval
- Manage site monitoring activities, and

- All other actions necessary to accomplish the duties and functions enumerated in items above, after approval has been given by Sponsor.

5.2 Steering Committee

Comprises the Chief Investigators, Co-Investigators, Study Project Managers and national coordinators from all regions.

Responsibilities

To oversee all aspects of study management globally, including

- Development of study protocol and data collection materials (CRF, data dictionary etc)
- Trial protocol review
- Liaising with coordinating centres (ICC-CTN and ZU-CCRG)
- Overseeing national and international funding applications
- Managing fiscal responsibilities
- Overseeing study timelines, progress and recruitment rates
- Overseeing the global study conduct

Project managers will have further day-to-day project management duties including day-to-day budget, site liaison, setup, data collection/management including supporting approvals, monitoring/close-out, liaison with coordinating centres and trial committees.

5.3 Regional Management Committees

Regional Management Committees are responsible for overseeing study management in their country/region including:

- Liaising and supporting the steering committee, ICC-CTN and ZU-CCRG with global coordination
- Study set-up in their region
- Assistance with HREC applications
- Protocol training of regional OXYGENATE-Global investigators and coordinators
- Managing investigator payments, as required
- Regional site initiation, monitoring and close-out visits
- Regional management of the study
- Liaising with sites
- Managing regional fiscal responsibilities
- Oversight of study timelines, progress and recruitment rates

5.4 Independent Data and Safety Monitoring Board (DSMB)

Prior to study commencement, an independent DSMB will be appointed with expertise in critical care, biostatistics, respiratory, and clinical trials. The DSMB will ensure participants are not exposed to unnecessary or unreasonable risks and the study is conducted to high scientific and ethical standards.

Responsibilities

- Assess trial performance with respect to recruitment, retention and follow-up, protocol adherence, data quality and completeness to ensure the likelihood of timely and successful completion.
- Monitor interim data regarding the safety and efficacy of the study regimens, so that the trial will be concluded as soon as there is convincing evidence of treatment effects.
- Review abstract and publications of main findings prior to submission to ensure the study is being reported appropriately.
- Review and consider any protocol modifications or ancillary studies proposed by investigators to ensure that these do not negatively impact on the main trial. Protocol modifications will be considered in the context of their potential impact on scientific integrity and participant safety.
- Advise the trial management/steering committee as to whether a protocol should continue as scheduled or undergo a modification due to a finding from the monitoring process.
- In line with above, the DSMB will perform ongoing reviews of predefined safety parameters, safety related data, study outcomes and overall conduct.

The DSMB will conduct two planned interim safety analyses:

- After 500 patients, separation in oxygenation values and reported Adverse Events (AEs) /Serious Adverse Events (SAEs).
- After 2500 patients (half of total sample) recruitment data, all safety related data and outcome data.
- The DSMB will also assess the differential cumulative “serious adverse events” reports received to each interim analysis time point. Full details of the DSMB processes and procedures can be found in the DSMB charter.

a. Contact details

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6. OXYGENATE-GLOBAL AUTHORISATION PAGE

We the chief investigators have read the attached protocol and authorise it as the official protocol for the study entitled '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: OXYGENATE-Global'.

Chief Investigator(s):

Alistair Nichol	Madiha Hashmi
Date:	Date:

7. BACKGROUND AND RATIONALE

7.1. Oxygen is a life-saving treatment

Oxygen is a common, life-saving intervention for acutely ill hospitalized patients, forming part of the WHO essential medicines list since 1979 with huge global disparities in its availability and equipment for oxygen delivery. Medical oxygen therapy is a highly purified form of oxygen, used to support patients who cannot maintain adequate blood oxygen levels through normal breathing. AHRF is a major condition that requires oxygen therapy, affecting ~5 million patients annually. ~30% of patients will die (Bellani 2016), rising to 35% in low- and middle-income countries (LMICs) (Sulani 2024, ACIOS 2025), and to 38% for Severe Acute Respiratory Infections (SARI) during COVID-19 in Africa (Kwizera 2025).

Oxygen is delivered through several methods depending on hospitalized patient severity and resources available. The patient's symptoms, respiratory rate and effort, mental status and their arterial oxygen saturation by arterial blood gas analysis (ABGs measuring SaO2) or by peripheral pulse oximetry (SpO2) are measured. SpO2 is a simpler, low-cost and thus, more widely available measure with an SpO2 <88-90% on room air considered hypoxaemia globally.

Intubation and invasive mechanical ventilation (IMV) may be required for the most severely ill patients. However, supplemental oxygen delivery without the need for IMV is required for the majority of hospitalized and ICU patients. Types of non-invasive respiratory support provide pressurised oxygen through a sealed face-mask, nasal mask, mouthpiece, full face visor or helmet such as Continuous positive airway pressure (CPAP) and Bilevel positive airway pressure (BIPAP)/NIPPV. High-flow nasal cannula (HFNC) delivers high flows of heated and humidified air or oxygen through nasal prongs. The use of these non-invasive supports has increased following COVID-19.

While the type of non-invasive support provided depends largely on the hospital and resource availability, there is a lack of clear guidance and often training in the identification of patients that need oxygen, how to interpret oxygen saturations and titrate oxygen safely and effectively. A WHO observational study conducted during the COVID-19 pandemic (O2CoV2, REF) provided pulse oximeters to LMIC sites and mapped oxygen resource use across 30 countries, informing the design of OXYGENATE-Global.

7.2. Non-invasive oxygen needs to be optimised: The Goldilocks principle

Traditionally, to avoid hypoxaemia and associated cell, organ damage and death, oxygen was delivered liberally. Such liberal therapy ensured adequate blood oxygen levels with a perceived safety net that high oxygen meant hypoxia was unlikely. It is well known that hypoxia increases mortality risk, however, this means patients are often exposed to a supraphysiological concentration of oxygen (fraction of inspired oxygen (FiO_2) of >0.50) compared to the air humans breathe (FiO_2 of 0.21). Research identified that excessive

oxygen (hyperoxaemia) is potentially harmful, increasing production of reactive oxygen species, and oxidative stress which may damage cells (Kallet 2013). It may also increase the risk of areas of lung collapse and arterial hypercapnia (Suzuki 2015). Conservative oxygen therapy may reduce these risks safely resulting in better outcomes while also using less oxygen in regions where it is a scarce resource.

Large multicentre trials to date have focused on investigating conservative oxygen therapy in ICU patients receiving IMV, with limits of oxygen saturation varying between 88-96%, compared to a no-limit approach or ≥95% (ICU-ROX 2020, Barrot 2020, Mezidi 2016, Girardis 2016). Conservative oxygen therapy has consistently been found to be safe, however a benefit in mortality or other outcomes remains unclear and with little data on oxygen consumption or cost-effectiveness. For example, the UK-ROX trial, reported no significant reduction in all-cause mortality at 90 days in 16500 IMV patients randomised to conservative oxygen therapy (88-92%) versus usual clinician-directed care (Martin 2025), while the Mega-ROX trial concluded in November 2025, enrolling 40,000 IMV patients to either liberal or conservative oxygen strategies, with results expected in June 2026. Mega-ROX will likely definitively answer this research question in adult patients on IMV, however this result is not generalizable beyond this patient group.

Systematic reviews have demonstrated the evidence gap for all other patients receiving oxygen (i.e. patients receiving non-invasive respiratory support). Almost all studies to date have enrolled mixed populations, including both IMV and non-invasively ventilated patients. Previous systematic reviews including mixed studies across a variety of conditions with few showing treatment separation, identified no significant difference in non-invasive subgroups (RR 1.21 [0.97-1.51]) (Chu 2018) and (RR 1.18 [0.37, 3.81]) (Klitgaard 2023). A recent systematic review and meta-analysis carried out by the OXYGENATE-Global trial team focused on data only from patients on non-invasive support in acute and critical care (PROSPERO:CRD420251150767). Very few RCTs were identified (6), with all except one small, single-country study with risk of bias also enrolling IMV patients (mixed populations) and no multicentre trials including LMICs. Only 4 studies provided data on mortality for the smaller proportion of non-IMV patients with a RR 0.94 [0.83 , 1.06] (P = 0.33), very low certainty. Adverse events were only reported for the mixed populations which favoured conservative RR 0.89 [0.82, 0.96] (P = 0.004), n=6 RCTs, further highlighting safety. Oxygen consumption was significantly reduced in studies where it was reported. While a clinical benefit remains unclear, the safety of conservative has been continually observed. This data confirms the paucity of evidence with no multicentre clinical trial addressing this question of liberal versus conservative oxygen therapy in non-invasively ventilated patients.

7.3. OXYGENATE-Global is a prioritized question globally

This trial is aligned with international health policy priorities, health-related sustainable development goals and global pandemic/public health challenges. OXYGENATE-Global reflects the mandate of WHO to improve both oxygen provision (WHA resolution 76.3 “Increasing access to medical oxygen”), and to strengthen the global clinical trials ecosystem (WHA resolution 75.8 “Strengthening clinical trials to provide high-quality evidence on health interventions and to improve research quality and coordination.”) This reflects the clinical equipoise, high priority and global interest in addressing this question in this patient cohort and LMIC settings. Furthermore, methods like HFNC use the highest amount of

oxygen in resource constrained environments, where oxygen is limited and costs are often paid directly by patients and families, creating unequal access. If less oxygen could improve outcomes, or at least without compromising patient care, this would greatly benefit patients and healthcare systems.

8. OBJECTIVES

8.1. Aim

We aim to conduct a multicentre randomised pragmatic phase lll trial of conservative oxygen therapy to identify clinical and cost-effectiveness benefits. This trial will determine whether conservative oxygen therapy, when compared to liberal oxygen therapy, reduces mortality at 28-days in hospitalized respiratory failure 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.

In low-resourced settings OXYGENATE-Global also aims to:

- Improve overall care of patients on oxygen through staff training on oxygen delivery and research conduct in an embedded run-in phase at selected sites
- Increase trial capacity and leadership for more equitable research

8.2. Null Hypothesis

That there is no difference in mortality at 28-days in hospitalized respiratory failure patients on non-invasive respiratory support who receive conservative oxygen therapy compared to liberal oxygen therapy (usual care).

9. Trial Design

9.1 Population

Patients admitted to a participating institution with Acute Hypoxaemic Respiratory Failure (AHRF) who require any type of non-invasive respiratory support.

9.1.1 Inclusion criteria

The OXYGENATE-Global trial will enrol a broad population of adult AHRF patients requiring non-invasive respiratory support through the following 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)

* In a run-in phase at a small number of selected sites, pulse oximeters will be provided if not available with training in the O_2 delivery protocol

9.1.2 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

9.1.3 Assessment of eligibility and Randomisation

Eligible patients will be screened for inclusion/exclusion criteria by site investigators and their teams. Patients will be randomised using our easy to use, centralised

secure password protected web-based system. Randomisation will be stratified by study site, and in permuted blocks of variable size.

9.2 Run-in phase

A run-in phase will be conducted at sites (approx. 10-15%) who:

- Have not participated in a multicentre respiratory randomized controlled trial (RCT) in the last 5 years OR feel their participation would benefit from a run-in phase.

This will be decided in collaboration with the steering committee, regional and national coordinating centres and the site Principal Investigator during final site selection and feasibility assessment.

The Run-in phase will include:

- The provision of pulse oximeters if not available
- Additional training sessions and drop-in sessions for troubleshooting alongside a web-based training platform on the protocol (titration of oxygen guided by SpO_2 measurements)
- Clinical Research training on trial conduct fundamentals for site investigators, doctors, allied health and research coordinators/assistants
- Followed by 6 randomised patients (a permuted block) who are assigned to conservative oxygen or liberal oxygen therapy with monitoring and titration as per the protocol.
- All other processes including consent and data will be collected as per the main trial.

This run-in phase will allow coordinating centres to resolve any unforeseen clinical, safety, logistical or trial issues and optimise and refine operational aspects. This allows coordinating centres to check protocol adherence, ensure minimum site variance in management, allows sites familiarise themselves with the intervention protocol, ensures participant safety (data provided to DSMB) while providing an opportunity for sites to feedback about any aspects they find challenging before entering the main trial.

These run-in patients are additional and not included in the target sample size and

main trial statistical analysis.

Outcomes for the run-in phase include:

- Adherence to oxygen therapy protocol defined as oxygen being titrated at least 80% of the time per protocol when SpO_2 is outside of target range (e.g. for conservative oxygen, if SpO_2 >94% FiO_2 is decreased towards 0.21)
- The final 2 run-in patients: Data completion and accuracy is ≥80% and adherence to consent process is 100%
- The primary clinical outcome will be 28-day mortality censored at hospital discharge

This will allow us to assess:

- Trial adherence, feasibility and treatment separation at research naïve sites
- Improvement in clinical outcomes and oxygen delivery (healthcare systems) although the sample size is likely too small to detect an effect, but may be hypothesis-generating

9.3 Main Trial Interventions

All other sites will start the main trial where patients are randomised to one of two study groups: Conservative Oxygen Therapy or Liberal Oxygen Therapy.

9.3.1 Conservative Oxygen Therapy

Conservative Oxygen Therapy aims to provide adequate oxygenation while minimising exposure to hyperoxaemia (where FiO_2 is > required).

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 acceptable lower limit, this lower limit can be adjusted based on site preference with a maximum lower limit of 90%). The aim is to achieve the lowest FiO_2 as quickly as possible while maintaining an SpO_2 ≥88%. A lower limit alarm of 88% will be set.

The SpO_2 in this group should be maintained between 88-94% at all times. SpO_2>94% will be avoided with upper SpO_2 alarms set at 94%.

If the level of oxygen therapy is de-escalated (e.g. to nasal cannula, face mask or non-

rebreather) the target SpO_2 will continue whenever the patient is receiving any form of supplemental oxygen. If SpO_2 is >94% oxygen will be titrated down to 0.21.

9.3.2 Liberal Oxygen Therapy

Liberal Oxygen Therapy aims to minimize the risk of exposure to hypoxaemia and will follow standard / usual care at the clinician's discretion.

This group will have no upper limits (no upper alarms) or specific measures for avoiding high FiO_2 or SpO_2. To minimize contamination this group will have a lower limit of $SpO_2 \geq 95\%$ (a lower limit alarm of 94% is set).

9.3.3 Oxygen monitoring

Continuous or intermittent (4-8 hours) patient monitoring is mandated either by pulse oximetry or Arterial Blood Gases to ensure patient safety, particularly in the conservative oxygen group.

9.3.4 Duration of administration and Permitted Deviations

The allocated oxygen target in both groups will continue while the patient is receiving non-invasive respiratory support or any other form of supplemental oxygen.

In both groups oxygen can be reduced and ceased when it is no longer needed, based on clinician discretion, with deviations from the allocated oxygen targets allowed for the following reasons:

- Deviations above the SpO_2 target if FiO_2 is 0.21 and deviations below the target if FiO_2 is 1.00
- For discrepancies in oxygen readings (between pulse oximetry and ABGs)
- If increased oxygen is required for other clinical reasons

Interventions will continue until supplemental oxygen is discontinued, death or hospital/ICU (depending on the setting) discharge, whichever occurs first. Patients will not be intubated to reach any target, only according to clinical judgement.

9.3.5 Concomitant care

All other aspects of non-invasive support such as device used, settings (e.g. pressure), weaning, and adjunctive therapies will be at clinician discretion.

9.4 Outcome measures

9.4.1 Primary Outcome

All-cause mortality at 28-days, censored at hospital discharge.

The primary outcome has been selected to optimise clinical relevance, is deemed extremely important by our Irish and Global PPI groups and is feasible at a large number of hospitals with diverse resources. All-cause mortality has been utilised in similar respiratory trials in these settings facilitating generalizability and future comparisons. Our Irish-PPI group felt 28-days was a reasonable timeframe to measure survival and recovery in acutely ill patients.

As an objective outcome, it will minimise bias as the intervention cannot be blinded and is easily interpreted by clinicians, patients, families and policymakers.

9.4.2 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 and hospital discharge, 90- and 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 at 180-days in as many sites

as feasible*

* Quality of Life (EQ-5-D) outcome is patient-centred and important to our PPI groups. EQ-5-D requires follow-up with patients and / or families after hospital discharge which may not be feasible in all settings. OXYGENATE-Global will conduct these assessments across as many sites as possible, potentially improving outcome measurement globally.

10. ETHICS

10.1 Study Ethics

This study will be performed in accordance with all relevant ethical and regulatory approvals and guidelines including the Declaration of Helsinki and amendments, ICH-GCP guidelines on the ethical conduct of research, and local ethical and regulatory requirements in the jurisdictions where the trial is being conducted. Ethics applications will be submitted to all relevant ethics boards in every country that is participating, and all required approvals will be in place prior to commencing study activities.

10.2 Consent procedures

Consent in advance of randomisation will be sought from participants who are deemed to have capacity. This study will be conducted in settings where some participants, depending on the severity of their illness, their reliance on medical care, and their mental capacity may be unable to consent. For OXYGENATE-Global consent will be obtained in line with local and country-level ethical guidelines and regulations. Consent may be obtained following local approvals from the patient's substitute decision maker (SDM) if the patient lacks capacity. If the participant regains capacity during the hospital admission, they will be asked for their consent to continue in the trial. This method is well established and supported by the public, with focus groups (PMID:28960624) and public surveys of >1600 members of the public (2019: PMID:31557667) including >850 members of the public in Ireland and 2200 in LMICs highlighting public trust and acceptability of our consent processes in the acute care (>90% find them acceptable). This has been further emphasised in systematic reviews (Gobat 2015) and in collaboration with our Irish, Pakistan and Global public, patient and involvement groups, including review of consent documents. Our OXYGENATE-Global study within a trial also aims to improve the quality of consent for our patients and their families improving acute care trials.

11. DATA MANAGEMENT

In line with the guidance on Research Data Management, a Data Management Plan (DMP), incorporating FAIR data principles, will be completed for OXYGENATE-Global. This will be done in conjunction with the Sponsor; UCD, ICC-CTN as data steward. The DMP will include:

Data Protection

Compliance with these fundamental principles. OXYGENATE-Global will be conducted according to ICH-GCP and all relevant laws and standards. Consultation with DPOs will inform a data protection impact assessment (DPIA), to ensure appropriate safeguards are in place for securing patient data, including safeguarding the transfer of data (EEA-Standard Contractual Clauses). Importantly, staff training in data protection will ensure these principles are upheld.

During the trial

To summarise the data flow during the trial, patients will be screened in the ICU / HDU / Acute ward setting and eligible patients will be randomized using a secure web-based system. They will be given a unique study identifier (pseudonymised). Locally, data will be collected on paper CRF. Access will be restricted to local OXYGENATE-Global investigators and delegated staff. Data will be transferred to a secure password-protected database. Any data transferred from local sites will be pseudonymised. Data are analysed for interim and final analyses. Data remains de-identified/pseudonymised. Data will be maintained locally at each site until study conclusion, then archived as per local regulations.

Future Use and FAIR Data

OXYGENATE-Global supports the view that research data are used to maximum potential for maximum benefit with few restrictions, where possible, while complying with all appropriate safeguards and requirements. The OXYGENATE-Global DMP will outline a plan for long term safe storage, future use/re-use and availability to others that is Findable, Accessible, Interoperable and Reusable. A Data Access Committee DAC (including PPIE consultation) with appointed custodian and coordinator will be responsible for overseeing the management of stored trial data and metadata in usable formats (interoperable), and any relevant accompanying documents; e.g., protocol, SAP, PIL-ICF, codebook); and identifying appropriate repositories (Accessible/Reuse). Each dataset will have a unique identifier (DOI) (Findable). The DAC will also oversee procedures for data sharing, including open-access data/data access requests and eligibility for same/data sharing agreements/terms of sharing/periods and timelines/purpose/mechanism of sharing (Accessible). We will publish and share our DMP (HRB-ICC-CTN and DMP Online) (Findable). Similarly, dissemination of all collaborations arising from data access requests will be widely disseminated.

10.1 Monitoring

The study will be monitored by the project managers or a study representative

including:

- A site initiation visit (SIV) or teleconference before site activation
- At least 2 routine monitoring visits during recruitment
- A close out visit at following recruitment end

Monitoring reports will be prepared and approved by the management committee. A follow-up letter will be sent to the site principal investigator and research coordinator and filed in the investigator site file.

Monitoring will follow a risk-based approach. Additional monitoring will be conducted for run-in phase sites.

Monitoring visits will check:

- Data accuracy through source data verification
- Protocol deviations
- Primary and secondary outcomes
- Approved consent process is followed and original signed consent forms
- Safety: all AEs and SAEs
- Investigator site file completeness and accuracy

10.3 Protocol Deviations

A protocol deviation is an unanticipated or unintentional departure from the expected conduct of an approved study that is not consistent with the current research protocol or consent document. A protocol deviation may be an omission, addition or change in any protocol procedure.

Given that the investigator is responsible for patient safety and care he/she may implement a deviation from, or a change of, the protocol to eliminate an immediate hazard to trial patients without prior HREC approval. The implemented deviation or change must be reported in a protocol deviation form. The deviation must be reported via the study website by the principal investigator and reported to the coordinating centre and relevant HREC (if applicable).

12. Statistical Considerations

12.1 Sample size calculation

Given the goal of providing a definitive evaluation of an intervention under investigation, we will aim to recruit the largest possible sample of participants given time and funding constraints. We've determined that this will be n = 5000 total participants. A (very conservative) 10% loss to follow up would then result in

4500 evaluable participants. For the primary outcome, all cause 28-day mortality, this sample size will provide 90% power to detect a risk difference of -4.3 percentage points or a 16% reduction in risk, assuming a baseline rate of 30% mortality, a 1:1 allocation, and based on a 2-sided test of the treatment effect. Importantly, these are conservative estimates, in that planned covariate adjustment will increase the statistical efficiency of the analyses.

12.2 Statistical analysis plan

Prior to enrolment of the first patient, a detailed Statistical Analysis Plan (SAP) will be developed in collaboration between the trial statistician and the rest of the study investigators. The SAP will be developed in line with established guidelines (Gamble 2017) and standard operating procedures for statistics. The SAP will be pre-registered on the Open Science Framework, and any necessary deviations from this SAP will be documented, versioned, and explained in the final trial report. Once the electronic data capture platform is finalised, we will produce a comprehensive, descriptive monitoring report of all study data. This report will be produced at various points during recruitment and data collection, and follow the principles of Good Statistical Monitoring (de Viron 2024). It will feature various statistical summaries as appropriate (e.g. means, medians, ranges, etc), as well as comprehensive visualisations of study data, and be produced in a manner that maintains blinding. Any queries arising will then be resolved prior to database lock, at which point the blinded data will be made available to the study statistician to execute the SAP.

Generally, the statistical approach to OXYGENATE-Global will target a primary estimand (EMA) that evaluates the superiority of the conservative oxygen therapy over liberal oxygen therapy with respect to all-cause 28-day mortality using a treatment-policy strategy (EMA), following the principle of intention-to-treat. This treatment effect will be estimated by first fitting an adjusted logistic regression model and then by using marginal standardization (Morris 2022) to give an adjusted risk-difference and an adjusted risk-ratio (in addition to the conditional odds-ratio directly generated by the logistic regression model). The analysis model will be adjusted for randomization strata (EMA), and any additional key, prognostic baseline covariates, further increasing the statistical

efficiency of the analysis. These covariates will be specified in the SAP, following established guidance (Kahan 2020), but will generally include age, sex, and indicators of disease severity. Treatment effects with respect to other outcomes will be similarly analysed, using the appropriate generalized linear model with adjustment for key prognostic covariates and randomization strata. These would include the ordinal regression with a logit-link function (i.e. a cumulative odds model) for days-alive-and-out-of-hospital (Liu 2017). Model assumptions will be evaluated with standard sensitivity analyses and regression diagnostics. With a single primary outcome, we will not formally correct for multiplicity, but will transparently report results for all outcomes regardless of the result, providing enough information for readers to make whatever corrections they may consider appropriate (Althouse 2016). Planned interim analyses and a limited number of subgroup analyses will also be pre-registered in the SAP. Special attention will be made to missing data. Our approach to any missing data will depend on its nature, but likely to include both complete case and multiply imputed analyses, along with any relevant sensitivity analyses (Jakobson 2017). Reporting of the statistical analyses will carried out in accordance with CONSORT guidelines for clinical trials (Hopewell 2025).

12.3. Interim Analyses

We will conduct two planned interim analyses:

- After 500 patients, separation in oxygenation values and reported AE's/SAE's.
- After 2500 patients (half of total sample) recruitment data, all safety related data and outcome data.
- The DSMB will also assess the differential cumulative "serious adverse events" reports received to each interim analysis time point. Full details of the DSMB processes and procedures can be found in the DSMB charter (see website).

13. Safety

It is recognised that patients who are acutely and critically ill experience common aberrations in signs and symptoms and laboratory values due to their disease severity and standard therapies they receive. The incidence of death and organ failure is unfortunately high in this population regardless of optimal management and unrelated to trial interventions. Consistent with clinical trials in this setting, events considered to be part of the natural history of the disease or expected complications of severe illness will not be reported as serious adverse events.

All adverse events considered, in the investigator's judgement, to be potentially causally related to the trial interventions or are of concern will be reported. Serious Adverse Events must be reported to the coordinating centre within 24 hours of the site team becoming aware. All events are also submitted to specific forms on the electronic case report form. They are reviewed by the trial management and DSMB.

13.1 Data and Safety Monitoring Board

An independent Data Safety Monitoring Board (DSMB) will be established for OXYGENATE-Global comprising experts in statistics, clinical trials, particularly in LMICs, critical and acute illness, and respiratory failure (5 members). The DSMB will provide oversight to the conduct and safety of OXYGENATE-Global. The DSMB will be established prior to patient enrolment to review serious adverse events (SAEs), mortality and related data. They will conduct two planned interim safety analyses (after 500 and 2500 patients) and advise whether the study should be amended, stopped or continue unchanged. They will also review data from sites who have completed the run-in phase. SAEs and AEs will be reported on a separate case report form and SAEs must be reported to the coordinating centre within 24 h of study staff becoming aware. To ensure and enhance safety, we will carry out a review of all 6 run-in patients at selected sites and the first 3 intervention patients enrolled at each global site. Our systematic review, previous studies, and colleagues did not identify additional risks with conservative oxygen therapy.

The DSMB will ensure participants are not exposed to unnecessary or unreasonable risks and the study is conducted to high scientific and ethical standards. They will:

- Assess trial performance with respect to recruitment, retention and follow-up, protocol adherence, data quality and completeness to ensure the likelihood of timely and successful completion.
- Monitor interim data regarding the safety and efficacy of the study regimens, so that the trial will be concluded as soon as there is convincing evidence of treatment effects.
- Review abstract and publications of main findings prior to submission to ensure the study is being reported appropriately.
- Review and consider any protocol modifications or ancillary studies proposed by investigators to ensure that these do not negatively impact on the main trial. Protocol modifications will be considered in the context of their potential impact on scientific integrity and participant safety.
- Advise the trial management/steering committee as to whether a protocol should continue as scheduled or undergo a modification due to a finding from the monitoring process.
- In line with above, the DSMB will perform ongoing reviews of predefined safety parameters, safety related data, study outcomes and overall conduct.

14. Patient and Public Involvement

Our team has established a Global Critical Care Patient and Public Advisory (GCC-PPI) group to provide input into OXYGENATE-Global, together with REMAP-CAP, PANTHER and PRACTICAL. This group includes representatives with lived experience as ICU patients, their relatives/carers, members of the public and community leaders from participating regions worldwide. They have reviewed this trial prior to protocol development including its research priorities, trial design, processes, outcomes and will review its consent forms with representation at our in-person investigator meeting in Kigali 2025. This group connects to a network of national PPIE groups including in South Asia, with engagement of Brazil and Africa with this application.

OXYGENATE-Global will work alongside these groups to achieve PPIE throughout. Our Irish Patient Public Involvement group have informed our respiratory and pandemic-preparedness research priorities, trial design, processes and outcomes.

These groups will continue to review the trial (meet bi-monthly) during its conduct and all patient/public-facing materials ensuring the trial stays patient-centred and is communicated effectively.

18. Substudies

To be added in finalised version

19. Authorship and Publication

To be added in finalised version

20. Research

To be added in finalised version

21. Funding

To be added in finalised version

22. Trial Registration

To be added in finalised version

23. References

To be added in finalised version

24. Appendices