Master Protocol: OZUHN-004

Platform of Randomized Adaptive Clinical Trials in Critical Illness (PRACTICAL) Randomized Control Trial

Domain Protocol: **OZUHN-004-5**

The Corticosteroid Early and Extended (CORT-E^2) Randomized Controlled Trial

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Sponsor's Agreement to Domain Protocol #OZUHN-004-5 v.3.0, 27-Jun-2024

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Date of Approval: 08-July-2024
DD-MMM-YYYY

Domain Lead Investigators Agreement to the Domain Protocol #OZUHN-004-5 v.3.0, 27-Jun-2024

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Signature and Date: July 3, 2024

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Signature and Date: 05-JUL-2024

SYNOPSIS

Master Protocol Title:	**P**latform of **R**andomized **A**daptive **C**linical **T**rials **I**n **C**critic**al** Illness (PRACTICAL) Randomized Control Trial
Domain Protocol Title:	**The Corticosteroid Early and Extended (CORT-E^2) RCT**
Patient States:	This domain will enrol patients in the following platform defined states; • Non-intubated patients; • Intubated patients, not on extracorporeal life support, with low normalized respiratory system elastance (<2.5 cm H_2O/(ml/kg predicted body weight)); • Intubated patients, not on extracorporeal life support, with high normalized respiratory system elastance (≥2.5 cm H_2O/(ml/kg predicted body weight)); • Patients on extracorporeal life support.
Domain Arms:	The arms being studied in this domain are: <u>Early Cohort</u> - Intervention arm – Early corticosteroid use in patients with AHRF - Control arm – Usual care without corticosteroids <u>Extended Cohort</u> - Intervention arm – extending corticosteroid use (for another 10 days) in AHRF patients still requiring invasive or non-invasive respiratory support after receiving 10 days of corticosteroids - Control arm – Usual care without extending corticosteroids
Hypothesis	Early corticosteroids will improve survival (Early Cohort) in patients with AHRF; and extending corticosteroids (Extended Cohort) will improve survival in those with AHRF still requiring invasive or non-invasive respiratory despite already receiving 10 days of corticosteroids.
Domain Primary Outcome:	60-day mortality from the day of randomization

Domain Secondary Outcome:	1. Mortality at other endpoints (ICU/hospital discharge, 30 days and 6 months) 2. Hospital length of stay 3. Duration of NIV 4. Duration of supplemental oxygen use 5. Ordinal scale of daily respiratory support 6. Need for ECLS 7. Duration of ECLS (for those that require ECLS) 8. Ventilator-free days (VFDs) censored at day 30 9. Health-related quality of life at 6 months (measured with EQ-5D) 10. *Complications from Corticosteroids*: a. Hypernatremia (serum sodium > 150 mmol/L) b. Hyperglycemia (requiring new insulin or increase in insulin by >30% from initial/baseline dose) c. Delirium d. Clinically important GI bleeding (requiring endoscopy or RBC transfusion) e. Nosocomial infection f. Neuromuscular weakness
Domain Design:	A phase III, interventional, open-label, randomized, multi-site study
Duration:	2.5 years of accrual and 6 months follow-up for a total study duration of approximately 3 years.
Planned Total Sample Size:	The Bayesian approach does not require a fixed sample size as the trial will continue enrolling until a statistical trigger is met (see section ***Sample Size*** for additional details). It is estimated that a maximum of 2000 patients will be enrolled in each cohort at 30 to 40 sites.

Inclusion/Exclusion Criteria:	Patients will be eligible for enrolment in this domain if they meet the PRACTICAL platform eligibility criteria **and** the criteria specific to either cohort in the CORT-E^2 domain. PRACTICAL Inclusion Criteria 1) Acute hypoxemic respiratory failure meeting all of the following criteria; a) New or worsening respiratory symptoms developing within 2 weeks prior to the onset of need for oxygen or respiratory support b) Receiving any of the following types of oxygen or respiratory support for at least 4 hours prior to the time of randomization; supplemental oxygen at 10 L/min or higher, high flow nasal oxygen (at any flow rate),

	non-invasive ventilator support, invasive ventilator support, or extracorporeal life support (ECLS) c) $FiO_2 \geq 0.40$ (for venturi mask, high flow nasal cannula, or invasive or non-invasive ventilation) or oxygen flow rate ≥10 L/min on face mask for at least 4 hours at the time of evaluation for eligibility unless already on extra-corporeal life support 2) Age ≥ 18 years <u>PRACTICAL Exclusion Criteria</u> 1. Hypoxemia is **primarily** attributable to acute heart failure or fluid overload 2. Hypoxemia is **primarily** attributable to pulmonary embolism 3. Hypoxemia is **primarily** attributable to status asthmaticus 4. Extubation is planned or anticipated on the day of screening 5. ICU discharge is planned or anticipated on the day of screening 6. The patient is moribund and deemed unlikely to survive past 24 hours (as determined by the clinical team) 7. The patient is being transitioned to a fully palliative philosophy of care **CORT-E^2 Domain Eligibility Criteria** **<u>Early Cohort:</u>** <u>Inclusion Criteria</u> 1. Within 72 hours of admission to an ICU 2. New unilateral or bilateral airspace disease <u>Exclusion Criteria</u> 1. Receiving only low flow oxygen therapy less than or equal to 15L/min 2. More than two doses of corticosteroids (oral or IV, at any dose) received any time during the previous 14 days prior to screening 3. Existing indication for corticosteroids 4. High suspicion for/or confirmed COVID infection 5. Acute traumatic brain injury during the index hospital admission

	6. Allergy to dexamethasone **<u>Extended Cohort:</u>**

	Inclusion Criteria 1. Are admitted to an ICU 2. Have already received a short course (defined below) of corticosteroid specifically for acute respiratory failure, this will include patients: a. randomized to corticosteroid arm in Early Cohort and completed 10 days of corticosteroid as per Early Cohort protocol b. patients with COVID who have received between 8-12 days of corticosteroids as standard of care c. others who have received between 8-12 days of corticosteroids for AHRF OF NOTE: the initial corticosteroid does not have to be dexamethasone and corticosteroids can be at any initial dose 3. Ongoing AHRF requiring HFNC, NIV (continuous positive airway pressure [CPAP] or bilevel) or invasive ventilation Exclusion Criteria 1. An alternate indication for ongoing corticosteroids 2. Acute traumatic brain injury this hospital admission.
Study Assessments:	Study assessments are depicted in the ***Study Schema*** section.
Safety Variables & Analysis:	The safety and tolerability of corticosteroid administration will be evaluated by recording frequency and type of serious adverse events in both groups.
Statistical Analysis:	All analyses, interim and final, will use the intention-to-treat principle. The baseline characteristics comparing randomized groups will be reported using means (and standard deviations), medians (and interquartile ranges) or proportions. Trial data will be analyzed using Bayesian hierarchical generalized linear models to estimate the posterior probability of superiority (or inferiority) and equivalence for each intervention within each cohort. Additional details on statistical analysis are included in section ***Analyses*** and the PRACTICAL Master Statistical Analysis Plan (SAP).

TABLE OF CONTENTS

LIST OF ABBREVIATIONS

ABG	Arterial Blood Gases
AE	Adverse Event
AHRF	Acute Hypoxemic Respiratory Failure
ARDS	Acute Respiratory Distress Syndrome
CAP	Community acquired pneumonia
CCCTG	Canadian Critical Care Trials Group
CIHR	Canadian Institutes of Health Research
CORT-E2	Corticosteroid Early and Extended
COVID	Coronavirus Disease
CPAP	Continuous Positive Airway Pressure
CRF	Case Report Form
DSMB	Data Safety Monitoring Board
ECLS	Extracorporeal Life Support
ECMO	Extracorporeal Membrane Oxygenation
HFNC	High Flow Nasal Cannula
ICU	Intensive Care Unit
IRB	Institutional Review Board
NIV	Non-Invasive Ventilation
$PaCO_2$	Partial pressure of carbon dioxide
PaO_2	Partial pressure of Oxygen
PEEP	Positive End Expiratory Pressure
REB	Research Ethics Board
RCT	Randomized Controlled Trial
SAE	Serious Adverse Events

SAP	Statistical Analysis Plan
SCCM	Society of Critical Care Medicine
SDM	Substitute Decision Maker
SOC	Standard of Care
SpO_2	Percent Saturation of Oxygen

BACKGROUND

Complete background information of the **P**latform of **R**andomized **A**daptive **C**linical **T**rials **i**n **C**ritic**al** Illness (PRACTICAL) Randomized Control Trial can be found in the Master Protocol.

The Problem to be Addressed

AHRF is a clinical syndrome defined by the development of acute hypoxemia requiring respiratory support with high flow nasal cannula (HFNC), non-invasive ventilation (NIV), invasive ventilation, or extracorporeal life support (ECLS). AHRF is caused by varying etiologies, including COVID and non-COVID-related (such as aspiration, bacterial pneumonia, trauma, sepsis), and is common, affecting about 15% of all ICU patients and >30,000 Canadians annually[1-3] with mortality ranging between 20% and 50% depending on severity of illness[4]. Survivors of AHRF experience increased healthcare utilization and costs in the year following ICU admission[5]. AHRF results from altered permeability of the alveolar capillary membrane due to systemic and pulmonary inflammatory/immune responses[6-8], and is essentially synonymous with acute respiratory distress syndrome (ARDS)[9]. However, different from ARDS, AHRF does not require the presence of bilateral airspace opacities on chest imaging, which has proven to be poorly reproducible[10], and does not mandate intubation, thereby including a large proportion of patients requiring noninvasive methods of oxygen support such as HFNC[11,12]. In fact, two quadrant infiltrate in the same lung (not meeting ARDS criteria) and two quadrant infiltrate in different lungs (meeting ARDS criteria) have almost identical outcomes[13]. Given this and the challenges with recognizing ARDS[1], clinicians and researchers are increasingly focused on the more pragmatically defined and recognizable syndrome of AHRF, reflected by a growing number of RCTs focused on this population[14,15].

Early Cohort – Early Corticosteroids in non-COVID AHRF

Given the profound inflammatory response associated with AHRF, various immune modulators, have been evaluated as potential treatment options[16,17]. A meta-analysis of 7 RCTs in 1703 COVID patients with AHRF, which included RECOVERY (Randomized Evaluation of COVID-19 Therapy) data[18], showed a reduction in mortality with the use of corticosteroids (odds ratio [OR] 0.66, 95% confidence interval [CI] 0.53 to 0.82)[19]. The 7 RCTs used various regimens with different formulations, doses and durations of therapy. These results informed a WHO living guideline, coauthored by members of our team, which provided a strong recommendation for corticosteroids in patients with COVID-related AHRF[20]. Whether these results from COVID studies are generalizable to non-COVID AHRF patients is unknown[20].

To address this question, our group performed a meta-analysis of 18 RCTs examining the role of corticosteroids in ARDS of any etiology (see Appendix)[16]. Pooled analysis suggested that corticosteroids probably reduce 28-day mortality (relative risk [RR] 0.82, 95% CI 0.72 to 0.95, moderate certainty) and may reduce the duration of mechanical ventilation (mean difference [MD] 4.0 days, 95% CI 2.5 to 5.5 days fewer, low certainty), with an uncertain effect on corticosteroid-related complications such as neuromuscular weakness, gastrointestinal bleeding and metabolic derangements. These finding were consistent across both COVID and various nonCOVID etiologies of ARDS. Despite our findings, corticosteroid use in non-COVID AHRF remains highly variable[21]. Of note, the recently published CAPE-COD RCT demonstrated improved outcomes with corticosteroids in patients with severe CAP[47]. A large, robust, multicentre RCT, enrolling non-COVID AHRF patients, including patients who are receiving non-invasive and invasive oxygen support, is needed to address whether non-COVID patients with AHRF will benefit from early corticosteroid therapy.

Extended Cohort – Extended Corticosteroids in COVID or non-COVID AHRF

As part of our meta-analysis, we examined a number of pre-defined subgroups including dose, timing, and molecule[16]. Of the subgroups, only duration of corticosteroid therapy demonstrated credible effect modification, with patients who received longer courses (> 7days) experiencing lower mortality compared to those who received shorter courses (<= 7 days) (p-value for interaction = 0.04, moderate credibility of subgroup effect) with no evidence to suggest an increase in adverse events with the longer duration.

The duration of therapy subgroup finding is interesting, given that, despite ubiquitous use of corticosteroids in COVID AHRF, uncertainty persists regarding optimal duration[22]. Although most clinicians follow the RECOVERY protocol of 10 days, this duration was arbitrary. Throughout the pandemic, clinicians have struggled with the decision of what to do when a patient is not improving at the end of the 10-day treatment window, with persistent AHRF requiring invasive or non-invasive respiratory support. We have argued (published review describing the principles guiding corticosteroid therapy in AHRF) based on corticosteroid plasma concentration-time profiles and pharmacodynamic studies that optimal response may require a prolonged course of corticosteroids longer than 10 days[23]. The question regarding optimal duration, especially in those with persisting AHRF, is relevant to all patients regardless of the etiology of their AHRF. A large, multicentre RCT, enrolling AHRF patients with persisting respiratory failure despite an initial course of corticosteroids, is needed to address whether extended corticosteroids in this population impacts outcomes.

Why This Study Is Needed

This clinical trial is designed to inform clinical practice and address two knowledge gaps in COVID and non-COVID respiratory failure.

Early Cohort – ***There is uncertainty whether lessons learned from corticosteroids in COVID AHRF are generalizable to non-COVID AHRF.*** The DEXA-ARDS trial randomized 277 critically ill patients with non-COVID ARDS to receive dexamethasone 20mg daily or placebo and found a reduction in mortality (-15.3%, 95% CI -4.9 to -25.9%) and an increase in ventilator-free days at 28 days (MD 4.8 days more, 95% CI 2.57 to 7.03 days more) with dexamethasone[24]. A 2015 meta-analysis suggested that corticosteroids reduced mortality in patients with severe community-acquired pneumonia (RR 0.67, 95% CI 0.45 to 1.01)[25]. Despite these data suggesting benefit of corticosteroids in non-COVID AHRF, use of this therapy remains highly variable. The 2017 Society of Critical Care Medicine (SCCM) guidelines made a conditional recommendation for corticosteroids in both ARDS and CAP based on moderate certainty evidence, with a rationale that further high quality data was needed before a strong recommendation could be made[26].

Patients with non-COVID AHRF, not meeting traditional ARDS criteria, but receiving HFNC or NIV may benefit from corticosteroids but have not been sufficiently studied. Use of HFNC has increased markedly in patients with AHRF[27]. In fact, the most recent 2020 European guideline made a strong recommendation for HFNC in patients with AHRF[28]. We are aware of planned updates to the ARDS definition that will include patients on HFNC. Studies evaluating the effect of corticosteroids in critically ill COVID patients demonstrated a trend towards greater effect of corticosteroids in those requiring HFNC or NIV compared to invasive mechanical ventilation (ratio of ORs 4.34, 95% CI 1.46 to 12.91) with the hypothesis that modulating the inflammatory response early before it becomes too severe may be optimal[19]. Corticosteroids also reduce the need for invasive mechanical ventilation in patients with COVID AHRF (25 fewer per 1000, 95% CI 1 to 44 fewer)[29]. It is unclear whether these lessons learned from COVID AHRF are generalizable to non-COVID AHRF patients on HFNC or NIV.

Extended Cohort - ***The benefit of corticosteroids in COVID AHRF is substantial; however the optimal duration of treatment is unknown. This issue is also unresolved for non-COVID AHRF.*** Despite availability of effective vaccines, ICUs worldwide are continuing to see patients with AHRF from COVID, due to new variants, vaccine hesitancy, and host vulnerability. Although corticosteroids have become ubiquitous for treatment of COVID AHRF, the optimal duration of therapy remains unclear, especially in those with non-resolving disease. COVID patients with progressive clinical deterioration and ongoing requirement for life support have higher persisting

levels of inflammatory biomarkers[30] and therefore continuing corticosteroids beyond 10 days could lead to important benefits. The question related to optimal duration in those with persisting AHRF, is relevant to all patients, including both COVID and non-COVID AHRF. Answering this question is a global priority and has the potential to improve outcomes for millions of patients who develop AHRF each year.

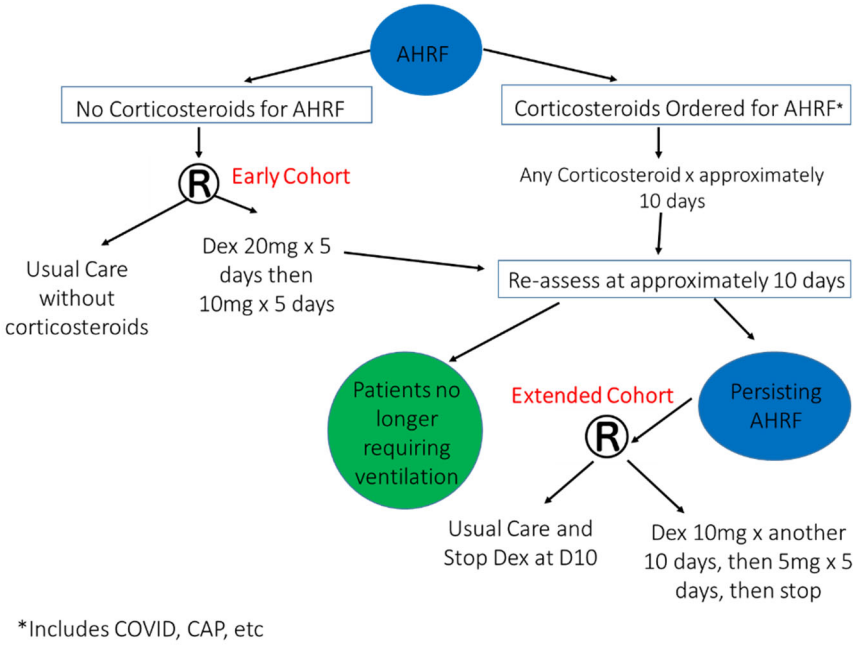
Safety of Intervention

Although corticosteroid administration has been associated with potential harms (e.g. immunosuppression, metabolic derangements, obesity, osteoporosis, gastric ulceration, etc.) these adverse effects are generally associated with durations of therapy over 1 month. The RECOVERY trial did not show an increased risk of serious adverse events in patients randomized to dexamethasone compared to those that did not receive corticosteroid[18]. Our meta-analysis examining corticosteroids in all patients with ARDS found corticosteroids probably increase hyperglycemia (RR 1.11, 95% CI 1.01 to 1.23, moderate certainty) with an uncertain effect on neuromuscular weakness (RR 0.85, 95% CI 0.62 to 1.18, very low certainty) and GI bleeding (RR 1.20, 95% CI 0.43 to 3.34, low certainty)[16]. Duration of corticosteroid therapy among included studies ranged from 5 to 30 days, with the majority (10/18) using a duration of 14 days or longer. In general, metabolic changes associated with short-term corticosteroid administration are easily treated in the ICU setting. Although there is no demonstrated increased risk of nosocomial infection associated with short-course corticosteroids in critically ill patients, this is an ongoing concern and therefore this will be carefully captured and adjudicated as part of the CORT-E^2 trial.

Domain Set-Up

The Corticosteroid Early and Extended (CORT-E^2) Trial is a phase III, multicentre Bayesian randomized controlled trial (RCT), embedded within the PRACTICAL platform trial (refer to the Master Protocol), which includes two cohorts within the domain; early corticosteroids in AHRF (Early Cohort) and extended corticosteroids in persisting AHRF (Extended Cohort). Patients enrolled in the Early Cohort may be eligible for randomization into the Extended Cohort after they have completed their corticosteroid treatment as part of the Early Cohort. Figure 1 below provides a flow-chart summary of the structure of the domain.

Figure 1: CORT-E^2 Study Schema



Summary

The results of the CORT-E^2 trial may change the management of patients with AHRF in ICUs worldwide. Lessons learned from this trial will impact both COVID and non-COVID patients, with large-scale applicability irrespective of the pandemic waning or evolving. Compared to many interventions, corticosteroids are inexpensive and easily administered. Thus, if early corticosteroids in AHRF or extended corticosteroids prove beneficial, operationalizing their use will be straightforward. If no difference is seen, our results will still be very informative and support not using corticosteroids in early non-COVID AHRF and using for only short durations (10 days) in those with COVID or other conditions for which corticosteroids are used.

PRIMARY RESEARCH QUESTIONS, HYPOTHESIS, AND STUDY OUTCOMES

Primary Research Questions

Early Cohort: In patients with AHRF not already treated with corticosteroids who are requiring HFNC, NIV, invasive ventilation or ECLS, what is the effect of 10 days of dexamethasone compared to no dexamethasone on 60-day mortality?

Extended Cohort: In patients with AHRF of any etiology who have been treated with approximately 10 days of corticosteroids, and who have ongoing requirement for HFNC, NIV, invasive ventilation, or ECLS, what is the effect of extending therapy with dexamethasone for another 10 days compared to stopping dexamethasone on 60-day mortality ?

Hypothesis

Early corticosteroids will improve survival (Early Cohort) in patients with AHRF; and extending corticosteroids (Extended Cohort) will improve survival in those with AHRF still requiring invasive or non-invasive respiratory despite already receiving approximately 10 days of corticosteroids.

The CORT-E2 Study Outcomes

Primary Outcome

60-day mortality from the day of randomization

Secondary Outcomes

1. Mortality at other endpoints (ICU/hospital discharge, 30 days and 6 months)
2. Hospital length of stay
3. Duration of NIV
4. Duration of supplemental oxygen use
5. Ordinal scale of daily respiratory support**
6. Need for ECLS
7. Duration of ECLS (for those that require ECLS)
8. Ventilator-free days (VFDs) censored at day 30
9. Health-related quality of life at 6 months (measured with EQ-5D)
10. *Complications from Corticosteroids*:
    a. Hypernatremia (serum sodium > 150 mmol/L)

b. Hyperglycemia (requiring new insulin or increase in insulin by >30% from initial/baseline dose)
c. Delirium
d. Clinically important GI bleeding (requiring endoscopy or RBC transfusion)
e. Nosocomial infection
f. Neuromuscular weakness

**The daily respiratory support ordinal scale will use longitudinal proportional odds to categorize each patient's daily respiratory support needs for 30 days. Each patient will be assigned one of the following ordinal categories each day: 6 (no support), 5 (supplemental oxygen), 4 (high flow nasal cannula), 3 (non-invasive ventilation), 2 (invasive mechanical ventilation), 1 (extracorporeal life support), 0 (death). We will assess daily respiratory support needs using Markov longitudinal proportional odds modelling to estimate an odds ratio[48,49]. This represents a novel scale that will be assessed compared to the other patient-important outcomes listed above.

PATIENT POPULATION, ELIGIBILITY AND ENROLLMENT

Any questions about eligibility criteria must be addressed ***prior*** to patient randomization. This trial will be conducted in compliance with the master and domain protocols, GCP and Health Canada regulations (as applicable).

Patient Population

The CORT-E^2 trial is a phase III, multi-centre (30-40 centres), randomized, open-label trial, embedded as a domain within the PRACTICAL platform trial. This domain will enrol patients in the following platform defined states (in both trial cohorts);

- Non-intubated patients;
- Intubated patients, not on extracorporeal life support, with low normalized respiratory system elastance (<2.5 cm H_2O/ml/kg predicted body weight);
- Intubated patients, not on extracorporeal life support, with high normalized respiratory system elastance (≥2.5 cm H_2O/ml/kg predicted body weight);
- Patients on extracorporeal life support.

Patients who satisfy the PRACTICAL platform eligibility criteria **and** the criteria specific to **either** cohort in the CORT-E^2 domain will be considered.

PRACTICAL Platform Eligibility Criteria

<u>PRACTICAL Inclusion Criteria</u>

1. Acute hypoxemic respiratory failure meeting all of the following criteria;
    a. New or worsening respiratory symptoms developing within 2 weeks prior to the onset of need for oxygen or respiratory support
    b. Receiving any of the following types of oxygen or respiratory support for at least 4 hours prior to the time of randomization; supplemental oxygen at 10 L/min or higher, high flow nasal oxygen (at any flow rate), invasive ventilator support, extra-corporeal life support (ECLS), or non-invasive ventilator support
    c. Minimum FiO2 ≥ 0.40 (for venturi mask, high flow nasal cannula, or invasive or noninvasive ventilation) or oxygen flow rate ≥10 L/min on face mask for at least 4 hours at the time of evaluation for eligibility unless already on extra-corporeal life support

2. Age ≥ 18 years

PRACTICAL Exclusion Criteria

1. Hypoxemia is **primarily** attributable to acute heart failure or fluid overload
2. Hypoxemia is **primarily** attributable to pulmonary embolism
3. Hypoxemia is **primarily** attributable to status asthmaticus
4. Extubation is planned or anticipated on the day of screening
5. ICU discharge is planned or anticipated on the day of screening
6. The patient is moribund and deemed unlikely to survive past 24 hours (as determined by the clinical team)
7. The patient is being transitioned to a fully palliative philosophy of care

CORT-E2 Domain Eligibility Criteria

Early Cohort

Inclusion Criteria

1. Within 72 hours of admission to an ICU
2. New unilateral or bilateral airspace disease

Exclusion Criteria

1. Receiving only low flow oxygen therapy less than or equal to 15L/min
2. More than two doses of corticosteroids (oral or IV, at any dose) received any time during the previous 14 days prior to screening
3. Existing indication for corticosteroids
4. High suspicion for/or confirmed COVID infection
5. Acute traumatic brain injury during the index hospital admission
6. Allergy to dexamethasone

Extended Cohort

Inclusion Criteria

1. Are admitted to an ICU
2. Have already received a short course (defined below) of corticosteroid specifically for acute respiratory failure, this will include patients:

a. randomized to corticosteroid arm in Early Cohort and completed 10 days of corticosteroid as per Early Cohort protocol
b. patients with COVID who have received between 8-12 days of corticosteroids as standard of care
c. others who have received between 8-12 days of corticosteroids for AHRF

OF NOTE: the initial corticosteroid does not have to be dexamethasone and corticosteroids can be at any initial dose

3. Ongoing AHRF requiring HFNC, NIV (continuous positive airway pressure [CPAP] or bilevel) or invasive ventilation

Exclusion Criteria

1. An alternate indication for ongoing corticosteroids
2. Acute traumatic brain injury this hospital admission

Eligible non-randomized patients will be identified and reasons for non-enrolment classified as:

1. Lack of consent from patient or substitute decision maker (specifying reason);
2. Refusal from attending physician (specifying reason);
3. Enrolment in a confounding RCT;
4. Research coordinator or drug not available

To better characterize the generalisability of our randomized population, baseline, demographic, and outcome data may be recorded on eligible non-randomized patients.

Patient Consent

Patient / substitute decision maker (SDM) (as applicable for patients lacking decision making capacity) consent must be obtained prior to any domain-specific screening procedures, randomization and start of study intervention. Consent process will be conducted as per local REB/IRB requirements and recommendations, Health Canada's notice "Management of Clinical Trials during the COVID-19 pandemic: Notice to clinical trial sponsors", and FDA Guidance on Conduct of Clinical Trials of Medical Products during COVID-19 Public Health Emergency – Guidance for Industry, Investigators.

This requirement may be waived in cases of emergencies when deferred consent is obtained post study intervention, if this is allowable per the site REB. It will be the responsibility of the local participating investigator to obtain the necessary clearance, and to indicate in writing to Ozmosis

Research Inc. that such clearance has been obtained, before the trial can commence at that centre. Sample English consent forms for the trial will be provided. A copy of the initial full board REB/IRB approval and approved consent form must be sent to Ozmosis Research Inc.

Patient Randomization

General registration information can be found in the PRACTICAL Master Protocol.

Prior to randomizing a patient, each institution must have submitted all necessary regulatory documentation to Ozmosis Research Inc. and received a local activation letter. Access to the eCRFs will be granted once this has been received and randomization will occur online via the REDCap database.

Patient eligibility must be confirmed by the principal investigator or one of the sub-investigators at the site prior to randomization into either cohort in this domain. An explanation of the study, discussion of the expected side effects, and full disclosure of the "informed consent" document must take place. Eligible and consented patients will be randomized into individual cohorts within the domain.

Early Cohort Screening: Patients will be screened for eligibility at the time of ICU admission. After-hours screening should be performed where possible, however the 72-hour window for enrolment in the Early Cohort should allow most patients to be captured with weekday screening alone. Patients who do not meet oxygen support thresholds for Cohort #1 at initial screening will be followed to determine if they deteriorate and meet criteria within the 72-hour post-ICU admission window.

Extended Cohort Screening: Patients receiving corticosteroids for any type of AHRF in the ICU should be tracked (including patients that are receiving treatment as part of the Early Cohort). Patients that were included in the Early Cohort that remain on treatment for 10 days should be screened for eligibility for a second randomization into the Extended Cohort, and randomized on day 10 of treatment, if eligible. Patients that are receiving their initial course of corticosteroid as part of SOC (and not as part of the Early Cohort), can be screened and if they meet Extended Cohort eligibility criteria after 8-12 days of corticosteroid treatment, they can be approached for consent and possible randomization into the Extended Cohort.

For patients who are receiving their initial course of corticosteroids as part of standard of care and are eligible for the Extended Cohort, randomization into the Extended Cohort should be prioritized at 10 days, or as close to 10 days as possible. However, randomization into the Extended Cohort two days shorter or two days longer are acceptable depending on the initial

corticosteroid prescription (e.g., if only 8 or 9 days were prescribed) or practicalities (e.g., to avoid weekends or holidays). If there is uncertainty as to whether corticosteroids were prescribed for AHRF or another indication, the treating team should be consulted to confirm eligibility.

Sites will maintain a screening log documenting all patients reviewed and reasons for exclusion.

Eligible and consented patients for either cohort will be randomized via REDCap, following a 1:1 (intervention arm: control arm) schedule stratified by study centre and level of oxygen support (non-invasive, invasive or ECLS) at the time of randomization.

STUDY PLAN

Study Schedule

As per the above section, patients will be screened, consented and their eligibility will be confirmed by an investigator prior to randomization.

Patients will receive the study intervention as described in the 'TRIAL INTERVENTIONS' section below.

We will collect data on patients during the ICU and hospital stay. The only planned post-ICU discharge follow-up is for vital status (dead or alive) at 60 days and 6 months and for quality of life at 6 months. This will be assessed by monitoring available electronic medical records, obituaries and contacting the patient/family by telephone, if required.

Randomization is Day 0.

Study Assessment Schema

Required Investigations*	**Baseline**	**Daily****	**D3**	**D7**	**D28 or ICU DC[15]**	**D60[13,14]**	**6 Months[13]**
Window	*Within 72 hours prior to randomization[6]*	*N/A*	*N/A*	*N/A*	*N/A*	*+10 days*	*+/- 14 days*
Consent[1] & Randomization	X						
Demographics[2]	X						
Medical History[3]	X						
Vitals[4]	X	X					
Hemodynamics[5]	X	X					
Hematology[7]	X	X					
Biochemistry[8]	X	X					
Arterial Blood Gases (ABG)[9]	X	X					
Study Drug Administration	*Refer to the 'TRIAL INTERVENTIONS' section for details related to each cohort*						
Optional: Blood Sample Collection	X		X	X	X		
Mechanical Ventilation Data		X					
Readiness to Wean	X	X					
Spontaneous Breathing Trial		X[10]					
EQ-5D-5L							X

Glasgow Coma Scale and Sofa Score	X	X					
Vital Status						X	X
Serious Adverse Events		X[11]					
Concomitant Medications		X					

[1] Consent should be done prior to any baseline assessments and according to site institutional timelines. Site should follow their institutional guidelines for consenting window (timeframe for prior to enrollment/protocol treatment). Please refer to section "Patient population, eligibility and enrollment".
[2] Demographics include age, gender, height, and weight.
[3] Hospital admission (date/time), ICU admission (date/time), APACHE IV, Charlson Comorbidity Index, COVID-19 infection status
[4] Vitals include temperature, heart rate, respiratory rate, and blood pressure.
[5] Hemodynamics include BP, PCWP, Sv02
[6] If multiple time points for baseline data are available within the time point window, values closest to randomization should be entered.
[7] Hematology reporting on Hg, WBCs, and platelets.
[8] Biochemistry will include reporting the following values: sodium, glucose, creatinine, albumin, bilirubin, potassium, bicarbonate.
[9] ABG testing will include the following parameters: pH, $PaCO_2$, HCO_3, SaO_2, lactate, hemoglobin.
[10] Spontaneous breathing trials will be conducted only when patient is deemed ready for weaning and per standard of care and/or institutional guidelines.
[11] SAEs will be reported at the start of randomization and for a period of up to 30 days, or while in ICU, whichever is shorter.
[12] EQ-5D-5L administered via phone or e-mail at 6 months.
[13] The timing of the D60 and 6 Month follow-up are based on calendar days from the day of randomization (D0). The second randomization date (Extended Cohort randomization) will be used as the starting point for this follow-up for patients randomized into both the Early Cohort and Extended Cohort. These patients do not have to have these follow-up assessment's done twice.
[14] The Day 60 vital status check can be done based on review of medical records if the site has access. In those cases, it is not necessary to contact the patient.
[15] Day 28 or ICU discharge (DC) (whichever is sooner)
*All highlighted and blue fields are standard-of-care assessments and data being collected for study purposes.
**Daily data common to all groups will be collected for the duration of ICU stay and up to day 30 (no daily data will be collected on the ward).

Optional Correlative Sample Collection

Blood sample collection, for the assessment of lung, muscle, and brain injury biomarkers, and other future research studies will occur at the time points indicated in the Study Schema for patients that have provided informed consent on the optional consent for blood sample collection. It is not mandatory for all sites to participate in the collection of correlative samples and each site's willingness and ability to participate will be discussed on a case-by-case basis. Further details are available in the Manual of Procedures.

TRIAL INTERVENTIONS

Early Cohort

Intervention Arm:

Patients randomized to receive corticosteroids will receive dexamethasone 20mg daily for 5 days and then 10mg for an additional 5 days, for a total of 10 days or until ICU discharge or death, whichever comes first. After 10 days dexamethasone will be stopped without a taper. If a patient is discharged from the ICU prior to completing the protocol, then ongoing corticosteroid management will be up to the treating team as per SOC.

Dexamethasone will be administered parenterally (intravenous administration). Specific details on the timing of administration are provided below;

- 20mg dexamethasone is to be administered as soon as possible and on the day of randomization (Day 0), and this dose will be administered daily for a total of 5 days of treatment (Day 0 – Day 4). Then, the dexamethasone dose will be reduced to 10mg and this dose will be administered daily for a total of 5 days (Day 5 – Day 9).
- In rare cases where it is not possible to administer the first dose of study drug on the same day as randomization (e.g., if the patient is randomized very close to midnight), 20 mg dexamethasone can be started the day following randomization (Day 1), and will be administered daily for a total of 5 days of treatment (Day 1 – Day 5). Then, the dexamethasone dose will be reduced to 10mg and this dose will be administered daily for a total of 5 days (Day 6 – Day 10).

Patients finishing 10 days of dexamethasone as part of the Early Cohort will be eligible for randomization in the Extended Cohort if they are still requiring HFNC, NIV, IMV or ECLS, and according to the other eligibility criteria for the Extended Cohort.

Control Arm: Those randomized to usual care will receive routine AHRF management without corticosteroids. All other aspects of care will be at the discretion of the treating team including antibiotics, intravenous fluids, mechanical ventilation and ECLS.

Early Cohort Study Treatment Schedule Tables:

Early Cohort – Intervention Arm Patients		
Treatment	**Day 0 (Early Cohort Randomization) to Day 4***	**Days 5 to 9***
20 mg Dexamethasone	X	
10 mg Dexamethasone		X

Early Cohort – Control Arm Patients	
Treatment	**Day 0 (Early Cohort Randomization) to Day 9**
Routine AHRF management without corticosteroids	X

**The Day numbers may be shifted back by 1 day for patients that are not able to receive their first dose of study drug on the same day as randomization (per the section above).*

Extended Cohort

Intervention Arm: Patients randomized to receive extended dexamethasone will receive dexamethasone 10mg for an additional 10 days. At the end of the additional 10 days , the dexamethasone dose will be halved to 5mg for another 5 days (to reduce the risk of adrenal insufficiency) and then stopped (including taper, a total of 23-27 days (depending on the length of their initial course of dexamethasone [8-12 days]) or until ICU discharge or death, whichever comes first). A taper is encouraged, however not mandated even if the patient is sent to the ward. If a patient is discharged from the ICU prior to completing the protocol, then ongoing corticosteroid management will be up to the treating team as per SOC.

Dexamethasone will be administered parenterally (intravenous administration). Specific details on the timing of administration are provided below;

- Dexamethasone is to be administered such that there is no lapse in dexamethasone treatment (no dexamethasone free day in between their last dose from Early Cohort or SOC and their first day of dexamethasone treatment as part of the Extended Cohort).
- If the patient is randomized the day after they received their last dexamethasone dose as part of the Early Cohort or SOC; 10mg dexamethasone will be administered on the day of randomization (Day 0) and this dose will be administered daily for a total of 10 days of treatment (Day 0 – Day 9). Then, the dexamethasone dose will be reduced to 5mg and this dose will be administered daily for a total of 5 days (Day 10 – Day 14).
- If the patient is randomized on the same day they are receiving their last dexamethasone dose as part of the Early Cohort or SOC; 10mg dexamethasone will be administered on the next day (Day 1) and this dose will be administered daily for a total of 10 days of treatment (Day 1 – Day 10). Then, the dexamethasone dose will be reduced to 5mg and this dose will be administered daily for a total of 5 days (Day 11 – Day 15).

Control Arm: Those randomized to the comparator arm will stop corticosteroids after their initial course without a taper. All other aspects of care will be directed by the treating team.

Extended Cohort Study Treatment Schedule Tables:

Extended Cohort – Intervention Arm Patients		
Treatment	**Day 0 (Extended Cohort Randomization) to Day 9***	**Days 10 to 14***
10 mg Dexamethasone	X	
5 mg Dexamethasone		X

Extended Cohort – Control Arm Patients	
Treatment	**Day 0 (Extended Cohort Randomization) to Day 14**
Routine AHRF management without corticosteroids	X

**The Day numbers may be shifted back by 1 day for patients that are not able to receive their first dose of study drug on the same day as randomisation (per the section above).*

Characterization and Accountability of Study Drug

Dexamethasone is an approved corticosteroid that is routinely stocked and used in hospital settings; it will be provided from the local site supply. Sites will be responsible for assuring adequate local supply, accountability and destruction in coordination with local pharmacy practice and any applicable regulations.

In jurisdictions where it is labeled as an investigational medicinal product for the purpose of this study, it should not be used for any purpose outside the scope of this protocol, nor can it be transferred or licensed to any party not participating in the study.

For more information, please refer to the study pharmacy manual (if applicable).

Participant Compliance and Dropout

We do not expect issues with protocol adherence as corticosteroids are commonly used, and all study drugs will be administered by ICU nurses. We will capture open label corticosteroid use in those randomized to SOC in the Early Cohort, and extended corticosteroid use in those randomized to stop corticosteroids at 10 days in the Extended Cohort but we expect the number of crossovers to be small.

Premature Withdrawal/Discontinuation Criteria

Treating physicians may choose to discontinue therapy at their discretion, including any situation that occurs such that continued participation in the study would not be in the best interest of the participant.

Participants are free to withdraw from participation in the study at any time upon request. Discontinuation of the study drug regardless of the reason (e.g. patient or physician request, or adverse event), does not constitute study withdrawal. Patient follow-up data will still be collected as planned and analyzed as intent to treat unless the participant withdraws consent for continued follow-up.

Patients that are withdrawn at any time after randomization will not be replaced.

CONCOMITANT MEDICATION/PROCEDURES

The administration of the following concomitant medications will be collected for study purposes from time of consent to time of ICU discharge or for 30 days, whichever is shorter.

- Antivirals (e.g., Remdesivir; COVID specific medications)
- Interleukin (IL)-6 Inhibitors
- Janus Kinase (JAK) Inhibitors
- Neuromuscular blocking agents (e.g., Rocuronium, Cisatracurium)
- Sedatives and Opiods (e.g., Propofol, Midazolam, Fentanyl, Ketamine, Hydromorphone)
  - Inotropes (e.g., Dobutamine, Milrinone)
- Vasopressors (e.g., Norepinephrine, Vasopressin, Epinephrine)

Additionally, the following procedures are to be documented:

- ECMO
- Prone positioning
- Renal replacement therapy

SAFETY AND REPORTING REQUIREMENTS

Critically ill patients are admitted to the ICU for life-sustaining therapies (e.g. mechanical ventilation, vasopressors, renal replacement therapy). Many of the potential participants will be admitted with the expectation of receiving end-of-life care and possibly dying in the ICU. Furthermore, medical complications are likely to occur in this population, consistent with the nature of their severe illness (e.g., nosocomial infections; septic shock; multi-organ failure; need for vasopressors; acute renal failure and need for renal replacement therapy; arrhythmias; cardiac arrest; coma; aspiration; venous thromboembolism). Due to these relatively unique morbidity and mortality expectations in the critically ill patient population and the intervention's safety profile, generic adverse events will not be collected for this study and only studyprocedure related SAEs will be collected and reported (see section below). Expected events occurring in the course of critical illness, and not related to the study drug, will not be reported as SAEs in the CORT-E2 trial.

Serious Adverse Event

A serious adverse event (SAE) in the CORT-E2 trial is defined as:

a) any event that is fatal or immediately life threatening, permanently disabling, severely incapacitating, or requires prolonged inpatient hospitalization,

OR…

b) any event that may jeopardize the patient and requires medical or surgical intervention to prevent one of the outcomes listed above,

AND…

c) which the attending physician believes to be **related*** to the study drug

**A related event is an event in which there is a reasonable possibility that the study procedure caused or contributed (definitely, probably, or possibly) to the SAE; this conclusion may be supported by the following observations, though these are not required for the determination of relatedness:*

- *There is a plausible time sequence between study drug administration and onset of the SAE;*
- *There is a plausible biological mechanism through which study drug may have caused or contributed to the SAE;*

Reporting Serious Adverse Events

All SAEs as defined above must be recorded on case report forms. In addition, they must be reported using the SAE form and submitted to Ozmosis within 24 hours of becoming aware of the event.

All reportable SAEs must be reported as follows:

Within 24 hours: Report initial information (on trial specific SAE report form) by email to:

Ozmosis Research Inc.
Phone: 416-634-8300
E-mail: ozmsafety@ozmosisresearch.ca

The initial information should always include:

- Name of Reporter/Investigator
- Participant Identification
- Adverse Event Term

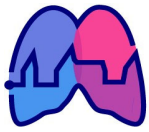
Within 3 calendar days: E-mail completed trial-specific SAE form including:

- Any information required per the SAE report form that was not included in the initial report
- Any additional, relevant and **de-identified** clinical notes, diagnostic test results and medical interventions
- Ensure that the patient eCRF pages are complete

Procedure for Expedited Reporting

Responsibility for Reporting SAEs to Health Canada

Ozmosis Research Inc. will provide expedited reports of SAEs to Health Canada according to applicable guidelines and regulations (including the 7-day notification for death and lifethreatening events), i.e. events which are BOTH serious AND unexpected, AND which are thought to be related to protocol treatment (or for which a causal relationship with protocol treatment can not be ruled out).



Responsibility for Reporting SAEs to Sponsor

Ozmosis will be responsible for submitting SAE reports (Initial and/or Follow-up reports) received from the sites, to the Sponsor and the domain Principal Investigators within 1 business day after receipt of the SAE form at Ozmosis.

Reporting SAEs to the Data Safety Monitoring Board (DSMB)

Ozmosis will be responsible for submitting SAE reports received from the sites to the DSMB chair.

The SAE reports will be sent along with a synthesis from Sponsor and Domain Lead Investigators.

Reporting Serious Adverse Events to Local Research Ethics Boards

Investigators must follow their local Research Ethics Boards (REBs)/Institutional Review Boards (IRBs) guidelines for SAE reporting. Documentation of correspondence with REBs/IRBs should be forwarded to Ozmosis.

Documentation can be any of the following:

- letter from the REB/IRB acknowledging receipt
- stamp from the REB/IRB, signed and dated by REB/IRB chair, acknowledging receipt
- letter stating the SAE was sent to the board

Reporting & Follow Up of Serious Adverse Events

All SAEs (as defined above) occurring from the time of randomization to time of ICU discharge or 30 days (whichever is shorter) must be reported to Ozmosis.

The investigator shall provide follow-up information as and when available in a new follow-up SAE form. All SAEs must be followed until resolved, become chronic, or stable unless the participant is lost to follow up. Resolution status of such each SAE must be documented in the eCRF.

STATISTICAL ANALYSES

Study Population

We plan to recruit approximately 2 patients per site per month per domain. Given how ubiquitous AHRF is (30-50 admissions per site per month), this is a very conservative estimation of potentially eligible patients. With 30-40 sites, this will translate into approximately 70-90 patients enrolled per month and 800-1000 per year. We plan to recruit for 2.5 years to allow for a rolling start given

that sites will be initiating recruitment in a staggered fashion due to anticipated delays in ethics and contract approval, exacerbated by delays associated with COVID.

Sample Size

The Bayesian approach does not require a fixed sample size as the trial will continue enrolling until any of the following statistical triggers are met:

A. Superiority (≥99% posterior probability of OR<1 for 60-day mortality) or

B. Inferiority (≥99% posterior probability of OR>1 for 60-day mortality) or

C. Equivalence (≥90% posterior probability of 0.8<OR<1.2 for 60-day mortality).

These triggers will be evaluated separately in Early Cohort and Extended Cohort with decisions for stopping made separately in each Cohort. To estimate potential sample size requirements, ensure adequate statistical power and compute the risk of incorrectly concluding superiority in the absence of any benefit (Type I error), we conducted statistical simulations for a range of plausible scenarios for treatment effects (OR = 0.75, 0.8, 0.9, 1.0). These scenarios were based on our previous meta-analysis[16] that demonstrated an OR of 0.73-0.79 for corticosteroids in reducing mortality in COVID or non-COVID AHRF, depending on baseline risk, estimated from a large Toronto registry (https://criticalcare.utoronto.ca/icore). We adjusted for differences in baseline risk using Bayesian logistic regression. Our simulations suggest a maximum expected sample size of approximately 2000 patients for each of Early Cohort and Extended Cohort (simulations were extremely similar for both domains) would be suitable. This provides a power of 94% for an OR of 0.75, the most plausible OR given the previous meta-analysis, 0% probability of concluding inferiority when OR>1 and a Type I error under the null scenario (OR=1.0) of below 5% at any time during enrolment.

Evaluation of Safety

The safety and tolerability of corticosteroid administration will be evaluated by means of recording serious adverse events in both groups (frequency and type of SAEs). The DSMB will review all serious adverse events.

Analyses

Any deviation from the original statistical plan will be described in the final report.

All analyses, interim and final, will use the intention-to-treat principle. The baseline characteristics comparing randomized groups will be reported using means (and standard deviations), medians (and interquartile ranges) or proportions. Trial data will be analyzed using Bayesian hierarchical generalized linear models to estimate the posterior probability of superiority (or inferiority) and equivalence for each intervention within each domain. The hierarchical model will account for centre, time period, sex and oxygen support at the time of randomization (HNFC, NIV, invasive mechanical ventilation or ECLS). Posterior probability distributions will be computed by combining the likelihood function with minimally informative priors and updated every three months as information (observations) accumulate in the trial. Statistical analysis will be adjusted for whether a patient was enrolled in one CORT-E^2 cohort or both CORT-E^2 cohorts. We do not expect interaction between CORT-E^2 and the other PRACTICAL domains. The final study analysis, separate for each cohort, will be completed once either superiority, inferiority or equivalence has been observed and confirmed by the DSMB and Platform Steering Committee.

We will collect sex and perform subgroup analysis based on this variable. It is less feasible to collect gender as most patients will not be conscious at the time of enrolment. We don't expect effect modification for either cohort based on sex or gender. Understanding the CORT-E^2 eligibility criteria, we plan to enroll a diverse population of patients representative of the demographics of ICU patients presenting at the participating sites.

As above, in keeping with the Bayesian framework, frequent reassessments of posterior distribution will occur. We plan to perform these analyses after each 200 patients have been randomized (after we have primary outcome data for each 200 patients). We will not start these interim analyses until at least 750 patients have been enrolled (again, until we have outcome data for at least 750 patients) in each domain in order to decrease the likelihood of spurious early findings based on an insufficient number of observations. These analyses will remain blinded to all study investigators and will be reviewed only by the DSMB. If stopping criteria are met, the DSMB may suggest stopping enrolment to one or both cohorts. The stopping criteria are intentionally conservative to avoid inappropriately stopping the trial early[39].

Six subgroups apply to both cohorts: 1) patients < 65 versus ≥ 65 years (hypothesizing that younger patients will benefit more from early and extended corticosteroids); 2) patients requiring HFNC or NIV versus invasive mechanical ventilation at the time of randomization (hypothesizing that patients receiving invasive ventilation will benefit more from early and extended corticosteroids); 3) male vs. female sex (hypothesizing no difference); 4) those requiring ECLS at baseline versus not requiring ECLS (hypothesizing that those requiring ECLS will benefit more

from early and extended corticosteroids; and 5) patients requiring versus not requiring vasopressor support at randomization (hypothesizing that those requiring vasopressor support will benefit more from early and extended corticosteroids). Two subgroups will apply exclusively to Extended Cohort 1) patients with COVID versus those with non-COVID AHRF (hypothesizing that those with COVID will benefit more from extended corticosteroids), 2) patients enrolled only in Extended Cohort versus those enrolled in both Early Cohort and Extended Cohort (to assess for interaction between cohorts). We will collect plasma samples at baseline to allow for post-hoc subgroup analysis for Early Cohort and Extended Cohort based on inflammatory groups (hypothesizing that those with elevated inflammatory markers [IL-6, sTNFr1 and IL-8][40,41] will benefit more from corticosteroids). We will perform these subgroup analyses only for the primary outcome.

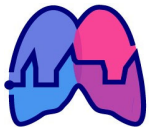
Randomization Scheme

We will randomize using an online centralized password-protected randomization system (REDCap) following a 1:1 schedule, stratified by study site and level of oxygen support (noninvasive, invasive or ECLS) at the time of randomization.

MINIMIZING SOURCES OF BIAS

The online randomization system will ensure allocation concealment and employ variable block sizes. Patients and treating healthcare providers will not be blinded. While blinding is an important mechanism to mitigate performance and detection bias, blinding would not allow for subsequent randomization of those that receive dexamethasone in the Early Cohort to further randomization in the Extended Cohort, thereby eliminating our efficiency and ability to answer multiple questions within the same trial. We will mitigate outcome ascertainment bias by using relatively objective outcomes not easily influenced by knowledge of treatment assignment (e.g. mortality). We will blind data analysts and statisticians. For the few subjective outcomes (e.g., nosocomial infections), we will establish a blinded adjudication committee that will evaluate events using standardized and accepted definitions to limit risk of bias.

We will collect data related to co-interventions to evaluate whether lack of blinding leads to differential use of specific interventions or treatments and will provide protocols for ventilation, and supportive therapy best practices to help ensure consistency. We will also minimize bias by using an intention-to-treat analysis and minimizing loss to follow-up. Missing data will also be minimized through use of a clear and comprehensive data dictionary with online data entry using logical consistency rules.



DOCUMENTATION, RECORD ACCESS AND MAINTENANCE OF STUDY RECORDS

Documentation of Participants Participation

A statement acknowledging the participation of a participant in this clinical trial must be documented in the participant's medical records along with the signed ICF.

Regulatory Requirements

The following documents are required for participating centres within Canada:

- All Investigators must complete and sign the Health Canada Qualified Investigator Undertaking form. The completed forms must be returned to Ozmosis Research Inc. prior to any drug shipment.
- Ozmosis Research Inc. will submit via fax or e-mail to Health Canada a completed Health Canada Clinical Trial Site Information Form after local activation of each participating Canadian centre.

The following documents are required for all participating centres:

- All applicable regulatory documents as listed in the Protocol Activation Checklist provided by Ozmosis Research Inc. to the sites.

Participant Confidentiality and Access to Source Data/Documents

Any research information obtained about the participant in this study will be kept confidential. A participant will not be identified by name, only by his/her initials. The participant's name or any identifying information will not appear in any reports published as a result of this study.

However, information obtained from individual participant's participation in the study may be disclosed with his/her consent to the health care providers for the purpose of obtaining appropriate medical care. The participant's medical records/charts, tests will be made available to Ozmosis Research Inc., UHN, its potential eventual partners, the Canadian HPFB/PPD, the REB/IRB and any other regulatory authorities. This is for the purpose of verifying information obtained for this study. Confidentiality will be maintained throughout the study within the limits of the law.

A participant's name will not be given to anyone except the researchers conducting the study. All identifying information will be kept behind locked doors, under the supervision of the study Principal Investigator and will not be transferred outside of the hospital.

A participant may take away his/her permission to collect, use and share information about him/her at any time. If this situation occurs, the participant will not be able to remain in the study. No new information that identifies the participant will be gathered after that date. However, the information about the participant that has already been gathered and transferred may still be used and given to others as described above in order to preserve the scientific integrity and quality of the study.

Confidentiality of the Study

Data generated as a result of this study are to be available for inspection on request by local health authority auditors, the Sponsor's Study Monitors and other personnel (as appropriate) and by the IRB/EC. The Investigator shall permit sponsor, authorized agents of the sponsor, CRO and regulatory agency employees to enter and inspect any site where the drug or records pertaining to the drug are held, and to inspect all source documents. The protocol and other study documents contain confidential information and should not be shared or distributed without the prior written permission of sponsor.

Registration of Clinical Trial

Prior to the first participant being registered/enrolled into this study, the Sponsor will be responsible for ensuring that the clinical trial is registered appropriately to remain eligible for publication in any major peer-reviewed journal, adhering to the guidelines put forth by the International Committee of Medical Journal Editors (ICMJE).

Maintenance of Study Records

To enable evaluations and/or audits from Regulatory Authorities, Ozmosis Research Inc. or the Sponsor, the Investigator agrees to keep records, including the identity of all participants (sufficient information to link records, eCRFs and hospital records), all original signed informed consent forms, copies of all source documents and detailed records of treatment disposition. The Investigator should retain these records for 15 years after study close-out as required by Canadian regulations or as specified in the Clinical Trial Agreement, whichever is longer.

If the investigator relocates, retires, or for any reason withdraws from the study, then the Sponsor should be prospectively notified. The study records must be transferred to an acceptable designee, such as another investigator, another institution, or to the Sponsor. The investigator must obtain the Sponsor's written permission before disposing of any records.

PUBLICATION POLICIES AND DISCLOSURE OF DATA

This section is in accordance with the PRACTICAL master trial.

Intellectual Property

Intellectual property guidelines will conform with UHN Policy for Principal Investigator.

Data Sharing

Please refer to PRACTICAL Master Protocol for details.

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