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REVISE: Re-Evaluating the Inhibition of Stress Erosions in the ICU: A Randomized Trial Protocol

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Complete List of Authors:	Deane, Adam M; University of Melbourne, Department of Critical Care, Melbourne Medical School Alhazzani, Waleed ; McMaster University, Departments of Medicine and Health Research Methods, Evidence & Impact Guyatt, Gordon; Mcmaster University, Department of Health Research Methods, Evidence & Impact Finfer, Simon; The George Institute for Global Health, Critical Care Program Marshall, John; University of Toronto, Interdepartmental Division of Critical Care Myburgh, John; The George Institute for Global Health, Critical Care Program Zytaruk, Nicole; McMaster University, Department of Medicine and Health Research Methods, Evidence & Impact Hardie, Miranda; The George Institute for Global Health, Critical Care Program Saunders, Lois; St Joseph's Healthcare Hamilton, Research Institute Knowles, Serena; The George Institute for Global Health, Critical Care Program Lauzier, Francois; Centre de Recherche du CHU de Québec - Université Laval, Departments of Anesthesiology, Medicine & Critical Care Medicine Chapman, Marianne J.; The University of Adelaide, Discipline of Acute Care Medicine English, Shane; University of Ottawa, Division of Critical Care, Department of Medicine; Ottawa Hospital Research Institute, Clinical Epidemiology Program Muscedere, John; Queens University, Department of Critical Care Medicine Arabi, Yaseen; King Abdullah International Medical Research Center, Intensive Care Department Ostermann, Marlies; King's College London, Guy's & St Thomas' Hospital , Department of Critical Care Venkatesh, Balasubramanian; The George Institute for Global Health, Critical Care Program Young, Paul ; Wellington Hospital, Intensive Care Department Thabane, Lehana; McMaster University, Department of Health Research Methods, Evidence, and Impact Billot, Laurent; The George Institute for Global Health, Statistics Division Heels-Ansdell, Diane; Mcmaster University, Health Research Methods,

	Evidence & Impact Al-Fares, Abdulrahman A; Al-Amiri Hospital, Departments of Anesthesia, Critical Care Medicine and Pain Medicine Hammond, Naomi ; The George Institute for Global Health, Critical Care Medicine Hall, R.; Dalhousie University, Departments of Anesthesia, Critical Care and Pharmacology Rajbhandari, Dorrilyn; The George Institute for Global Health, Critical Care Medicine Poole, Alexis; The University of Adelaide, Discipline of Acute Care Medicine Johnson, Daniel; University of Nebraska Medical Center, Departments of Critical Care and Anesthesia Iqbal, Mobeen; Maroof International Hospital, Intensive Care Department Reis, Gilmar; Pontifical Catholic University of Minas Gerais, Cardresearch – Cardiologia Assistencial e de Pesquisa LTDA Xie, Feng; McMaster University, Health Research Methods, Evidence & Impact Cook, Deborah; McMaster University, Departments of Medicine and Health Research Methods, Evidence & Impact * Deane and Alhazzani are co-first authors, for the CCCTG & ANZICS-CTG; McMaster University Faculty of Health Sciences
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REVISE: Re-Evaluating the Inhibition of Stress Erosions in the ICU: A Randomized Trial Protocol

*Adam Deane Adam.Deane@mh.org.au
*Waleed Alhazzani alhazzaw@mcmaster.ca
Gordon Guyatt guyatt@mcmaster.ca
Simon Finfer sfinfer@georgeinstitute.org.au
John Marshall John.Marshall@unityhealth.to
John Myburgh jmyburgh@georgeinstitute.org.au
Nicole Zytaruk zytarn@mcmaster.ca
Miranda Hardie mhardie@georgeinstitute.org.au
Lois Saunders lsaunde@mcmaster.ca
Serena Knowles sknowles@georgeinstitute.org.au
François Lauzier Francois.Lauzier@fmed.ulaval.ca
Marianne Chapman Marianne.Chapman@sa.gov.au
Shane English senglish@toh.ca
John Muscedere John.Muscedere@kingstonhsc.ca
Yaseen Arabi Arabi@mngha.med.sa
Marlies Ostermann Marlies.Ostermann@gstt.nhs.uk
Bala Venketesh bmvenkat@bigpond.net.au
Paul Young Paul.Young@ccdhb.org.nz
Lehana Thabane thabanl@mcmaster.ca
Laurent Billot lbillot@georgeinstitute.org
Diane Heels-Ansdell ansdell@mcmaster.ca
Abdulrahman Al Fares abdulrahman.alfares@gmail.com
Naomi Hammond nhammond@georgeinstitute.org.au
Richard Hall r.i.hall@dal.ca
Dorrilyn Rajbhandari drajbhandari@georgeinstitute.org.au
Alexis Poole alexis.poole@adelaide.edu.au
Daniel Johnson dan.johnson@unmc.edu
Mobeen Iqbal iqmob@yahoo.com
Feng Xie fengxie@mcmaster.ca
Gilmar Reis greisbh@uol.com.br
Deborah Cook debcook@mcmaster.ca

*co-first authors
for the REVISE Investigators, the Canadian Critical Care Trials Group
and the Australian and New Zealand Intensive Care Society Clinical Trials Group

Corresponding author: Deborah Cook, McMaster University, 1280 Main Street West, Hamilton, Ontario, Canada. L8N 3Z5. debcook@mcmaster.ca. 905-979-9805

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ABSTRACT

Introduction: The REVISE (Re-Evaluating the Inhibition of Stress Erosions) Trial aims to determine the impact of the proton pump inhibitor pantoprazole compared to placebo on clinically important upper gastrointestinal (GI) bleeding in the intensive care unit (ICU), 90-day mortality, and other endpoints in critically ill adults. The objective of this report is to describe the rationale, methodology, ethics and management of REVISE.

Methods and Analysis: REVISE is an international, randomized, concealed, stratified, blinded parallel group individual patient trial being conducted in ICUs in Canada, Australia, Saudi Arabia, UK, US, Kuwait, and Pakistan. Patients ≥18 years old expected to remain invasively ventilated beyond the calendar day after enrolment are being randomized to either 40 mg pantoprazole intravenously or an identical placebo daily while mechanically ventilated in the ICU. The primary efficacy outcome is clinically important upper GI bleeding within 90 days of randomization. The primary safety outcome is 90-day all-cause mortality. Secondary outcomes include rates of ventilator-associated pneumonia, *Clostridioides difficile* infection, new renal replacement therapy, ICU and hospital mortality, and patient-important GI bleeding. Tertiary outcomes are total red blood cells transfused, peak serum creatinine level in the ICU, and duration of mechanical ventilation, ICU and hospital stay. The sample size is 4,800 patients; one interim analysis was conducted after 2,400 patients had complete 90-day follow-up; the Data Monitoring Committee recommended continuing the trial.

Ethics and Dissemination: All participating centers receive research ethics approval before initiation. The results will inform clinical practice and guidelines worldwide.

Clinical Trial Registration: www.clinicaltrials.gov NCT03374800

Article Summary: Strengths and Limitations of this Study

- This 4800-patient randomized clinical trial at low risk-of-bias will evaluate the effect of pantoprazole versus placebo on clinically important gastrointestinal bleeding (primary efficacy outcome), 90-day mortality (primary safety outcome) and other relevant endpoints.
- Blinded to allocation, outcomes will be adjudicated (clinically important gastrointestinal bleeding), classified (ventilator-associated pneumonia), and validated (*Clostridioides difficile* infection severity)
- Patient and family engagement in a mixed-methods study will inform a novel secondary outcome of patient-important bleeding
- Patients not receiving invasive mechanical ventilation are excluded and most eligible patients will receive enteral nutrition; trial results may have limited applicability to fasting patients and those receiving parenteral nutrition or non-invasive ventilation
- Enrolment of heterogenous patients in 7 countries will enhance the generalizability of the findings

Keywords: Clinical trial; gastroduodenal disease; intensive and critical care

INTRODUCTION

To prevent gastrointestinal (GI) bleeding from stress-induced ulceration during critical illness, physicians prescribe stress ulcer prophylaxis for over 70% of patients in the intensive care unit (ICU) [1]. However, more recently, clinicians have questioned the effect of acid suppression for seriously ill patients. The randomized clinical trials that first provided support for stress ulcer prophylaxis with acid-suppressing medications were conducted several decades ago, in an era characterized by different practices. Since then, concerns have emerged including that histamine-2-receptor antagonists (H2RAs) and proton pump inhibitors (PPIs), may increase the risk of pneumonia and *Clostridioides difficile* (*C. difficile*) infection – two healthcare-associated infections that may confer greater morbidity, mortality and costs than upper GI bleeding [2].

Two large trials recently rejuvenated interest in this topic [3,4]. In October 2018, the Stress Ulcer Prevention in the ICU (SUPICU) trial [3] randomized 3,298 patients to pantoprazole or placebo and found no difference in the primary outcome of 90-day mortality, nor the secondary composite outcome (GI bleeding, pneumonia, *C. difficile* infection, and acute myocardial ischemia). Pantoprazole reduced GI bleeding rates (4.2% vs. 2.5%, p =0.006); however many of these bleeds did not result in hypotension, transfusion, endoscopy or other interventions. Subgroup analysis suggested that patients with higher illness severity receiving pantoprazole may have a increased risk of death at 90-day compared to those receiving placebo (relative risk [RR] 1.13; 95%CI, 0.99-1.30, interaction p=0.05) – an effect not observed in less severely ill patients. Further misgivings about widespread PPI use were raised in January 2019 when a cluster crossover trial of 26,771 patients evaluating PPIs against the active comparator of H2RAs also suggested an increased risk of death in the most severely ill subgroup of patients receiving PPIs [4].

Building on prior studies through international collaboration [5-14,2,3], the REVISE (Re-Evaluating the Inhibition of Stress Erosions) Trial was developed. The objective is to determine the effect of pantoprazole versus placebo on the primary *efficacy* outcome of clinically important upper GI bleeding, and the primary *safety* outcome of 90-day all-cause mortality [15]. Secondary outcomes include ventilator-associated pneumonia (VAP), *C. difficile* infection, new renal replacement therapy, ICU and hospital mortality, and patient-important GI bleeding. The REVISE protocol was designed within the Stress Ulcer Prophylaxis Research Program [Figure 1], in collaboration with the Canadian Critical Care Trials Group (CCCTG) [16], Australian and New Zealand Intensive Care Society Clinical Trials Group (ANZICS-CTG) [17] and international colleagues (Protocol# CCT38473; Version 3.0, 10 April 2019) [18].

Background and Rationale

The current impact of PPIs for patients in the ICU is unclear. In the 4,011 critically ill patients enrolled in 7 randomized trials comparing PPI to no PPI, only 118 cases of clinically important bleeding, 565 cases of pneumonia and 48 cases of *C. difficile* were observed. Our updated network meta-analysis [14], using GRADE methodology [19], incorporating direct [3] and indirect [4] evidence further highlighted uncertainties regarding the net effect of PPIs across outcomes of mortality, pneumonia, *C. difficile* infections, and even – because of very small effects in lower-risk groups – GI bleeding. The certainty of evidence regarding GI bleeding reduction for 3 of 4 bleeding risk subgroups (low, high and highest risk) was *moderate* given the potential for risk-of-bias [20]. All 4 risk groups shared the same relative effect estimate and credible interval [CrI] (RR 0.46, 95% CrI 0.29-0.66). For the *moderate* risk group, where the certainty of evidence was high, the credible interval spanned a range from a 2.1% absolute reduction in bleeding to a 1.0% absolute reduction, illustrating imprecision and contributed to a low certainty evidence rating. Thus, the BMJ Rapid Recommendation initiative [20] issued a weak recommendation against stress ulcer prophylaxis administration in patients at low bleeding risk of bleeding, and a weak recommendation for those at higher bleeding risk.

Regarding the risk of VAP (network RR 1.08, CrI 0.88-1.45) and of *C. difficile* infection (network RR 0.76, CrI 0.28-2.16), existing trials have failed to exclude important harm with PPIs. Regarding mortality, the network meta-analysis RR of 1.03 is consistent with a small increased risk of death with PPIs. Given the baseline mortality of ICU patients, the CrI of 0.93-1.14 includes an important mortality increase; for a baseline of 30%, a 14% relative increase would represent a 4.2% absolute increase. By adding REVISE results to the network meta-analysis, we hope to decrease imprecision of estimates, establishing an increased risk, or a trivial or no increase in mortality.

Based on these considerations, after grant funding and before launching the trial, protocol modifications were made to reflect the foregoing recent evidence. The trial was changed to a superiority design instead of a non-inferiority design. The primary safety outcome of mortality was included in response to subgroup analyses of earlier trials suggesting concern in patients at high-risk of death [21,22]. The follow-up was extended from 60-day to 90-day mortality to better inform future meta-analyses. Patients and families were actively engaged in a study to refine the secondary endpoint of patient-important bleeding, outlined in the patient engagement section of this report [23]. The sample size was increased from 3,600 to 4,800 patients, informed by the updated network meta-analysis [14]. Relevant regulatory agencies, ethics boards and the Data Safety & Monitoring Committee re-approved the protocol. Enrolment began in July 2019.

METHODS AND ANALYSIS

Design

REVISE is a randomized, stratified, concealed, blinded, parallel-group trial.

Inclusion criteria:

- Adults ≥18 years old receiving invasive mechanical ventilation
- Expected to remain mechanically ventilated beyond the calendar day after randomization

Exclusion criteria:

- Already invasively mechanically ventilated ≥72 hours during this hospital admission
- Acid suppression for active GI bleeding or high risk of bleeding (e.g., current bleeding, peptic ulcer bleeding within 8 weeks, recent severe esophagitis, Barrett's esophagus, Zollinger-Ellison syndrome); [dyspepsia or gastroesophageal reflux is not an exclusion criterion]
- Acid suppression in the ICU for >1 PPI or H2RA daily-dose-equivalent
- Dual antiplatelet therapy, or combined antiplatelet use and therapeutic anticoagulation
- Pantoprazole contraindication per local product information
- Palliative care or anticipated withdrawal of life support
- Pregnancy
- Previous enrolment in REVISE, a related trial, or a trial prohibiting coenrolment
- Patient, substitute-decision-maker (SDM) or physician declines

Informed Consent

Research staff and investigators in the ICU screen patients for eligibility. Once eligibility is confirmed, the protocol allows either *a priori informed consent* or informed *consent to continue*. Consent encounters accord with guidelines [24]. When not possible to obtain consent prior to randomization, eligible patients are enrolled without prior consent (deferred consent). As soon as possible and appropriate thereafter, the patient or SDM is informed of the patient's participation and offered the option to consent to continue or withdraw from the trial at any time. The patient or SDM may withdraw consent for receipt of study drug and/or for data collection. If withdrawal of study drug is requested, it is stopped and permission to use trial-related data is sought. Consent models and labels

vary by region. In Canada and the UK, for those randomized under a *deferred consent* model, patients or SDMs can withdraw consent for continued participation whereas in Kuwait, they can *opt out* of continued participation. In some settings, telephone consent allows witnessed verbal *a priori consent* or *consent to continue* with signature confirmation as soon as possible.

Randomization

When notified by research staff or investigators about eligible patients, research pharmacists or designated unblinded staff not caring for patients use a password-protected website to access the central computerized randomization program to ensure concealed 1:1 allocation using randomly-permuted variable unspecified block sizes. Randomization is stratified by center and pre-hospital acid suppression (i.e., prior PPI or H_2RA or not), generating *start or no start*, and *continue or discontinue* strata. The latter stratification will allow exploration of possible rebound hypersecretion of gastric acid upon acid suppression termination [25] and possible microbiome modification by long-term acid suppression which may modify infection risk [26].

Interventions

Patients are randomly assigned to receive locally-sourced intravenous pantoprazole 40 mg reconstituted with 0.9% sodium chloride (NaCl) or matched placebo (0.9% NaCl). Research pharmacists or designated unblinded staff prepare blinded placebo and study drug labelled per local regulations, dispensed to the ICU for daily bedside nurse administration.

The colour stability of reconstituted pantoprazole or placebo formulations from 5 companies up to 5 days without unblinding has been verified [27]. These clear, colourless indistinguishable solutions are dispensed daily until 90 days after randomisation or until death, mechanical ventilation discontinuation, or clinically important GI bleeding.

When patients receive study drug, open-label PPI or H_2RA use is documented and considered a protocol violation unless clinically indicated. Study drug continues regardless of feeding status [28-30]. Study drug may be temporarily or permanently discontinued if a definite pantoprazole indication or contraindication develops. Regardless of study drug exposure, all patients are followed unless consent to follow-up is withdrawn. Study drug is restarted if invasive mechanical ventilation is reinstituted during the index ICU admission.

Other patient management during and following the trial is at the discretion of treating clinicians.

Risk-of-Bias

To protect against selection bias, prognostic imbalance, detection, performance and measurement bias, loss to follow-up, missing data and other threats to validity, 18 strategies for trial conduct, analysis and dissemination phases were incorporated. [Table 1]. Patients, families, clinicians, and research personnel (staff, investigators and adjudicators) are blinded. The analyst and biostatisticians remain blinded until the main analysis is complete. Unblinding is not permitted other than in emergency situations, requiring Methods Center contact.

Data Collection

Following protocol training, research staff collect baseline data (e.g., illness severity, comorbidities), daily data up to 90 days post-randomization (e.g., advanced life support), laboratory values (e.g., hemoglobin, INR, platelet count); cointerventions (e.g., enteral nutrition, anticoagulants), hospital reports (e.g., endoscopy, radiology), duration of mechanical ventilation, ICU and hospital stay, and mortality. Research staff follow patients daily to document study drug receipt including reasons for non-administration, while tracking trial outcomes. Patients discharged alive from hospital before 90 days

are followed for 90 days; vital status is obtained by patient, family or family physician contact, regional obituary or health-record review. No biological specimens are collected.

Enrolled patients are assigned a unique numerical code. Enrolment logs with identifiers are retained at each site. Research pharmacists or designated unblinded staff not caring for patients enter study drug dispensing details into a secure web-based electronic data-capture system (iDataFax, Seattle, Washington). Blinded research staff upload clinical data without personal health information. An audit trail tracks any data modifications.

Primary Outcomes

Primary Efficacy Outcome: *Clinically important upper GI bleeding* occurring in the ICU or resulting in ICU readmission during the index hospital stay up to 90-days post-randomization. Clinically important GI bleeding requires the presence of overt GI bleeding, defined as one of the following:

- Hematemesis
- Overt oro/nasogastric bleeding (frank blood or coffee-ground oro/nasogastric aspirate)
- Melena
- Hematochezia

plus one of the following in the absence of other causes:

- hemodynamic change defined as a spontaneous decrease in mean arterial pressure or non-invasive systolic or diastolic blood pressure of ≥20 mmHg, or an orthostatic increase in pulse rate of ≥20 beats/minute and a decrease in systolic blood pressure of ≥10 mmHg, with or without vasopressor initiation or increase
- vasopressor initiation
- hemoglobin decrease of ≥2 g/dl (20 g/L) within 24 h of bleeding
- transfusion of ≥2 units packed red blood cells within 24 h of bleeding
- therapeutic intervention (e.g., therapeutic endoscopy, angioembolization, surgery).

Our bleeding definition builds on prior studies [31,32], explicitly incorporating vasopressor initiation or increase [3] and endoscopy. Research staff prospectively collect data related to GI bleeding, allowing central duplicate blinded adjudication, described below.

***Primary Safety Outcome*:** *All-cause mortality* at 90 days post-randomization, ascertained by patient or SDM contact for those discharged alive before 90 days.

Secondary Outcomes

- *Incidence of VAP***:** is diagnosed in patients who received invasive mechanical ventilation for ≥48 hours when there is a new, progressive or persistent radiographic infiltrate *plus at least 2 of the following without other obvious cause*: 1) fever (temperature>38 °C) or hypothermia (temperature <36 °C); 2) leukopenia (<4.0 x 10^6/L) or leukocytosis (>12.0 x 10^6/L); 3) purulent sputum; or 4) gas exchange deterioration [33,34]. Research staff prospectively collect data allowing central classification by the Clinical Pulmonary Infection Score [35], and other definitions as below.
- *Incidence of C. difficile infection* is defined as clinical features (diarrhea [>3 episodes of unformed stools [36] or Bristol type 6 or 7 [37], ileus, or toxic megacolon) and either microbiological evidence of toxin-producing *C. difficile* or pseudomembranous colitis on colonoscopy [38] in hospital within 90 days.
- *New renal replacement therapy (RRT)* is defined as initiation of new RRT in the ICU.
- *ICU mortality* is defined as all-cause mortality in the ICU during the index hospitalization within 90 days.

- *Hospital mortality* is defined as all-cause mortality during the index hospitalization within 90 days.
- *Patient-important GI bleeding* is focused on GI bleeding characteristics that are important to patients and families [23]. The criteria will be derived from a mixed-methods study involving interviews and focus groups of ICU survivors and family members not involved in REVISE, eliciting perspectives on concerning bleeding features for incorporation into the database to define this outcome.

Tertiary outcomes

- *Total units of red blood cells transfused in the ICU*
- *Peak serum creatinine level in the ICU*
- *Duration of mechanical ventilation (days)*
- *ICU length of stay (days)*
- *Hospital length of stay (days)*

Central Adjudication, Classification and Validation of Morbidity Outcomes

Clinically Important GI Bleeding: Research staff and investigators will identify all possible GI bleeding events, complete the bleeding case report form and submit redacted clinical notes, laboratory data and procedural reports. All GI bleeding events will be *adjudicated* by at least two investigators from of a five-member GI bleeding adjudication committee to determine if the event meets the definition of clinically important GI bleeding and to confirm GI bleeding site. Initial calibration of the committee members will involve independent review by all five members (blinded to study drug and centre) case report forms and source data for the first 10 bleeding patients. Committee members will convene and discuss their assessments, clarify reasons for disagreements and arrive at consensus for each event. Subsequent bleeding events will be independently adjudicated by one primary adjudicator (for all events) and a secondary adjudicator (randomly assigned, stratified by study drug). Adjudicators will be blinded to allocation and center. Disagreements will resolve by discussion and consensus or a third researcher if necessary.

VAP: Local research staff and investigators will report any lower respiratory tract infections on the pneumonia outcome case report form. Data will be *classified* in duplicate by the Clinical Pulmonary Infection Score [35] and other definitions (e.g., American College of Chest Physicians [33,34], Centers for Disease Control [39], the International Sepsis Forum [40] and by invasive microbiological confirmation [41]. Disagreements will resolve by discussion and consensus or a third researcher if necessary.

In addition, early VAP is defined as arising on day 3, 4 or 5 after mechanical ventilation is initiated, and late VAP as arising on day 6 of mechanical ventilation or later, including up to 2 days after mechanical ventilation discontinuation [42]. Pneumonia arising 3 or more days after mechanical ventilation discontinuation will be considered post-extubation pneumonia. We do not report ventilator-associated conditions (VACs) or infection-related VACs, as surveillance metrics are modifiable by volume status and ventilator settings and do not predict VAP [43].

***C. difficile infection*:** *C. difficile* outcome case report forms will be *validated* in duplicate by two researchers assessing severity (non-severe, severe, fulminant) [38]. Disagreements will resolve by discussion and consensus or a third researcher if necessary.

Patient and Public Involvement

Patients and families will be involved in several ways. We completed two pilot trials, documenting consent rates of 98.1% [11] and 77.8% [12]. Second, enrolled patients who regain capacity after critical illness are notified about the trial and approached for consent to continued

participation. A mixed-method study eliciting perspectives of patients and families not involved in REVISE is refining the secondary outcome of patient-important bleeding [23]. Fourth, in the UK, patients are involved at all stages as per the Health Research Authority standards [44]; patients reviewed the protocol, provided feedback, and supported approval. When REVISE results are available, lay language summaries, visual abstracts and infographics will be created by patient partners for traditional media (paper, radio, television) and public social media feeds (twitter, blogs).

Sample Size

The sample size of 4,800 patients was chosen on the basis of plausible baseline risks of GI bleeding, plausible relative risk reductions, a target of 85% power and feasible enrolment. The best estimate of the GI bleeding event rate in the placebo arm ranging from 3% to 6% is based on the following: an international period-prevalence study (2.6%; 95% CI, 1.6-3.6) [1]; the REVISE Pilot trial (placebo 6.1%; 95% CI 2.1-16.5) [12]; and the SUPICU trial placebo rate of 4.2% [3]. The relative risk associated with pantoprazole was 0.6 in the SUPICU trial. Table 2 highlights sample size considerations for clinically important upper GI bleeding. The table presents combinations of relative risk reductions ranging from 30% to 50%, and baseline risks between 3% and 6% for which we will achieve 85% power. With a baseline risk of 3% and a relative risk reduction of 50%, the absolute benefit will be a 1.5% difference. Other highlighted cells correspond to absolute risk reduction of greater than 1.5%. In summary, across the range of plausible baseline risks, 4,800 patients will provide at least 85% power to detect effects of pantoprazole as large as, or greater than, the smallest clinically important reduction in GI bleeding.

Table 3 highlights sample size implications for 90-day mortality. The estimates of relative risk are informed by SUP-ICU in which the upper confidence limit around the increased mortality in the high-risk group (SAPS II >53) included 1.30. Among the first 25% of patients enrolled, the mortality rate was 44% across both groups in the comparable high-risk of death group of concern (APACHE II score >25). Our power calculations are based on the estimated 40% of REVISE patients who will fall in the high-risk group (~1,920 patients). The table presents combinations of relative risks ranging from 1.1 to 1.3, and baseline risks between 4% and 38%, demonstrating power of $\geq$ 70% for combinations of higher levels of baseline risk and relative risk increase. The relative risk of 1.13 is the point estimate in patients with high illness severity in SUPICU [3]. In summary, across the range of higher baseline risks, 4,800 patients will provide at least 70% power to detect effects of pantoprazole at levels that would likely preclude use of pantoprazole in patients at higher risk of death.

Trial Management

Two Methods Centers with extensive experience running international clinical trials oversee REVISE, at McMaster University in Hamilton, Canada and The George Institute for Global Health in Sydney, Australia for Australian sites [Figure 2]. Methods Center teams meet twice monthly to harmonize approaches, track progress and share management efficiencies. Within Canada, the Québec Lead investigator ensures valid scientific cross-cultural, bilingual alignment with provincial ethical and regulatory directives. Methods Center personnel train local investigators and research staff on the protocol, ensure optimal conduct and validate all data at least thrice.

Central statistical monitoring will occur twice annually at McMaster University. Site-specific data monitoring and auditing will follow national guidance.

Upon trial completion, original research records will be retained at participating sites in accordance with relevant regulations. Study drug will be destroyed per jurisdictional regulations. The database will be maintained for at least 15 years.

Statistical Analysis

The *main analyses* will be conducted by analyzing patients in the group to which they were allocated regardless of protocol adherence, per the intention-to-treat principle. We will compare the time to the primary and secondary binary outcomes using Cox proportional hazards regression with threshold P-values of 0.05. Randomization is stratified for center and pre-hospital acid suppression. Because APACHE II score is strongly associated with mortality, to maximize statistical efficiency, we will also adjust for baseline APACHE II score for the mortality outcome. For binary outcomes, we will report hazard ratios with 95% confidence intervals (CIs) as well as the absolute risk increase or decrease and 95% CIs. For continuous outcomes, we will use linear regression on the original scale or on the log-scale. Subgroup analyses will be conducted for the primary *efficacy* outcome and primary *safety* outcome in five *a priori* subgroup pairs: 1) Pre-hospital acid suppression (PPIs or H2RAs) vs. none, 2) Illness severity per APACHE II score of ≥25 or <25, 3) 3) Medical vs. surgical/trauma ICU admitting diagnosis, 4) SARS-CoV-2 positive vs. negative status, and 5) Female vs. male.

Data Monitoring Committee

The independent REVISE Data Monitoring Committee (DM)C requested review of 90-day mortality results after 1,200 patients were recruited (25% enrolment), recommending trial continuation. The formal interim analysis was conducted after 2,400 patients (50% enrolment) had 90-day mortality ascertainment. To maintain the overall type-I error rate for the interim analysis, a Haybittle-Peto stopping rule with a critical value of 3 standard deviations and fixed conservative α=0.001 was used [45,46]. After examining recruitment, consent, coenrolment, protocol adherence and all trial outcomes, the DMC advised the Steering Committee to continue enrolment.

ETHICS AND DISSEMINATION

Ethics

Relevant Research Ethics Boards (REBs) and/or Human Research Ethics Committees (HRECs) of each participating hospital and/or region approved REVISE. Protocol implementation and database training accords with the International Council for Harmonisation Guidelines for Good Clinical Practice and other locally applicable regulations.

Adverse Events

Key adverse events and serious adverse events (SAEs) relevant to REVISE are already predefined primary or secondary trial outcomes. Beyond these events, ICU patients can develop many other complications due to critical illness or its treatment, which may be life-threatening or fatal. However, they do not constitute adverse events or SAEs unless considered by the treating clinicians to possibly relate to the study drug. REVISE follows guidance for rational reporting of SAEs in investigator-initiated ICU trials of drugs in common use [47]. The trial report will document all deaths and report only SAEs meeting the foregoing five published recommendations, regardless of local reporting requirements.

COVID-19 Pandemic

After the pandemic was declared, acknowledging the imperative of timely, rigorous research to optimize outcomes for patients with COVID-19, REVISE paused for variable periods of time at each center. We proposed ethical principles for concurrent conduct of research that is and is not pandemic-focused, whenever safe, feasible and locally approved [48]. Relevant to patients with [49] and without COVID-19, enrolment restarted as soon as possible without protocol modification, ensuring local research capacity, protocol fidelity and infection control.

Knowledge Translation

REVISE will provide low risk-of-bias estimates that more than double trial evidence on the impact of pantoprazole on outcomes, increasing the strength of inferences regarding clinically important GI bleeding, mortality, VAP, and *C. difficile* infection. REVISE will not provide direct evidence about pantoprazole's effect on patients requiring non-invasive ventilation or no support, or patients without enteral nutrition.

We will publish the main results within one year of the last patient follow-up, presenting concurrently at an international congress. We will host videoconferences and regional rounds, and disseminate structured abstracts and slide-decks to local quality councils, provincial and state organizations, national policy makers and professional groups. CCCTG, ANZICS-CTG and other websites will feature multilingual REVISE results. Findings will be communicated through conventional academic channels (e.g., abstracts, posters, peer-review manuscripts) and at professional fora (e.g., grand rounds, teaching sessions, in-services, quality improvement councils).

We will update our network meta-analysis, and aligned with recent BMJ Rapid Recommendations, consider groups at differing bleeding risk, optimizing prevention while limiting potential harm and unnecessary expenditure. Results will be incorporated into guidance documents such as BMJ Rapid Recommendations and Surviving Sepsis Guidelines.

Status

REVISE study was launched in response to multi-professional stakeholder interests, serving public, professional and policy needs. As of May 1, 2023, 4,124 patients have been recruited in 63 centers [50]. Led by two seasoned research consortia, supported by the Canadian Community ICU Research Network [51], and energized by international collaborators, prevailing uncertainty about acid suppression has fuelled recruitment. By October 2023, 4,800 patients are anticipated, with 90-day follow-up ascertained by January 2024.

REVISE re-addresses the benefits, harms, or disutility of acid suppression in the ICU, aligned with the *Declaration of Helsinki* stating that 'even the best-proven interventions' must be continually re-evaluated through research for their safety, effectiveness, efficiency, accessibility and quality [52].

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Authors' Statement

Concept and design: A Al Fares, W Alhazzani, Y Arabi, L Billot, M Chapman, D Cook, A Deane, S English, S Finfer, G Guyatt, R Hall, N Hammond, M Hardie, D Heels-Ansdell, M Iqbal, D Johnson, S Knowles, F Lauzier, J Marshall, J Muscedere, J Myburgh, M Ostermann, A Poole, D Rajbhandari, G Reis,L Saunders, L Thabane, B Venkatesh, F Xie, P Young, N Zytaruk.

Acquisition, analysis, or interpretation of data: D Cook, N Hammond, M Hardie, D Heels-Ansdell, S Knowles, L Saunders, L Thabane, N Zytaruk.

Drafting of the manuscript: D Cook, A Deane, G Guyatt, M Hardie, D Heels-Ansdell, F Lauzier, L Thabane, P Young, N Zytaruk.

Critical revision of the manuscript for important intellectual content: A Al Fares, W Alhazzani, Y Arabi, L Billot, M Chapman, S English, S Finfer, R Hall, N Hammond, M Iqbal, D Johnson, S Knowles, J Marshall, J Muscedere, J Myburgh, M Ostermann, A Poole, D Rajbhandari, G Reis, L Saunders, B Venkatesh, F Xie.

Statistical analysis: L Billot, D Cook, S Finfer, G Guyatt, D Heels-Ansdell, L Thabane.

Obtained funding: A Al Fares, W Alhazzani, Y Arabi, L Billot, M Chapman, D Cook, A Deane, S English, S Finfer, G Guyatt, R Hall, N Hammond, D Heels-Ansdell, D Johnson, S Knowles, F Lauzier, J Marshall, J Muscedere, J Myburgh, M Ostermann, A Poole, D Rajbhandari, G Reis, L Thabane, B Venkatesh, P Young, F Xie, N Zytaruk.

Administrative, technical, or material support: W Alhazzani, D Cook, A Deane, S Finfer, G Guyatt, N Hammond, M Hardie, D Heels-Ansdell, S Knowles, D Rajbhandari, L Saunders, A Poole, L Thabane, N Zytaruk.

Data Integrity: D Cook, M Hardie, D Heels-Ansdell, S Knowles, L Saunders, N Zytaruk.

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Data Monitoring Committee: The independent REVISE Data Monitoring Committee was comprised of Professor Ian Roberts (University of Oxford), Dr. Danny McAuley (Queen's University, Belfast), and Dr. George Thomlinson (University of Toronto) (Chair).

Data Statement: Following the publication of REVISE, the dataset will be used for secondary observational studies addressing additional hypothesis-driven questions (e.g., predictors of gastrointestinal bleeding). Access by REVISE investigators will follow a submitted rationale, analysis plan and approval by the Management Committee. Requests for access to the dataset by external investigators will be considered following a submitted rationale, analysis plan and approval by the Management Committee and research ethics boards as relevant. Requirements will be stipulated in a pre-specified data sharing agreement. Only de-identified data will be provided and will be transferred via a secure web portal.

Table 1. Strategies to Minimize Bias

Stage and Type of Bias	Strategy Implemented
Protocol Development	
Design bias	Extensive scientific, clinical and ethical input on the protocol; patient and family input to refine the patient-important bleeding outcome
Corporate conflicts of interest	Peer-review funded trial; locally sourced pantoprazole
Procedural bias	Standard Operating Procedures guide protocol implementation; central statistical monitoring is ongoing throughout the trial
Omission bias	Eligibility criteria are broad; enrolment is in 5 continents
Surveillance bias	Rigorous training of research personnel
Detection of Ventilator-Associated Pneumonia (VAP)	To avoid biased choice of VAP definition: VAP reporting has 1 main and 7 alternate definitions
Protocol Implementation	
Prognostic imbalance	At point of randomization patients are stratified for pre-hospital acid suppression which may influence outcomes
Selection bias	Allocation is concealed; Research personnel screening, consenting, and enrolling patients are unaware of randomization sequence
Detection & performance bias	Patients, families, all clinical and research personnel are blinded
Measurement bias	Primary Efficacy Outcome: Clinically important GI bleeding is centrally adjudicated by 2 physicians trained in study procedures, and blinded to allocation and center
Loss to follow-up	Primary Safety Outcome: For 90-day mortality status, multiple methods used for patients discharged alive before 90 days; all other outcomes are hospital-based as recorded in medical charts
Missing data	Each research record is reviewed and validated at least 3 times by Methods Center staff
Analysis	
False claims of benefit	*A priori* statistical approach is very conservative for stopping early for apparent benefit before full sample size reached
False claims of no difference	*A priori* statistical approach does not include stopping early for futility before full sample size reached
Confirmation bias	Analyst is blinded to allocation until after the final analysis
Analytic bias	Analysis will adhere to the intention-to-treat principle
Dissemination	
Reporting bias	Trial reporting will adhere to trial registration (NCT03374800), protocol and statistical analysis plan
Publication bias	Results will be disseminated through many knowledge translation strategies including peer-review journals

Legend for Table 1: These are the strategies we protocolized to minimize bias in four different phases of the trial.

VAP=ventilator-associated pneumonia

Table 2: Sample Size With Respect to Clinically Important Bleeding Outcome

		True Underlying Relative Risk (PPI vs Placebo)		
		0.7	**0.6**	**0.5**
Event Rate in Placebo group	**3%**	47.1%	74.6%	92.6%
	4%	60.1%	86.6%	97.8%
	5%	70.7%	93.4%	99.4%
	6%	79.1%	96.9%	99.9%

Power to reject the null of no difference in proportion of patients developing GI bleeding, with a sample size of 4,800 patients (2,400 per group). Alpha=0.05, 2-sided testing

Legend for Table 2: This table highlights consideration for clinically important GI bleeding. It presents combinations of relative risk reductions ranging from 30% to 50%, and baseline risks between 3% and 6% for which we will achieve 85% power. With a baseline risk of 3% and a relative risk reduction of 50%, the absolute benefit of will be a 1.5% difference. Other highlighted cells correspond to absolute risk reduction of greater than 1.5%. In summary, across the range of plausible baseline risks in the shaded boxes, 4,800 patients will provide at least 85% power to detect effects of pantoprazole as large as, or greater than, the smallest important reduction in clinically important GI bleeding. This sample size reflects feasible enrolment in an acceptable 2-year time frame, accounting for any non-compliance or loss to follow-up, in the context of hybrid serial funding for REVISE.
PPI=proton pump inhibitor

Table 3: Sample Size With Respect to 90-Day Mortality

		True Underlying Relative Risk (PPI vs Placebo)			
		1.1	**1.13**	**1.2**	**1.3**
Event rate in Placebo group	**38%**	38.0%	57.9%	91.5%	99.9%
	40%	40.9%	61.7%	93.7%	>99.9%
	42%	43.9%	65.6%	95.5%	>99.9%
	44%	47.1%	69.4%	96.9%	>99.9%

Power to reject the null of no difference in proportion of patients who die among those at higher risk of death (APACHE II ≥25), with sample size of 1,920 patients (960 per group). Alpha=0.05, 2-sided testing

Legend for Table 3: This table highlights sample size implications for 90-day mortality. The estimates of relative risk are informed by SUP-ICU in which the upper confidence limit around the increased mortality in the high-risk group (SAPS II >53) included a value of 1.30. Among the first 25% of patients enrolled, the mortality rate was 44% across both groups in the comparable high-risk of death group of concern (APACHE II score >25). Our power calculations are based on the 40% of REVISE patients who will fall in the high-risk group (1,920 patients). The table presents combinations of relative risks ranging from 1.1 to 1.3, and baseline risks between 38% and 4%, showing power of ≥ 70% for combinations of higher levels of baseline risk and relative risk increase. The relative risk of 1.13 is the observed point estimate in patients with high illness severity in the SUPICU Trial. In summary, across the range of higher baseline risks, 4,800 patients will provide at least 70% power to detect effects of pantoprazole at levels that would preclude use of the drug in patients with high illness severity - those at higher risk of death.
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Figure 1: Stress Ulcer Prophylaxis Research Program

Legend for Figure 1: In preparation for this trial, with national and international collaborators, we developed this stress ulcer prophylaxis research program. We published several reviews and meta-analyses on acid suppression. We contributed to an international period prevalence epidemiologic study which assisted with some REVISE trial estimates. We completed 2 surveys about stress ulcer prophylaxis in Australia and Canada. We completed 2 pilot randomized trials in preparation for REVISE. The 214-patient, single-center Australian POP-UP Pilot trial achieved 3 objectives related to exploring overt signals of benefit or harm, ascertaining whether the study drug could be administered promptly after commencing mechanical ventilation, and estimating relevant outcome event rates. A second 91-patient, international REVISE Pilot Trial achieved 3 feasibility objectives related to rates of recruitment, informed consent, and protocol adherence. Other international studies provided key evidence to help inform the design of the main REVISE Trial.

Figure 2: Organizational Chart

Legend for Figure 2: In this figure we depict the organization and management relationships for the international REVISE Trial.

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Figure 1.
Stress Ulcer Prophylaxis Global Research Program

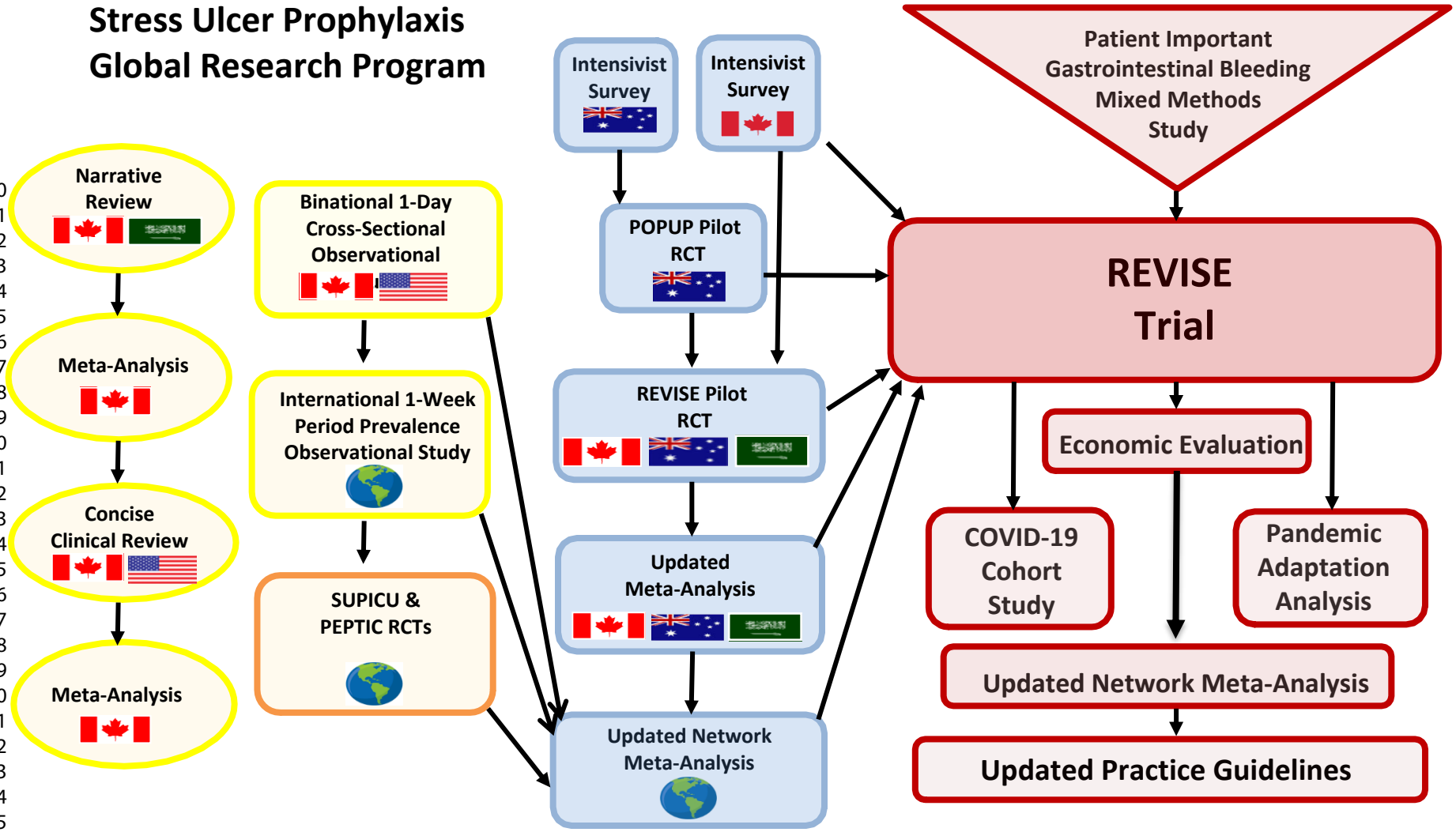
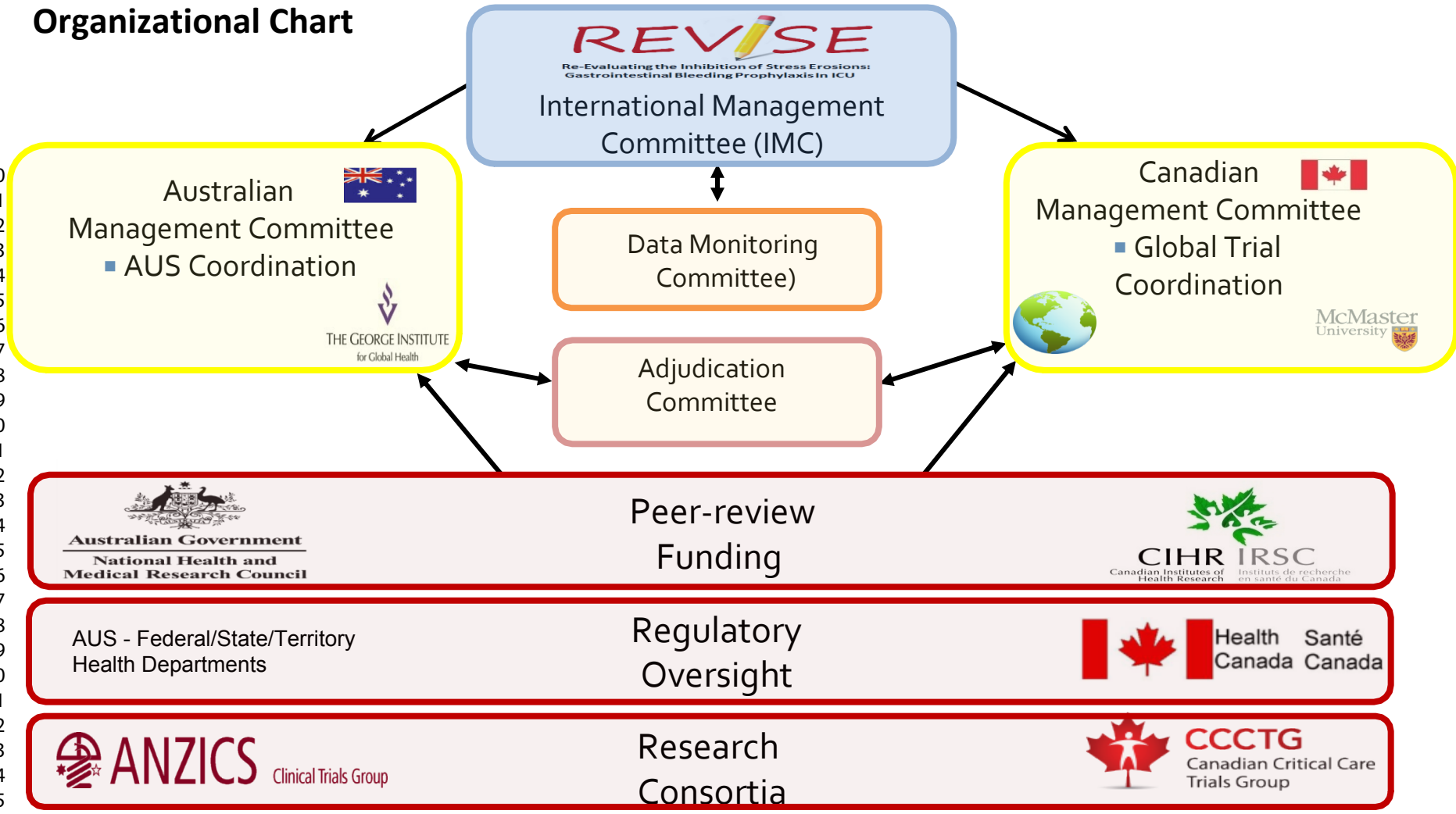


Figure 2.
Organizational Chart



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		Reporting Item	Page Number
Administrative information			
Title	#1	Descriptive title identifying the study design, population, interventions, and, if applicable, trial acronym	1
Trial registration	#2a	Trial identifier and registry name. If not yet registered,	2

		name of intended registry	
Trial registration: data set	#2b	All items from the World Health Organization Trial Registration Data Set	2
Protocol version	#3	Date and version identifier	4
Funding	#4	Sources and types of financial, material, and other support	15
Roles and responsibilities: contributorship	#5a	Names, affiliations, and roles of protocol contributors	15
Roles and responsibilities: sponsor contact information	#5b	Name and contact information for the trial sponsor	1
Roles and responsibilities: sponsor and funder	#5c	Role of study sponsor and funders, if any, in study design; collection, management, analysis, and interpretation of data; writing of the report; and the decision to submit the report for publication, including whether they will have ultimate authority over any of these activities	15
Roles and responsibilities: committees	#5d	Composition, roles, and responsibilities of the coordinating centre, steering committee, endpoint adjudication committee, data management team, and other individuals or groups overseeing the trial, if applicable (see Item 21a for data monitoring committee)	9

Introduction

Background and rationale	#6a	Description of research question and justification for undertaking the trial, including summary of relevant studies (published and unpublished) examining benefits and harms for each intervention	4,5
Background and rationale: choice of comparators	#6b	Explanation for choice of comparators	4,5
Objectives	#7	Specific objectives or hypotheses	5
Trial design	#8	Description of trial design including type of trial (eg, parallel group, crossover, factorial, single group), allocation ratio, and framework (eg, superiority, equivalence, non-inferiority, exploratory)	5
Methods: Participants, interventions, and outcomes			
Study setting	#9	Description of study settings (eg, community clinic, academic hospital) and list of countries where data will be collected. Reference to where list of study sites can be obtained	5,11
Eligibility criteria	#10	Inclusion and exclusion criteria for participants. If applicable, eligibility criteria for study centres and individuals who will perform the interventions (eg,	5

		surgeons, psychotherapists)	
Interventions: description	#11a	Interventions for each group with sufficient detail to allow replication, including how and when they will be administered	6
Interventions: modifications	#11b	Criteria for discontinuing or modifying allocated interventions for a given trial participant (eg, drug dose change in response to harms, participant request, or improving / worsening disease)	6
Interventions: adherance	#11c	Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence (eg, drug tablet return; laboratory tests)	6
Interventions: concomitant care	#11d	Relevant concomitant care and interventions that are permitted or prohibited during the trial	6
Outcomes	#12	Primary, secondary, and other outcomes, including the specific measurement variable (eg, systolic blood pressure), analysis metric (eg, change from baseline, final value, time to event), method of aggregation (eg, median, proportion), and time point for each outcome. Explanation of the clinical relevance of chosen efficacy and harm outcomes is strongly recommended	7,8
Participant timeline	#13	Time schedule of enrolment, interventions (including any run-ins and washouts), assessments, and visits for participants. A schematic diagram is highly recommended (see Figure)	5-7

Sample size	#14	Estimated number of participants needed to achieve study objectives and how it was determined, including clinical and statistical assumptions supporting any sample size calculations	9
Recruitment	#15	Strategies for achieving adequate participant enrolment to reach target sample size	5,6
Methods: Assignment of interventions (for controlled trials)			
Allocation: sequence generation	#16a	Method of generating the allocation sequence (eg, computer-generated random numbers), and list of any factors for stratification. To reduce predictability of a random sequence, details of any planned restriction (eg, blocking) should be provided in a separate document that is unavailable to those who enrol participants or assign interventions	6
Allocation concealment mechanism	#16b	Mechanism of implementing the allocation sequence (eg, central telephone; sequentially numbered, opaque, sealed envelopes), describing any steps to conceal the sequence until interventions are assigned	6
Allocation: implementation	#16c	Who will generate the allocation sequence, who will enrol participants, and who will assign participants to interventions	6

Blinding (masking)	#17a	Who will be blinded after assignment to interventions (eg, trial participants, care providers, outcome assessors, data analysts), and how	6
Blinding (masking): emergency unblinding	#17b	If blinded, circumstances under which unblinding is permissible, and procedure for revealing a participant's allocated intervention during the trial	6
Methods: Data collection, management, and analysis			
Data collection plan	#18a	Plans for assessment and collection of outcome, baseline, and other trial data, including any related processes to promote data quality (eg, duplicate measurements, training of assessors) and a description of study instruments (eg, questionnaires, laboratory tests) along with their reliability and validity, if known. Reference to where data collection forms can be found, if not in the protocol	6-9
Data collection plan: retention	#18b	Plans to promote participant retention and complete follow-up, including list of any outcome data to be collected for participants who discontinue or deviate from intervention protocols	9
Data management	#19	Plans for data entry, coding, security, and storage, including any related processes to promote data quality	9

		(eg, double data entry; range checks for data values). Reference to where details of data management procedures can be found, if not in the protocol	
Statistics: outcomes	#20a	Statistical methods for analysing primary and secondary outcomes. Reference to where other details of the statistical analysis plan can be found, if not in the protocol	10
Statistics: additional analyses	#20b	Methods for any additional analyses (eg, subgroup and adjusted analyses)	10
Statistics: analysis population and missing data	#20c	Definition of analysis population relating to protocol non-adherence (eg, as randomised analysis), and any statistical methods to handle missing data (eg, multiple imputation)	10
Methods: Monitoring			
Data monitoring: formal committee	#21a	Composition of data monitoring committee (DMC); summary of its role and reporting structure; statement of whether it is independent from the sponsor and competing interests; and reference to where further details about its charter can be found, if not in the protocol. Alternatively, an explanation of why a DMC is not needed	10
Data monitoring: interim analysis	#21b	Description of any interim analyses and stopping guidelines, including who will have access to these interim results and make the final decision to terminate the trial	10
Harms	#22	Plans for collecting, assessing, reporting, and managing	10

		solicited and spontaneously reported adverse events and other unintended effects of trial interventions or trial conduct	
Auditing	#23	Frequency and procedures for auditing trial conduct, if any, and whether the process will be independent from investigators and the sponsor	9
Ethics and dissemination			
Research ethics approval	#24	Plans for seeking research ethics committee / institutional review board (REC / IRB) approval	5,10
Protocol amendments	#25	Plans for communicating important protocol modifications (eg, changes to eligibility criteria, outcomes, analyses) to relevant parties (eg, investigators, REC / IRBs, trial participants, trial registries, journals, regulators)	10
Consent or assent	#26a	Who will obtain informed consent or assent from potential trial participants or authorised surrogates, and how (see Item 32)	5
Consent or assent: ancillary studies	#26b	Additional consent provisions for collection and use of participant data and biological specimens in ancillary studies, if applicable	10
Confidentiality	#27	How personal information about potential and enrolled participants will be collected, shared, and maintained in order to protect confidentiality before, during, and after the	7

		trial	
Declaration of interests	#28	Financial and other competing interests for principal investigators for the overall trial and each study site	15
Data access	#29	Statement of who will have access to the final trial dataset, and disclosure of contractual agreements that limit such access for investigators	16
Ancillary and post trial care	#30	Provisions, if any, for ancillary and post-trial care, and for compensation to those who suffer harm from trial participation	6
Dissemination policy: trial results	#31a	Plans for investigators and sponsor to communicate trial results to participants, healthcare professionals, the public, and other relevant groups (eg, via publication, reporting in results databases, or other data sharing arrangements), including any publication restrictions	11
Dissemination policy: authorship	#31b	Authorship eligibility guidelines and any intended use of professional writers	11
Dissemination policy: reproducible research	#31c	Plans, if any, for granting public access to the full protocol, participant-level dataset, and statistical code	16
Appendices			
Informed consent materials	#32	Model consent form and other related documentation given to participants and authorised surrogates	Uploaded
Biological specimens	#33	Plans for collection, laboratory evaluation, and storage of	N/A

	biological specimens for genetic or molecular analysis in the current trial and for future use in ancillary studies, if applicable

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REVISE: Re-Evaluating the Inhibition of Stress Erosions in the ICU: A Randomized Trial Protocol

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Complete List of Authors:	Deane, Adam M; University of Melbourne, Department of Critical Care, Melbourne Medical School Alhazzani, Waleed ; McMaster University, Departments of Medicine and Health Research Methods, Evidence & Impact Guyatt, Gordon; Mcmaster University, Department of Health Research Methods, Evidence & Impact Finfer, Simon; The George Institute for Global Health, Critical Care Program Marshall, John; University of Toronto, Interdepartmental Division of Critical Care Myburgh, John; The George Institute for Global Health, Critical Care Program Zytaruk, Nicole; McMaster University, Department of Medicine and Health Research Methods, Evidence & Impact Hardie, Miranda; The George Institute for Global Health, Critical Care Program Saunders, Lois; St Joseph's Healthcare Hamilton, Research Institute Knowles, Serena; The George Institute for Global Health, Critical Care Program Lauzier, Francois; Centre de Recherche du CHU de Québec - Université Laval, Departments of Anesthesiology, Medicine & Critical Care Medicine Chapman, Marianne J.; The University of Adelaide, Discipline of Acute Care Medicine English, Shane; University of Ottawa, Division of Critical Care, Department of Medicine; Ottawa Hospital Research Institute, Clinical Epidemiology Program Muscedere, John; Queens University, Department of Critical Care Medicine Arabi, Yaseen; King Abdullah International Medical Research Center, Intensive Care Department Ostermann, Marlies; King's College London, Guy's & St Thomas' Hospital , Department of Critical Care Venkatesh, Balasubramanian; The George Institute for Global Health, Critical Care Program Young, Paul ; Wellington Hospital, Intensive Care Department Thabane, Lehana; McMaster University, Department of Health Research Methods, Evidence, and Impact Billot, Laurent; The George Institute for Global Health, Statistics Division Heels-Ansdell, Diane; Mcmaster University, Health Research Methods,

	Evidence & Impact Al-Fares, Abdulrahman A; Al-Amiri Hospital, Departments of Anesthesia, Critical Care Medicine and Pain Medicine Hammond, Naomi ; The George Institute for Global Health, Critical Care Medicine Hall, R.; Dalhousie University, Departments of Anesthesia, Critical Care and Pharmacology Rajbhandari, Dorrilyn; The George Institute for Global Health, Critical Care Medicine Poole, Alexis; The University of Adelaide, Discipline of Acute Care Medicine Johnson, Daniel; University of Nebraska Medical Center, Departments of Critical Care and Anesthesia Iqbal, Mobeen; Maroof International Hospital, Intensive Care Department Reis, Gilmar; Pontifical Catholic University of Minas Gerais, Cardresearch – Cardiologia Assistencial e de Pesquisa LTDA Xie, Feng; McMaster University, Health Research Methods, Evidence & Impact Cook, Deborah; McMaster University, Departments of Medicine and Health Research Methods, Evidence & Impact * Deane and Alhazzani are co-first authors, for the CCCTG & ANZICS-CTG; McMaster University Faculty of Health Sciences
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REVISE: Re-Evaluating the Inhibition of Stress Erosions in the ICU: A Randomized Trial Protocol

*Adam Deane University of Melbourne, Melbourne, Australia Adam.Deane@mh.org.au
*Waleed Alhazzani McMaster University, Hamilton, Canada alhazzaw@mcmaster.ca
Gordon Guyatt McMaster University, Hamilton, Canada guyatt@mcmaster.ca
Simon Finfer The George Institute, Sydney, Australia sfinfer@georgeinstitute.org.au
John Marshall University of Toronto, Toronto, Canada John.Marshall@unityhealth.to
John Myburgh The George Institute, Sydney, Australia jmyburgh@georgeinstitute.org.au
Nicole Zytaruk McMaster University, Hamilton, Canada zytarn@mcmaster.ca
Miranda Hardie The George Institute, Sydney, Australia mhardie@georgeinstitute.org.au
Lois Saunders St. Joseph's Healthcare Hamilton, Hamilton, Canada lsaunde@mcmaster.ca
Serena Knowles The George Institute, Sydney, Australia sknowles@georgeinstitute.org.au
François Lauzier Université Laval, Québec City, Canada Francois.Lauzier@fmed.ulaval.ca
Marianne Chapman University of Adelaide, Adelaide, Australia Marianne.Chapman@sa.gov.au
Shane English University of Ottawa, Ottawa, Canada senglish@toh.ca
John Muscedere Queen's University, Kingston, Canada John.Muscedere@kingstonhsc.ca
Yaseen Arabi King Abdullah National Research Center, Riyadh, Saudi Arabia Arabi@mngha.med.sa
Marlies Ostermann King's College, London, United Kingdom Marlies.Ostermann@gstt.nhs.uk
Bala Venketesh The George Institute, Sydney, Australia bvenkatesh@georgeinstitute.org.au
Paul Young Wellington Hospital, Wellington, New Zealand Paul.Young@ccdhb.org.nz
Lehana Thabane McMaster University, Hamilton, Canada thabanl@mcmaster.ca
Laurent Billot The George Institute, Sydney, Australia lbillot@georgeinstitute.org
Diane Heels-Ansdell McMaster University, Hamilton, Canada ansdell@mcmaster.ca
Abdulrahman Al Fares Al-Amiri Hospital, Kuwait City, Kuwait abdulrahman.alfares@gmail.com
Naomi Hammond The George Institute, Sydney, Australia nhammond@georgeinstitute.org.au
Richard Hall Dalhousie University, Halifax, Canada r.i.hall@dal.ca
Dorrilyn Rajbhandari The George Institute, Sydney, Australia drajbhandari@georgeinstitute.org.au
Alexis Poole University of Adelaide, Adelaide, Australia alexis.poole@adelaide.edu.au
Daniel Johnson University of Nebraska, Omaha, Nebraska dan.johnson@unmc.edu
Mobeen Iqbal Maroof International Hospital, Islamabad, Pakistan iqmob@yahoo.com
Feng Xie McMaster University, Hamilton, Canada fengxie@mcmaster.ca
Gilmar Reis Pontifical Catholic University, Belo Horizonte, Brazil greisbh@uol.com.br
Deborah Cook McMaster University, Hamilton, Canada debcook@mcmaster.ca

*co-first authors
for the REVISE Investigators, the Canadian Critical Care Trials Group
and the Australian and New Zealand Intensive Care Society Clinical Trials Group

Corresponding author: Deborah Cook, McMaster University, 1280 Main Street West, Hamilton, Ontario, Canada. L8N 3Z5. debcook@mcmaster.ca. 905-979-9805

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ABSTRACT

Introduction: The REVISE (Re-Evaluating the Inhibition of Stress Erosions) Trial aims to determine the impact of the proton pump inhibitor pantoprazole compared to placebo on clinically important upper gastrointestinal (GI) bleeding in the intensive care unit (ICU), 90-day mortality, and other endpoints in critically ill adults. The objective of this report is to describe the rationale, methodology, ethics and management of REVISE.

Methods and Analysis: REVISE is an international, randomized, concealed, stratified, blinded parallel-group individual patient trial being conducted in ICUs in Canada, Australia, Saudi Arabia, UK, US, Kuwait, Pakistan and Brazil. Patients ≥18 years old expected to remain invasively mechanically ventilated beyond the calendar day after enrolment are being randomized to either 40 mg pantoprazole intravenously or an identical placebo daily while mechanically ventilated in the ICU. The primary efficacy outcome is clinically important upper GI bleeding within 90 days of randomization. The primary safety outcome is 90-day all-cause mortality. Secondary outcomes include rates of ventilator-associated pneumonia, *Clostridioides difficile* infection, new renal replacement therapy, ICU and hospital mortality, and patient-important GI bleeding. Tertiary outcomes are total red blood cells transfused, peak serum creatinine level in the ICU, and duration of mechanical ventilation, ICU and hospital stay. The sample size is 4,800 patients; one interim analysis was conducted after 2,400 patients had complete 90-day follow-up; the Data Monitoring Committee recommended continuing the trial.

Ethics and Dissemination: All participating centers receive research ethics approval before initiation by hospital, region or country, including: Australia: Northern Sydney Local Health District Human Research Ethics Committee and Mater Misericordiae Ltd Human Research Ethics Committee; Brazil: Comissão Nacional de Ética em Pesquisa; Canada: Hamilton Integrated Research Ethics Board; Kuwait: Ministry of Health Standing Committee for Coordination of Health and Medical Research; Pakistan: Maroof Institutional Review Board; Saudi Arabia: Ministry of National Guard Health Affairs Institutional Review Board: United Kingdom: Hampshire B Research Ethics Committee; United States: Institutional Review Board of the Nebraska Medical Center. The results of this trial will inform clinical practice and guidelines worldwide.

Clinical Trial Registration: www.clinicaltrials.gov NCT03374800

Article Summary: Strengths and Limitations of this Study

- This 4800-patient randomized clinical trial at low risk-of-bias will evaluate the effect of pantoprazole versus placebo on clinically important gastrointestinal bleeding (primary efficacy outcome), 90-day mortality (primary safety outcome) and other relevant endpoints.
- Blinded to allocation, outcomes will be adjudicated (clinically important gastrointestinal bleeding), classified (ventilator-associated pneumonia), and validated (*Clostridioides difficile* infection severity)
- Patient and family engagement in a mixed-methods study will inform a novel secondary outcome of patient-important bleeding
- Patients not receiving invasive mechanical ventilation are excluded; trial results may have limited applicability to spontaneously breathing patients and those receiving non-invasive ventilation
- Enrolment of heterogenous patients in 8 countries will enhance the generalizability of the findings

Keywords: Clinical trial; gastroduodenal disease; intensive and critical care

INTRODUCTION

To prevent gastrointestinal (GI) bleeding from stress-induced ulceration during critical illness, physicians prescribe stress ulcer prophylaxis for over 70% of patients in the intensive care unit (ICU) [1]. However, more recently, clinicians have questioned the effect of acid suppression for seriously ill patients. The randomized clinical trials that first provided support for stress ulcer prophylaxis with acid-suppressing medications were conducted several decades ago, in an era characterized by different practices. Since then, concerns have emerged including that histamine-2-receptor antagonists (H2RAs) and proton pump inhibitors (PPIs), may increase the risk of pneumonia and *Clostridioides difficile* (*C. difficile*) infection – two healthcare-associated infections that may confer greater morbidity, mortality and costs than upper GI bleeding [2].

Two large trials recently rejuvenated interest in this topic [3,4]. In October 2018, the Stress Ulcer Prevention in the ICU (SUPICU) trial [3] randomized 3,298 patients to pantoprazole or placebo and found no difference in the primary outcome of 90-day mortality, nor the secondary composite outcome (GI bleeding, pneumonia, *C. difficile* infection, and acute myocardial ischemia). Pantoprazole reduced GI bleeding rates (4.2% vs. 2.5%, p =0.006); however many of these bleeds did not result in hypotension, transfusion, endoscopy or other interventions. Subgroup analysis suggested that patients with higher illness severity receiving pantoprazole may have an increased risk of death at 90-day compared to those receiving placebo (relative risk [RR] 1.13; 95%CI, 0.99-1.30, interaction p=0.05) – an effect not observed in less severely ill patients. Further misgivings about widespread PPI use were raised in January 2019 when a cluster crossover trial of 26,771 patients evaluating PPIs against the active comparator of H2RAs also suggested an increased risk of death in the most severely ill subgroup of patients receiving PPIs [4].

Building on prior studies through international collaboration [5-14,2,3], the REVISE (Re-Evaluating the Inhibition of Stress Erosions) Trial was developed. The objective is to determine the effect of pantoprazole versus placebo on the primary *efficacy* outcome (clinically important upper GI bleeding), and the primary *safety* outcome (90-day all-cause mortality) [15]. Secondary outcomes include ventilator-associated pneumonia (VAP), *C. difficile* infection, new renal replacement therapy, ICU and hospital mortality, and patient-important GI bleeding. The REVISE protocol was designed within the Stress Ulcer Prophylaxis Research Program [Figure 1], in collaboration with the Canadian Critical Care Trials Group (CCCTG) [16], Australian and New Zealand Intensive Care Society Clinical Trials Group (ANZICS-CTG) [17] and international colleagues (Protocol# CCT38473; Version 3.0, 10 April 2019) [18].

Background and Rationale

The current impact of PPIs for patients in the ICU is unclear. In the 4,011 critically ill patients enrolled in 7 randomized trials comparing PPI to no PPI, only 118 cases of clinically important bleeding, 565 cases of pneumonia and 48 cases of *C. difficile* were observed. Our updated network meta-analysis [14], using GRADE methodology [19], incorporating direct [3] and indirect [4] evidence further highlighted uncertainties regarding the net effect of PPIs across outcomes of mortality, pneumonia, *C. difficile* infections, and even – because of very small effects in lower-risk groups – GI bleeding. The certainty of evidence regarding GI bleeding reduction for 3 of 4 bleeding risk subgroups (low, high and highest risk) was *moderate* given the potential for risk-of-bias [20]. All 4 risk groups shared the same relative effect estimate and credible interval [CrI] (RR 0.46, 95% CrI 0.29-0.66). For the *moderate* risk group, where the certainty of evidence was high, the credible interval spanned a range from a 2.1% absolute reduction in bleeding to a 1.0% absolute reduction, illustrating imprecision and contributed to a low certainty evidence rating. Thus, the BMJ Rapid Recommendation initiative [20] issued a weak recommendation against stress ulcer prophylaxis administration in patients at low bleeding risk of bleeding, and a weak recommendation for those at higher bleeding risk.

Regarding the risk of VAP (network RR 1.08, CrI 0.88-1.45) and of *C. difficile* infection (network RR 0.76, CrI 0.28-2.16), existing trials have failed to exclude important harm with PPIs. Regarding mortality, the network meta-analysis RR of 1.03 is consistent with a small increased risk of death with PPIs. Given the baseline mortality of ICU patients, the CrI of 0.93-1.14 includes an important mortality increase; for a baseline of 30%, a 14% relative increase would represent a 4.2% absolute increase. By adding REVISE results to the network meta-analysis, we hope to decrease imprecision of estimates, establishing an increased risk, or a trivial or no increase in mortality.

Based on these considerations, after grant funding and before launching the trial, protocol modifications were made to reflect the foregoing recent evidence. The trial was changed to a superiority design instead of a non-inferiority design. The primary safety outcome of mortality was included in response to subgroup analyses of earlier trials suggesting concern in patients at high-risk of death [21,22]. The follow-up was extended from 60-day to 90-day mortality to better inform future meta-analyses. Patients and families were actively engaged in a study to refine the secondary endpoint of patient-important bleeding, outlined in the patient engagement section of this report [23]. The sample size was increased from 3,600 to 4,800 patients, informed by the updated network meta-analysis [14]. Relevant regulatory agencies, ethics boards and the Data Safety & Monitoring Committee re-approved the protocol. Enrolment began in July 2019.

METHODS AND ANALYSIS

Design

REVISE is a randomized, stratified, concealed, blinded, parallel-group trial.

Inclusion criteria:

- Adults ≥18 years old receiving invasive mechanical ventilation
- Expected to remain mechanically ventilated beyond the calendar day after randomization

Exclusion criteria:

- Already invasively mechanically ventilated ≥72 hours during this hospital admission
- Acid suppression for active GI bleeding or high risk of bleeding (e.g., current bleeding, peptic ulcer bleeding within 8 weeks, recent severe esophagitis, Barrett's esophagus, Zollinger-Ellison syndrome); [dyspepsia or gastroesophageal reflux is not an exclusion criterion]
- Acid suppression in the ICU for >1 PPI or H2RA daily-dose-equivalent
- Dual antiplatelet therapy, or combined antiplatelet use and therapeutic anticoagulation
- Pantoprazole contraindication per local product information (in Australia: being treated with the human immunodeficiency virus protease inhibitors atazanavir or nelfinavir, being treated with high dose methotrexate (i.e. >300mg as part of a chemotherapy regimen), and documented cirrhosis or severe liver disease (e.g., as indicated by an international normalized ratio > 5.0 due to underlying liver disease); in Canada: being treated with rilpivirine or atazanavir, and patients who are hypersensitive to pantoprazole, substituted benzimidazoles, or to any ingredient in the formulation)Palliative care or anticipated withdrawal of life support
- Pregnancy
- Previous enrolment in REVISE, a related trial, or trial prohibiting coenrolment
- Patient, substitute-decision-maker (SDM) or physician declines

Informed Consent

Research staff and investigators in the ICU screen patients for eligibility. Once eligibility is confirmed, the protocol allows either *a priori informed consent* or informed *consent to continue*. Consent encounters accord with guidelines [24]. When not possible to obtain consent prior to

randomization, eligible patients are enrolled without prior consent (deferred consent). As soon as possible and appropriate thereafter, the patient or SDM is informed of the patient's participation and offered the option to consent to continue or withdraw from the trial at any time. The patient or SDM may withdraw consent for receipt of study drug and/or for data collection. If withdrawal of study drug is requested, it is stopped and permission to use trial-related data is sought. Consent models and labels vary by region. In Canada and the UK, for those randomized under a *deferred consent* model, patients or SDMs can withdraw consent for continued participation whereas in Kuwait, they can *opt out* of continued participation. In some settings, telephone consent allows witnessed verbal *a priori consent* or *consent to continue* with signature confirmation as soon as possible. An example consent form approved by Clinical Trials Ontario is found in Supplemental Appendix 1.

Randomization

When notified by research staff or investigators about eligible patients, research pharmacists or designated unblinded staff not caring for patients use a password-protected website to access the central computerized randomization program to ensure concealed 1:1 allocation using randomly-permuted variable unspecified block sizes. Randomization is stratified by center and pre-hospital acid suppression (i.e., prior PPI or H_2RA or not), generating *start or no start*, and *continue or discontinue* strata. The latter stratification will allow exploration of possible rebound hypersecretion of gastric acid upon acid suppression termination [25] and possible microbiome modification by long-term acid suppression which may modify infection risk [26].

Interventions

Patients are randomly assigned to receive locally-sourced intravenous pantoprazole 40 mg reconstituted with 0.9% sodium chloride (NaCl) or matched placebo (0.9% NaCl). Research pharmacists or designated unblinded staff prepare blinded placebo and study drug labelled per local regulations, dispensed to the ICU for daily bedside nurse administration.

The colour stability of reconstituted pantoprazole or placebo formulations from 5 companies up to 5 days without unblinding has been verified [27]. These clear, colourless indistinguishable solutions are dispensed daily until 90 days after randomisation or until death, mechanical ventilation discontinuation, or clinically important GI bleeding.

When patients receive study drug, open-label PPI or H_2RA use is documented and considered a protocol violation unless clinically indicated. Study drug continues regardless of feeding status [28-30]. Study drug may be temporarily or permanently discontinued if a definite pantoprazole indication or contraindication develops. Regardless of study drug exposure, all patients are followed unless consent to follow-up is withdrawn. Study drug is restarted if invasive mechanical ventilation is reinstituted during the index ICU admission.

All other patient management during and following the trial is at the treating team's discretion.

Risk-of-Bias

To protect against selection bias, prognostic imbalance, detection, performance and measurement bias, loss to follow-up, missing data and other threats to validity, 18 strategies for trial conduct, analysis and dissemination phases were incorporated. [Table 1]. Patients, families, clinicians, and research personnel (staff, investigators and adjudicators) are blinded. The analyst and biostatisticians remain blinded until the main analysis is complete. Unblinding is not permitted other than in emergency situations, requiring Methods Center contact.

Data Collection

Research staff collect baseline data about the patients (e.g., illness severity, comorbidities, pre-hospital acid suppression), and daily data up to 90 days post-randomization while in the ICU. This includes advanced life supports received, key laboratory values (e.g., hemoglobin, INR, platelet count); cointerventions (e.g., enteral nutrition, anticoagulants, non-steroidal anti-inflammatory agents, corticosteroids), and relevant hospital reports (e.g., endoscopy, radiology, surgery). Research staff follow patients daily to document study drug receipt or reasons for non-administration, while tracking trial outcomes as listed below. The duration of mechanical ventilation, ICU and hospital stay, and mortality are documented. Patients discharged alive from hospital before 90 days are followed for 90 days; vital status is obtained by patient, family or family physician contact, regional obituary or health-record review. No biological specimens are collected. The case report forms with additional details are found in Supplemental Appendix 2.

Enrolled patients are assigned a unique numerical code. Enrolment logs with identifiers are retained at each site. Research pharmacists or designated unblinded staff not caring for patients enter study drug dispensing details into a secure web-based electronic data-capture system (iDataFax, Seattle, Washington). Blinded research staff upload clinical data without personal health information. An audit trail tracks any data modifications.

Primary Outcomes

Primary Efficacy Outcome: *Clinically important upper GI bleeding* occurring in the ICU or resulting in ICU readmission during the index hospital stay up to 90-days post-randomization. Clinically important GI bleeding requires the presence of overt GI bleeding, defined as one of the following:

- Hematemesis
- Overt oro/nasogastric bleeding (frank blood or coffee-ground oro/nasogastric aspirate)
- Melena
- Hematochezia

plus one of the following in the absence of other causes:

- hemodynamic change defined as a spontaneous decrease in mean arterial pressure or non-invasive systolic or diastolic blood pressure of ≥20 mmHg, or an orthostatic increase in pulse rate of ≥20 beats/minute and a decrease in systolic blood pressure of ≥10 mmHg, with or without vasopressor initiation or increase
- vasopressor initiation
- hemoglobin decrease of ≥2 g/dl (20 g/L) within 24 h of bleeding
- transfusion of ≥2 units packed red blood cells within 24 h of bleeding
- therapeutic intervention (e.g., therapeutic endoscopy, angioembolization, surgery).

Our bleeding definition builds on prior studies [31,32], explicitly incorporating vasopressor initiation or increase [3] and endoscopy. Research staff prospectively collect data related to GI bleeding, allowing central duplicate blinded adjudication, described below.

***Primary Safety Outcome*:** *All-cause mortality* at 90 days post-randomization, ascertained by patient or SDM contact for those discharged alive before 90 days.

Secondary Outcomes

- *Incidence of VAP:* is diagnosed in patients who received invasive mechanical ventilation for ≥48 hours when there is a new, progressive or persistent radiographic infiltrate *plus at least 2 of the following without other obvious cause*: 1) fever (temperature>38 °C) or hypothermia (temperature <36 °C); 2) leukopenia (<4.0 x 10^6/L) or leukocytosis (>12.0 x 10^6/L); 3) purulent sputum; or 4) gas exchange deterioration [33,34]. Research staff prospectively collect data

allowing central classification by the Clinical Pulmonary Infection Score [35], and other definitions as below.

- *Incidence of C. difficile infection* is defined as clinical features (diarrhea [>3 episodes of unformed stools [36] or Bristol type 6 or 7 [37], ileus, or toxic megacolon) and either microbiological evidence of toxin-producing *C. difficile* or pseudomembranous colitis on colonoscopy [38] in hospital within 90 days.
- *New renal replacement therapy (RRT)* is defined as initiation of new RRT in the ICU.
- *ICU mortality* is defined as all-cause mortality in the ICU during the index hospitalization within 90 days.
- *Hospital mortality* is defined as all-cause mortality during the index hospitalization within 90 days.
- *Patient-important GI bleeding* is focused on GI bleeding characteristics that are important to patients and families [23]. The criteria will be derived from a mixed-methods study involving interviews and focus groups of ICU survivors and family members not involved in REVISE, eliciting perspectives on concerning bleeding features for incorporation into the database to define this outcome.

Tertiary outcomes

- *Total units of red blood cells transfused in the ICU*
- *Peak serum creatinine level in the ICU*
- *Duration of mechanical ventilation (days)*
- *ICU length of stay (days)*
- *Hospital length of stay (days)*

Central Adjudication, Classification and Validation of Morbidity Outcomes

Clinically Important GI Bleeding: Research staff and investigators will identify all possible GI bleeding events, complete the bleeding case report form and submit redacted clinical notes, laboratory data and procedural reports. All GI bleeding events will be *adjudicated* by at least two investigators from of a five-member GI bleeding adjudication committee to determine if the event meets the definition of clinically important GI bleeding and to confirm GI bleeding site. Initial calibration of the committee members will involve independent review by all five members (blinded to study drug and centre) case report forms and source data for the first 10 bleeding patients. Committee members will convene and discuss their assessments, clarify reasons for disagreements and arrive at consensus for each event. Subsequent bleeding events will be independently adjudicated by one primary adjudicator (for all events) and a secondary adjudicator (randomly assigned, stratified by study drug). Adjudicators will be blinded to allocation and center. Disagreements will resolve by discussion and consensus or a third researcher if necessary.

VAP: Local research staff and investigators will report any lower respiratory tract infections on the pneumonia outcome case report form. Data will be *classified* in duplicate by the Clinical Pulmonary Infection Score [35] and other definitions (e.g., American College of Chest Physicians [33,34], Centers for Disease Control [39], the International Sepsis Forum [40] and by invasive microbiological confirmation [41]. Disagreements will resolve by discussion and consensus or a third researcher if necessary.

In addition, early VAP is defined as arising on day 3, 4 or 5 after mechanical ventilation is initiated, and late VAP as arising on day 6 of mechanical ventilation or later, including up to 2 days after mechanical ventilation discontinuation [42]. Pneumonia arising 3 or more days after mechanical ventilation discontinuation will be considered post-extubation pneumonia. We do not report ventilator-

associated conditions (VACs) or infection-related VACs, as surveillance metrics are modifiable by volume status and ventilator settings and do not predict VAP [43].

***C. difficile infection*:** *C. difficile* outcome case report forms will be *validated* in duplicate by two researchers assessing severity (non-severe, severe, fulminant) [38]. Disagreements will resolve by discussion and consensus or a third researcher if necessary.

Trial Process Metrics

We will report informed consent rates and coenrolment rates, and any need for unblinding.

In terms of protocol adherence, we will report days of study drug exposure, and reasons for non-administration of study drug. Protocol deviations will include administration of open label proton pump inhibitor or histamine-2-receptor antagonist, missed doses of study drug, or dispensing the wrong study drug (e.g., pantoprazole given instead of placebo or vice versa).

Patient and Public Involvement

Patients and families will be involved in several ways. We completed two pilot trials, documenting consent rates of 98.1% [11] and 77.8% [12]. Second, enrolled patients who regain capacity after critical illness are notified about the trial and approached for consent to continued participation. A mixed-method study eliciting perspectives of patients and families not involved in REVISE is refining the secondary outcome of patient-important bleeding [23]. Fourth, in the UK, patients are involved at all stages as per the Health Research Authority standards [44]; patients reviewed the protocol, provided feedback, and supported approval. When REVISE results are available, lay language summaries, visual abstracts and infographics will be created by patient partners for traditional media (paper, radio, television) and public social media feeds (twitter, blogs).

Sample Size

The sample size of 4,800 patients was chosen on the basis of plausible baseline risks of GI bleeding, plausible relative risk reductions, a target of 85% power and feasible enrolment. The best estimate of the GI bleeding event rate in the placebo arm ranging from 3% to 6% is based on the following: an international period-prevalence study (2.6%; 95% CI, 1.6-3.6) [1]; the REVISE Pilot trial (placebo 6.1%; 95% CI 2.1-16.5) [12]; and the SUPICU trial placebo rate of 4.2% [3]. The relative risk associated with pantoprazole was 0.6 in the SUPICU trial. Table 2 highlights sample size considerations for clinically important upper GI bleeding. The table presents combinations of relative risk reductions ranging from 30% to 50%, and baseline risks between 3% and 6% for which we will achieve 85% power. With a baseline risk of 3% and a relative risk reduction of 50%, the absolute benefit will be a 1.5% difference. Other highlighted cells correspond to absolute risk reduction of greater than 1.5%. In summary, across the range of plausible baseline risks, 4,800 patients will provide at least 85% power to detect effects of pantoprazole as large as, or greater than, the smallest clinically important reduction in GI bleeding.

Table 3 highlights sample size implications for 90-day mortality. The estimates of relative risk are informed by SUP-ICU in which the upper confidence limit around the increased mortality in the high-risk group (SAPS II >53) included 1.30. Among the first 25% of patients enrolled, the mortality rate was 44% across both groups in the comparable high-risk of death group of concern (APACHE II score >25). Our power calculations are based on the estimated 40% of REVISE patients who will fall in the high-risk group (~1,920 patients). The table presents combinations of relative risks ranging from 1.1 to 1.3, and baseline risks between 4% and 38%, demonstrating power of $\geq$70% for combinations of higher levels of baseline risk and relative risk increase. The relative risk of 1.13 is the point estimate in patients with high illness severity in SUPICU [3]. In summary, across the range of higher baseline risks, 4,800 patients will provide at least 70% power to detect effects of pantoprazole at levels that

would likely preclude use of pantoprazole in patients at higher risk of death.

Trial Management

Two Methods Centers with extensive experience running international clinical trials oversee REVISE, at McMaster University in Hamilton, Canada and The George Institute for Global Health in Sydney, Australia for Australian sites [Figure 2]. Methods Center teams meet twice monthly to harmonize approaches, track progress and share management efficiencies. Within Canada, the Québec Lead investigator ensures valid scientific cross-cultural, bilingual alignment with provincial ethical and regulatory directives. Methods Center personnel train local investigators and research staff on the protocol, ensure optimal conduct and validate all data at least thrice.

Central statistical monitoring will occur twice annually at McMaster University. Site-specific data monitoring and auditing will follow national guidance.

Upon trial completion, original research records will be retained at participating sites in accordance with relevant regulations. Study drug will be destroyed per jurisdictional regulations. The database will be maintained for at least 15 years.

Statistical Analysis

The *main analyses* will be conducted by analyzing patients in the group to which they were allocated regardless of protocol adherence, per the intention-to-treat principle. We will compare the time to the primary and secondary binary outcomes using Cox proportional hazards regression with threshold P-values of 0.05. Randomization is stratified for center and pre-hospital acid suppression. Because APACHE II score is strongly associated with mortality, to maximize statistical efficiency, we will also adjust for baseline APACHE II score for the mortality outcome. For binary outcomes, we will report hazard ratios with 95% confidence intervals (CIs) as well as the absolute risk increase or decrease and 95% CIs. For continuous outcomes, we will use linear regression on the original scale or on the log-scale. Subgroup analyses will be conducted for the primary *efficacy* outcome and primary *safety* outcome in five *a priori* subgroup pairs: 1) Pre-hospital acid suppression (PPIs or H2RAs) vs. none, 2) Illness severity per APACHE II score of ≥25 or <25, 3) 3) Medical vs. surgical/trauma ICU admitting diagnosis, 4) SARS-CoV-2 positive vs. negative status, and 5) Female vs. male.

Peer-Review Funding

Global enrolment in REVISE is supported by serial hybrid peer-review funding including 3 grants from the Canadian Institutes of Health Research, one of which is the Accelerating Clinical Trials Fund, and the Hamilton Academy of Health Sciences Organization. The National Health and Medical Research Council of Australia grant funds enrolment in Australia. REVISE was approved by the National Institute for Health Research in the UK supported by the Clinical Research Network. The funders have no role in the conception, design, conduct, oversight, analysis, interpretation, write-up, or approval of the manuscript, or decision to submit for publication.

ETHICS AND DISSEMINATION

Data Monitoring Committee

The independent REVISE Data Monitoring Committee (DM)C requested review of 90-day mortality results after 1,200 patients were recruited (25% enrolment), recommending trial continuation. The formal interim analysis was conducted after 2,400 patients (50% enrolment) had 90-day mortality ascertainment. To maintain the overall type-I error rate for the interim analysis, a Haybittle-Peto stopping rule with a critical value of 3 standard deviations and fixed conservative α=0.001 was used

[45,46]. After examining recruitment, consent, coenrolment, protocol adherence and all trial outcomes, the DMC advised the Steering Committee to continue enrolment.

Ethics

Relevant Research Ethics Boards (REBs) and/or Human Research Ethics Committees (HRECs) of each participating hospital and/or region approved REVISE. These include: Australia: Northern Sydney Local Health District Human Research Ethics Committee and Mater Misericordiae Ltd Human Research Ethics Committee; Brazil: Comissão Nacional de Ética em Pesquisa; Canada: Hamilton Integrated Research Ethics Board; Kuwait: Ministry of Health Standing Committee for Coordination of Health and Medical Research; Pakistan: Maroof Institutional Review Board; Saudi Arabia: Ministry of National Guard Health Affairs Institutional Review Board: United Kingdom: Hampshire B Research Ethics Committee; United States: Institutional Review Board of the Nebraska Medical Center.

Protocol implementation and database training accords with the International Council for Harmonisation Guidelines for Good Clinical Practice and other locally applicable regulations.

Adverse Events

Key adverse events and serious adverse events (SAEs) relevant to REVISE are already predefined primary or secondary trial outcomes. Beyond these events, ICU patients can develop many other complications due to critical illness or its treatment, which may be life-threatening or fatal. However, they do not constitute adverse events or SAEs unless considered by the treating clinicians to possibly relate to the study drug. REVISE follows guidance for rational reporting of SAEs in investigator-initiated ICU trials of drugs in common use [47]. The trial report will document all deaths and report only SAEs meeting the foregoing five published recommendations, regardless of local reporting requirements.

COVID-19 Pandemic

After the pandemic was declared, REVISE paused for variable periods of time at each center. We proposed ethical principles for concurrent conduct of research that is and is not pandemic-focused, whenever safe, feasible and locally approved [48]. Relevant to patients with [49] and without COVID-19, enrolment restarted as soon as possible without protocol modification, ensuring local research capacity, protocol fidelity and infection control.

Data Deposition and Curation

The dataset will be used for secondary observational studies addressing additional hypothesis-driven questions (e.g., predictors of gastrointestinal bleeding). Access for REVISE investigators will follow a submitted rationale, analysis plan and Management Committee approval. Requests for access to the dataset by external investigators will be considered following a submitted rationale, analysis plan and approval by the Management Committee and research ethics boards, as relevant. Requirements will be stipulated in a pre-specified data sharing agreement. Only de-identified data will be provided and will be transferred via a secure web portal.

Knowledge Translation

REVISE will provide low risk-of-bias estimates that more than double trial evidence on the impact of pantoprazole on outcomes, increasing the strength of inferences regarding clinically important GI bleeding, mortality, VAP, and *C. difficile* infection. REVISE will not provide direct evidence about pantoprazole's effect on patients requiring non-invasive ventilation or no ventilatory support. Given

contemporary critical care practice, we anticipate that a small proportion of enrolled patients will receive no enteral nutrition, such that inferences about this population may be limited.

We will publish the main results within one year of the last patient follow-up, presenting concurrently at an international congress. We will host videoconferences and regional rounds, and disseminate abstracts and slide-decks to local quality councils, provincial and state organizations, national policy makers and professional groups. Interested websites will feature multilingual REVISE results. Findings will be communicated through conventional academic channels (e.g., abstracts, posters, peer-review manuscripts) and at professional fora (e.g., grand rounds, teaching sessions, in-services, quality improvement councils). We will update our meta-analysis, and results will be incorporated into guidance documents such as BMJ Rapid Recommendations and Surviving Sepsis Guidelines.

Status

REVISE study was launched in response to multi-professional stakeholder interests, serving public, professional and policy needs. As of May 1, 2023, 4,124 patients have been recruited in 63 centers [50]. Led by two seasoned research consortia, supported by the Canadian Community ICU Research Network [51], and energized by international collaborators, prevailing uncertainty about acid suppression has fuelled recruitment. By October 2023, 4,800 patients are anticipated, with 90-day follow-up ascertained by January 2024.

REVISE re-addresses the benefits, harms, or disutility of acid suppression in invasively mechanically ventilated patients the ICU, aligned with the *Declaration of Helsinki* stating that 'even the best-proven interventions' must be continually re-evaluated through research for their safety, effectiveness, efficiency, accessibility and quality [52].

Contributorship Statement:

Concept and design: A Al Fares, W Alhazzani, Y Arabi, L Billot, M Chapman, D Cook, A Deane, S English, S Finfer, G Guyatt, R Hall, N Hammond, M Hardie, D Heels-Ansdell, M Iqbal, D Johnson, S Knowles, F Lauzier, J Marshall, J Muscedere, J Myburgh, M Ostermann, A Poole, D Rajbhandari, G Reis,L Saunders, L Thabane, B Venkatesh, F Xie, P Young, N Zytaruk.

Acquisition, analysis, or interpretation of data: D Cook, N Hammond, M Hardie, D Heels-Ansdell, S Knowles, L Saunders, L Thabane, N Zytaruk.

Drafting of the manuscript: D Cook, A Deane, G Guyatt, M Hardie, D Heels-Ansdell, F Lauzier, L Thabane, P Young, N Zytaruk.

Critical revision of the manuscript for important intellectual content: A Al Fares, W Alhazzani, Y Arabi, L Billot, M Chapman, S English, S Finfer, R Hall, N Hammond, M Iqbal, D Johnson, S Knowles, J Marshall, J Muscedere, J Myburgh, M Ostermann, A Poole, D Rajbhandari, G Reis, L Saunders, B Venkatesh, F Xie.

Statistical analysis: L Billot, D Cook, S Finfer, G Guyatt, D Heels-Ansdell, L Thabane.

Obtained funding: A Al Fares, W Alhazzani, Y Arabi, L Billot, M Chapman, D Cook, A Deane, S English, S Finfer, G Guyatt, R Hall, N Hammond, D Heels-Ansdell, D Johnson, S Knowles, F Lauzier, J Marshall, J Muscedere, J Myburgh, M Ostermann, A Poole, D Rajbhandari, G Reis, L Thabane, B Venkatesh, P Young, F Xie, N Zytaruk.

Administrative, technical, or material support: W Alhazzani, D Cook, A Deane, S Finfer, G Guyatt, N Hammond, M Hardie, D Heels-Ansdell, S Knowles, D Rajbhandari, L Saunders, A Poole, L Thabane, N Zytaruk.

Data Integrity: D Cook, M Hardie, D Heels-Ansdell, S Knowles, L Saunders, N Zytaruk.

Competing Interests: All authors are involved in the REVISE Trial in some capacity and have been investigators on peer-review grants to support the trial. Otherwise, the authors declare that they have no competing interests.

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Data Sharing Statement: Following the publication of REVISE, the dataset will be used for secondary observational studies addressing additional hypothesis-driven questions (e.g., predictors of gastrointestinal bleeding). Access by REVISE investigators will follow a submitted rationale, analysis plan and approval by the Management Committee. Requests for access to the dataset by external investigators will be considered following a submitted rationale, analysis plan and approval by the Management Committee and research ethics boards as relevant. Requirements will be stipulated in a pre-specified data sharing agreement. Only de-identified data will be provided and will be transferred via a secure web portal.

Ethics Approval: The Hamilton Integrated Research Ethics Board is the Ethics Board of Record (CTO Project ID: 1360). Relevant Research Ethics Boards (REBs) and/or Human Research Ethics Committees (HRECs) of each participating hospital and/or region approved REVISE. These include: Australia: Northern Sydney Local Health District Human Research Ethics Committee and Mater Misericordiae Ltd Human Research Ethics Committee; Brazil: Comissão Nacional de Ética em Pesquisa; Canada: Hamilton Integrated Research Ethics Board; Kuwait: Ministry of Health Standing Committee for Coordination of Health and Medical Research; Pakistan: Maroof Institutional Review Board; Saudi Arabia: Ministry of National Guard Health Affairs Institutional Review Board: United Kingdom: Hampshire B Research Ethics Committee; United States: Institutional Review Board of the Nebraska Medical Center.

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Data Monitoring Committee: The independent REVISE Data Monitoring Committee was comprised of Professor Ian Roberts (University of Oxford), Dr. Danny McAuley (Queen's University, Belfast), and Dr. George Thomlinson (University of Toronto) (Chair).

Table 1. Strategies to Minimize Bias

Stage and Type of Bias	Strategy Implemented
Protocol Development	
Design bias	Extensive scientific, clinical and ethical input on the protocol; patient and family input to refine the patient-important bleeding outcome
Corporate conflicts of interest	Peer-review funded trial; locally sourced pantoprazole
Procedural bias	Standard Operating Procedures guide protocol implementation; central statistical monitoring is ongoing throughout the trial
Omission bias	Eligibility criteria are broad; enrolment is in 5 continents
Surveillance bias	Rigorous training of research personnel
Detection of Ventilator-Associated Pneumonia (VAP)	To avoid biased choice of VAP definition: VAP reporting has 1 main and 7 alternate definitions
Protocol Implementation	
Prognostic imbalance	At point of randomization patients are stratified for pre-hospital acid suppression which may influence outcomes
Selection bias	Allocation is concealed; Research personnel screening, consenting, and enrolling patients are unaware of randomization sequence
Detection & performance bias	Patients, families, all clinical and research personnel are blinded
Measurement bias	Primary Efficacy Outcome: Clinically important GI bleeding is centrally adjudicated by 2 physicians trained in study procedures, and blinded to allocation and center
Loss to follow-up	Primary Safety Outcome: For 90-day mortality status, multiple methods used for patients discharged alive before 90 days; all other outcomes are hospital-based as recorded in medical charts
Missing data	Each research record is reviewed and validated at least 3 times by Methods Center staff
Analysis	
False claims of benefit	*A priori* statistical approach is very conservative for stopping early for apparent benefit before full sample size reached
False claims of no difference	*A priori* statistical approach does not include stopping early for futility before full sample size reached
Confirmation bias	Analyst is blinded to allocation until after the final analysis
Analytic bias	Analysis will adhere to the intention-to-treat principle
Dissemination	
Reporting bias	Trial reporting will adhere to trial registration (NCT03374800), protocol and statistical analysis plan
Publication bias	Results will be disseminated through many knowledge translation strategies including peer-review journals

Legend for Table 1: These are the strategies we protocolized to minimize bias in four different phases of the trial.

VAP=ventilator-associated pneumonia

Table 2: Sample Size With Respect to Clinically Important Bleeding Outcome

		True Underlying Relative Risk (PPI vs Placebo)		
		0.7	**0.6**	**0.5**
Event Rate in Placebo group	**3%**	47.1%	74.6%	92.6%
	4%	60.1%	86.6%	97.8%
	5%	70.7%	93.4%	99.4%
	6%	79.1%	96.9%	99.9%

Power to reject the null of no difference in proportion of patients developing GI bleeding, with a sample size of 4,800 patients (2,400 per group). Alpha=0.05, 2-sided testing

Legend for Table 2: This table highlights consideration for clinically important GI bleeding. It presents combinations of relative risk reductions ranging from 30% to 50%, and baseline risks between 3% and 6% for which we will achieve 85% power. With a baseline risk of 3% and a relative risk reduction of 50%, the absolute benefit of will be a 1.5% difference. Other highlighted cells correspond to absolute risk reduction of greater than 1.5%. In summary, across the range of plausible baseline risks in the shaded boxes, 4,800 patients will provide at least 85% power to detect effects of pantoprazole as large as, or greater than, the smallest important reduction in clinically important GI bleeding. This sample size reflects feasible enrolment in an acceptable 4-year time frame, accounting for any non-compliance or loss to follow-up, in the context of hybrid serial funding for REVISE.
PPI=proton pump inhibitor

Table 3: Sample Size With Respect to 90-Day Mortality

	True Underlying Relative Risk (PPI vs Placebo)				
	1.1		1.13	1.2	1.3
Event rate in Placebo group	**38%**	38.0%	57.9%	91.5%	99.9%
	40%	40.9%	61.7%	93.7%	>99.9%
	42%	43.9%	65.6%	95.5%	>99.9%
	44%	47.1%	69.4%	96.9%	>99.9%

Power to reject the null of no difference in proportion of patients who die among those at higher risk of death (APACHE II ≥25), with sample size of 1,920 patients (960 per group). Alpha=0.05, 2-sided testing

Legend for Table 3: This table highlights sample size implications for 90-day mortality. The estimates of relative risk are informed by SUP-ICU in which the upper confidence limit around the increased mortality in the high-risk group (SAPS II >53) included a value of 1.30. Among the first 25% of patients enrolled, the mortality rate was 44% across both groups in the comparable high-risk of death group of concern (APACHE II score >25). Our power calculations are based on the 40% of REVISE patients who will fall in the high-risk group (1,920 patients). The table presents combinations of relative risks ranging from 1.1 to 1.3, and baseline risks between 38% and 44%, showing power of ≥ 70% for combinations of higher levels of baseline risk and relative risk increase. The relative risk of 1.13 is the observed point estimate in patients with high illness severity in the SUPICU Trial. In summary, across the range of higher baseline risks, 4,800 patients will provide at least 70% power to detect effects of pantoprazole at levels that would preclude use of the drug in patients with high illness severity - those at higher risk of death.
PPI=proton pump inhibitor

Figure 1: Stress Ulcer Prophylaxis Research Program

Legend for Figure 1: In preparation for this trial, with national and international collaborators, we developed this stress ulcer prophylaxis research program. We published several reviews and meta-analyses on acid suppression. We contributed to an international period prevalence epidemiologic study which assisted with some REVISE trial estimates. We completed 2 surveys about stress ulcer prophylaxis in Australia and Canada. We completed 2 pilot randomized trials in preparation for REVISE. The 214-patient, single-center Australian POP-UP Pilot trial achieved 3 objectives related to exploring overt signals of benefit or harm, ascertaining whether the study drug could be administered promptly after commencing mechanical ventilation, and estimating relevant outcome event rates. A second 91-patient, international REVISE Pilot Trial achieved 3 feasibility objectives related to rates of recruitment, informed consent, and protocol adherence. Other international studies provided key evidence to help inform the design of the main REVISE Trial.

Figure 2: Organizational Chart

Legend for Figure 2: In this figure we depict the organization and management relationships for the international REVISE Trial.

Figure 1
Stress Ulcer Prophylaxis Global Research Program

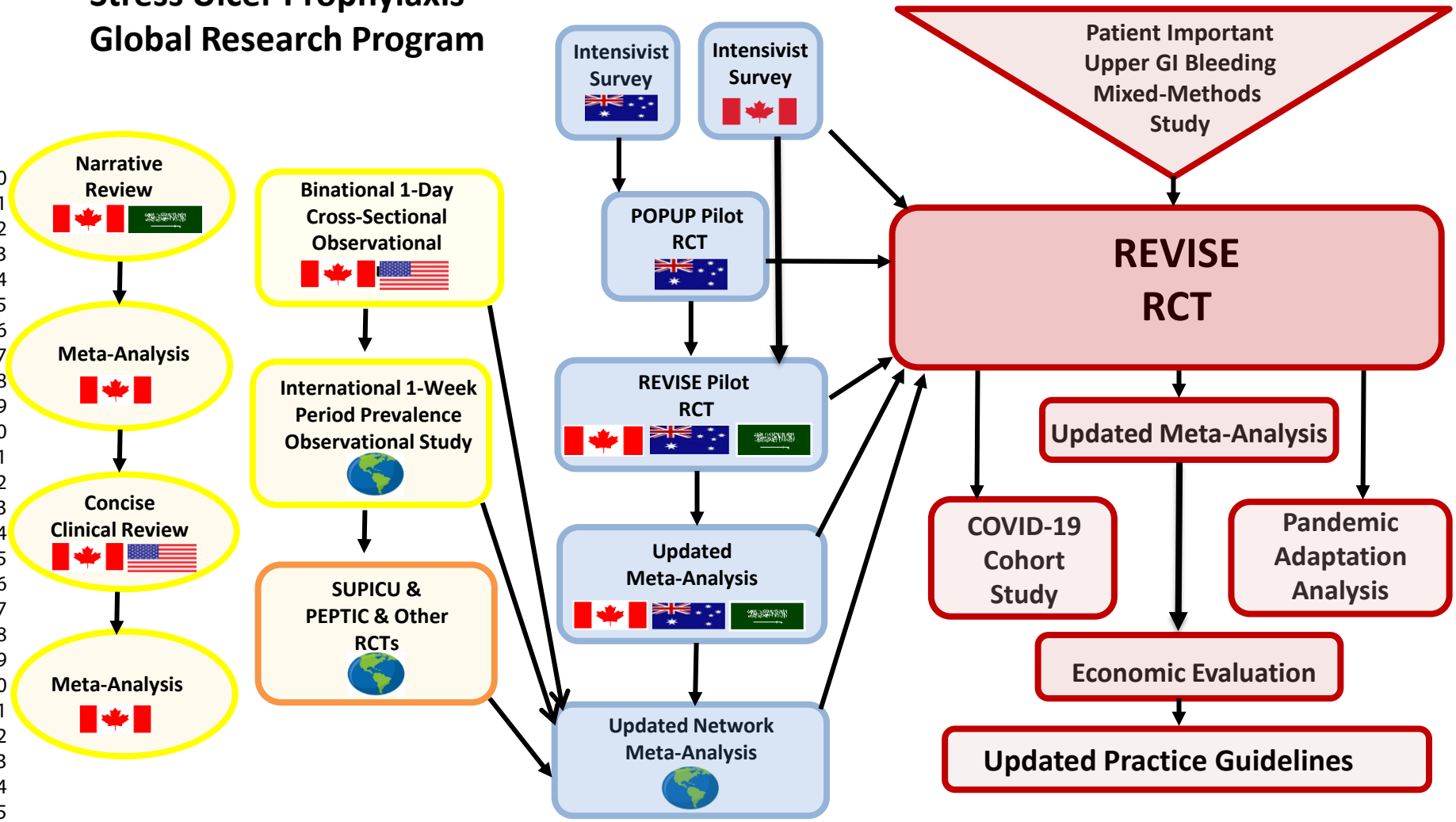
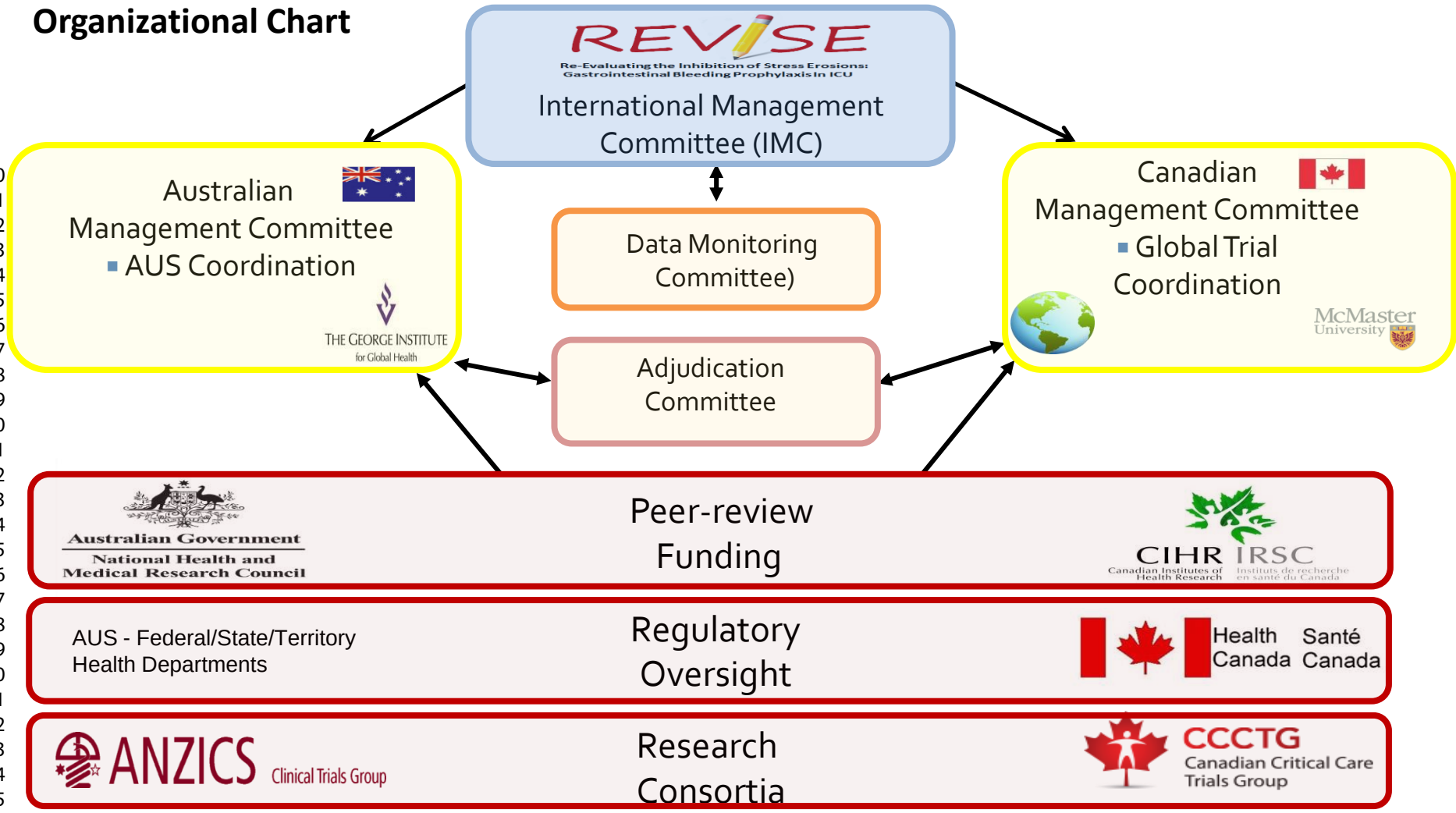


Figure 2.
Organizational Chart



Informed Consent Form for Participation in a Research Study

Study Title: **REVISE Trial: R**e-**EV**aluating the **I**nhibition of **S**tress **E**rosions in the critically ill

STUDY DOCTOR(S): *insert name, department and telephone or pager number*

Sponsor/Funder(s): The Canadian Institutes of Health Research (CIHR)

Emergency Contact Number (24 hours / 7 days a week): _____

INTRODUCTION

You may be considering participation in this study on behalf of yourself, or you may be asked to provide informed consent on behalf of a person who is unable to provide consent for themselves in the role of a Substitute Decision Maker (SDM). If you are an SDM, and the participant gains the capacity to consent, your consent for them will end and they will be able to make their own decisions. Throughout this form, "you" means the person taking part in the study (either yourself, or the person you are representing as an SDM).

You are being invited to participate in a clinical trial (a type of study that involves research) because you require mechanical breathing support in the Intensive Care Unit (ICU). This consent form provides you with information to help you make an informed choice. Please read this document carefully and ask any questions you may have. All your questions should be answered to your satisfaction before you decide whether to participate in this research study. The study staff will tell you about the study timelines for making your decision.

Taking part in this study is voluntary. You have the option to not participate at all or you may choose to leave the study at any time. If you choose not to participate, you will continue to receive the same and best care available.

WHAT IS THE BACKGROUND INFORMATION FOR THIS STUDY?

This is a study testing the benefit and harms of using a common drug called pantoprazole that reduces acid production in the stomach. Patients who are critically ill in the ICU needing a breathing machine can develop ulcers in the stomach that may bleed. Therefore, many such patients receive a drug that suppresses acid production to decrease the risk of bleeding. However, nowadays, patients very rarely develop bleeding compared to decades ago, which is believed to be due to modern critical care, earlier resuscitation and nutrition. In addition, recent research suggests that pantoprazole and other drugs that reduce acid in the stomach may actually increase the risk of more serious lung infections (pneumonia) and bowel infections (*Clostridioides difficile*). However, the quality of published studies in this area is poor. The benefits and possible harms of acid suppression are uncertain.

The intravenous form of pantoprazole is approved by Health Canada for short-term use up to 7 days to lower stomach acid and when medication cannot be taken by mouth. Health Canada is the regulatory body that oversees drug use in Canada. Although Health Canada has not previously approved the use of pantoprazole to prevent stress ulcers in patients on a breathing machine, this drug is currently very commonly used in the ICU. Therefore, Health Canada has allowed pantoprazole for use in this study, as in common practice.

WHY IS THIS STUDY BEING DONE?

The objective of this study is to determine in critically ill patients, if pantoprazole (a drug that decreases acid production in the stomach) is effective in preventing bleeding from stomach ulcers, or whether it causes more problems such as lung infection (pneumonia) and bowel infection (*Clostridioides difficile*).

WHAT OTHER CHOICES ARE THERE?
You do not have to take part in this study in order to receive care in the ICU. Drugs to prevent bleeding are commonly used for patients on a breathing machine. Even if you do not participate in this study, you will still receive whatever the treating team in the ICU decides.

HOW MANY PEOPLE WILL TAKE PART IN THIS STUDY?
This study will enrol 4800 patients in Canada and other countries. The study will take 4-5 years to finish overall, and the results will be available by 2025. Study results will inform the care of ICU patients around the world.

IS THERE A CONFLICT OF INTEREST?
The *insert recipient of funding e.g., hospital* is receiving financial payment from The Canadian Institutes of Health Research (CIHR) to cover the cost of conducting this study.

WHAT WILL HAPPEN DURING THIS STUDY?
If you agree to participate, you will be followed by the research team. You will receive a study drug which is either pantoprazole or a placebo (an inactive substance) while on a breathing machine. The study drug you receive will be determined by chance. That is, there is a 50% chance of receiving the pantoprazole and a 50% chance of receiving a placebo. Otherwise, you will receive the usual care in the ICU.

WHAT IS THE STUDY INTERVENTION?
Group 1: Pantoprazole: Patients allocated to receive pantoprazole will receive 40 mg of intravenous pantoprazole once daily, while on the breathing machine, for up to 90 days.
Group 2: Placebo: Patients allocated to placebo will receive an identical looking inactive substance (0.9% normal saline). Placebo will also be given intravenously once daily while on the breathing machine, for up to 90 days.
The first dose of either drug will be given as soon as possible (within 72 hours of starting the breathing machine).

WHAT ELSE DO I NEED TO KNOW ABOUT THE STUDY INTERVENTION?
You will be checked daily for signs of bleeding, lung or bowel infections. If any of these occur, these conditions will be promptly and thoroughly treated, as usual.

WHAT ARE THE STUDY PROCEDURES?
Aside from receiving the study drug daily (i.e., pantoprazole or placebo) there are no additional study procedures, blood samples, specimens or tests involved. The study drug does not continue after discharge from the ICU.

HOW LONG WILL PARTICIPANTS BE IN THE STUDY?
The study drug will be given only while you need the breathing machine, for up to 90 days. No matter which group you are in, and if you receive the study drug or not, we will check on you until hospital discharge. We will contact you by phone to verify your health when your participation in the study is completed (approximately 90 days).

CAN PARTICIPANTS CHOOSE TO LEAVE THE STUDY?
You can choose to stop participating in this study (called withdrawal) at any time by letting the investigator or research team know, without providing a reason. After you withdraw from the study, no study drug will be given. Information recorded before you withdraw consent will be used by the investigators to protect the scientific integrity of the study. The research team may seek your permission to continue to collect your information, including hospital outcome information.

CAN PARTICIPATION IN THIS STUDY END EARLY?
The investigator may stop your participation in the study early, and without your consent, for reasons such as:

- You are unable to tolerate the study drug
- Belief that it is no longer the best option for you to be in the study
- The study sponsor or Regulatory Authorities (e.g., Health Canada or Research Ethics Board) stop the study

If you are removed from this study, or the study stops, you will not receive the study drug as outlined in this consent form. The investigator will tell you why, and you will continue to be cared for outside of the study.

WHAT ARE THE POSSIBLE RISKS OF PARTICIPATING IN THIS STUDY?

Patients with recent stomach bleeding will not be considered for this study as they should receive pantoprazole or another drug from the same class. We are only approaching patients whose doctors consider them to be at very low risk of bleeding. We estimate the risk of bleeding to occur in less than 1 to 4 in 100 patients (1 to 4%); if this does occur, you will receive the appropriate treatment for bleeding. While you are in the study, your doctor, the investigator, and the research team will watch you closely to check if you have any problems related to the study.

There is a potential increased risk of developing pneumonia or *Clostridioides difficile* infection associated with pantoprazole. This is why doctors now question whether every ICU patient should receive acid suppression. Although the exact risk is not clear from prior studies, we estimate that 1-3 out of 100 patients (1-3%) receiving pantoprazole may develop *Clostridioides difficile* infection, and estimate that 10-15 of 100 patients (10-15%) receiving pantoprazole may develop pneumonia. These infections can also develop regardless of acid suppression.

WHAT ARE THE REPRODUCTIVE RISKS?

There are no adequate studies in pregnant women. It is unclear whether pantoprazole might harm a fetus. Pantoprazole should not be given to pregnant women unless the expected benefits outweigh the potential risks to the mother. Since pantoprazole is contraindicated in pregnancy, no pregnant women are involved in this study.

WHAT ARE THE POSSIBLE BENEFITS OF PARTICIPATING IN THIS STUDY?

You may or may not benefit directly from participating in this study. Avoiding acid suppressing drugs may lower the risk of pneumonia and bowel infections. However, a large modern trial is needed to know. While in this study, you will be monitored closely for signs of bleeding or infection; if they occur, treatment will be prompt. Future patients will benefit from the knowledge gained by this study.

HOW WILL PARTICIPANT INFORMATION BE KEPT CONFIDENTIAL?

If you decide to participate in this study, the research team will only collect the information they need for this study. Records identifying you at this centre will be confidential and, to the extent permitted by applicable laws, will not be disclosed or made public, except as described in this consent document.

Authorized representatives of the following organizations may look at your original (identifiable) medical/clinical study records (called study data), to check that the information collected is correct and follows proper laws and ethical guidelines. Your study data may also be sent to the organizations listed below:

- The Research Ethics Board overseeing the ethical conduct of this study in Ontario.
- This institution and affiliated sites, to oversee the conduct of research at this location
- Representatives of St. Joseph Healthcare, Hamilton or McMaster University, Hamilton (study Sponsor)

Representatives of Clinical Trials Ontario may see study data that is sent to the Research Ethics Board but your name, address, or other information that may directly identify you will not be used. The records received by these organizations may contain "indirect identifiers" only (e.g., participant code, age, sex).

If the results of this study are published, your identity will remain confidential. Information collected will be

maintained confidentially for 15 years after participation, as required by Health Canada. Information collected for this study will be analyzed and presented at scientific meetings and published in journals. Even though the chance that someone may identify you from the study data is very small, it can never be completely eliminated.

WILL FAMILY DOCTORS KNOW WHO IS PARTICIPATING IN THIS STUDY?

Your family doctor will not be informed by the study team that you are taking part in the study. The study drug will be finished when you leave the ICU. You are welcome to tell your family doctor of your participation.

WILL INFORMATION ABOUT THIS STUDY BE AVAILABLE ONLINE?

A description of this study is available on http://www.clinicaltrials.gov NCT03374800. This website will not include information that can identify you. You can search this website at any time.

WHAT IS THE COST TO PARTICIPANTS?

The study drug pantoprazole will be supplied at no charge while you are in this study. Neither you nor your health care insurance will have additional costs related to this study.

ARE STUDY PARTICIPANTS PAID TO BE IN THIS STUDY?

You will not be paid to participate in this study. In the case of research-related side effects or injury, medical care will be provided the same way as usual.

WHAT ARE THE RIGHTS OF PARTICIPANTS IN A RESEARCH STUDY?

You will be told, in a timely manner, about new information that may be relevant to participating in this study. You have the right to be informed of the results of this study once the entire study is complete. If you would like to be informed of the results of this study, please contact the investigator or research team.

Your rights to privacy are legally protected by federal and provincial laws that require safeguards to ensure that your privacy is respected. By signing this form, you do not give up any of your legal rights against the study doctor, sponsor or involved institutions for compensation, nor does this form relieve the study doctor, sponsor or their agents of their legal and professional responsibilities.

You will be given a copy of this signed and dated consent form.

WHO DO PARTICIPANTS CONTACT FOR QUESTIONS?

If you have questions about taking part in this study, or if you suffer a research-related injury, you can talk to the study investigator in charge of the study at this institution. That person is:

XXXXXXXX	XXXXXXXX
Name	Telephone

If you have questions about your rights as a participant or about ethical issues related to this study, you can talk to someone who is not involved in the study at all. That person is: The Office of the Chair, Hamilton Integrated Research Ethics Board at 905-521- 2100 x 42013.

Study Title: **REVISE Trial: R**e-**EV**aluating the **I**nhibition of **S**tress **E**rosions in the critically ill

SIGNATURES: By signing below, I confirm that

- All of my questions have been answered,
- I understand the information within this informed consent form,
- I allow access to my medical records as explained in this consent form,
- I do not give up any of my legal rights by signing this consent form,
- I agree, or agree to allow the person I am responsible for, to take part in this study.

A PRIORI CONSENT (PRE-RANDOMIZATION)

Verbal Consent - SDM or Participant

PRINTED NAME of Participant	PRINTED NAME of SDM (if applicable)	Date of Consent Discussion

Relationship of SDM to Participant (if applicable): _____

Signature of Person Conducting Consent Discussion	PRINTED NAME & ROLE	Date

Witness:
I was present when the information in this form was explained and discussed. I believe the participant/SDM understands what is involved in this study and provided informed consent.

Signature of Witness	PRINTED NAME & ROLE	Date

If required locally, please include the following: Whenever possible, we ask the SDM to physically sign the consent form after providing verbal consent (for example, if the SDM visits the patient in the ICU).

PRINTED NAME of SDM	Signature	Date

Written Consent – SDM (*If you are the SDM and you are signing the consent, please complete)*

PRINTED NAME of Participant	Relationship of SDM to Participant

PRINTED NAME of SDM	Signature	Date

Signature of Person Conducting the Consent Discussion	PRINTED NAME & ROLE	Date

Written Consent – Participant (*If you are the study participant signing the consent, please complete)*

PRINTED NAME of Participant	Signature	Date
Signature of Person Conducting the Consent Discussion	PRINTED NAME & ROLE	Date

If the participant is assisted during the consent process, please check the relevant box and complete the signature space below:

☐ The person signing below acted as an interpreter, and attests that the study as set out in the consent form was accurately sight translated and/or interpreted, and that interpretation was provided on questions, responses and additional discussion arising from this process.

PRINT NAME of Interpreter	Signature	Date

Language: _____

☐ The consent form was read to the participant. The person signing below attests that the study as set out in this form was accurately explained to the participant, and any questions have been answered.

PRINT NAME of witness	Signature	Date

Relationship to Participant: _____

DEFERRED CONSENT (POST RANDOMIZATION)

If applicable: As Substitute Decision Maker, you are being asked to provide informed consent on behalf of a person who is unable to provide consent. If the patient gains capacity to consent, your consent for them will end. In this form, "you" means the person you are representing.

You were enrolled in this study using deferred consent. This means that due to the low risk of study participation and the need for timely study procedures that you have been enrolled in this study already and are receiving either the study intervention or placebo. This may have happened because you were too sick to consent on your own behalf, and we were unable to reach your substitute decision maker before now.

We now require your consent to continue. If you are still in the ICU, we are asking if you would like to continue receiving the study drug or placebo. For all participants, we are asking for permission to contact you at the end of the study and to use the data we have collected so far. Before deciding on whether to continue to participate in the study, it is important that you read and understand the information in this consent form.

If, after all the information is provided, you decide not to continue in this study we ask that you clarify whether we have permission to use the data collected up until this point, whether we may continue to collect information about you while you are in hospital, and whether we may collect vital status only for you at 90 days.

You can still change your mind in the future. If you change your mind in the future, we would stop collecting new information but we would keep the information we've collected so far and use it for study purposes. The rest of the information in the consent form still applies.

Verbal Consent - SDM or Participant

☐ I ***consent*** to continue to participate in this study.

OR

I ***do not consent*** to continue to receive study drug, but I give my consent for the researchers to (select ONE):

- ☐ Use the data collected until this point and collect new data including vital status at 90 days
- ☐ Use the data collected until this point and collect new data while I'm in the hospital
- ☐ Use the data collected until this point only but no further data collection

PRINTED NAME of Participant	PRINTED NAME of SDM (if applicable)	Date of Consent Discussion

Relationship of SDM to Participant (if applicable): _____

Signature of Person Conducting the Consent Discussion	PRINTED NAME & ROLE	Date

Witness:

I was present when the information in this form was explained and discussed. I believe the participant/SDM understands what is involved in this study and provided informed consent.

Signature of Witness	PRINTED NAME & ROLE	Date

If required locally, please include the following: Whenever possible, we ask that the SDM to physically sign the consent form after providing verbal consent (for example, if the SDM visits the participant in the ICU).

PRINTED NAME of SDM	Signature	Date

Written Consent – SDM

☐ I ***consent*** to continue to participate in this study.

OR

I ***do not consent*** to continue to receive study drug, but I give my consent for the researchers to (select ONE):

- ☐ Use the data collected until this point and collect new data including vital status at 90 days
- ☐ Use the data collected until this point and collect new data while I'm in the hospital
- ☐ Use the data collected until this point only but no further data collection

PRINTED NAME of Participant	Relationship of SDM to Participant

PRINTED NAME of SDM	Signature	Date

Signature of Person Conducting the Consent Discussion	PRINTED NAME & ROLE	Date

Written Consent – Participant

☐ I ***consent*** to continue to participate in this study.
OR
I ***do not consent*** to continue to receive study drug, but I give my consent for the researchers to (select ONE):

☐ Use the data collected until this point and collect new data including vital status at 90 days
☐ Use the data collected until this point and collect new data while I'm in the hospital
☐ Use the data collected until this point only but no further data collection

PRINTED NAME of Participant	Signature	Date
Signature of Person Conducting the Consent Discussion	PRINTED NAME & ROLE	Date

If the participant is assisted during the consent process, please check the relevant box and complete the signature space below:

☐ The person signing below acted as an interpreter, and attests that the study as set out in the consent form was accurately sight translated and/or interpreted, and that interpretation was provided on questions, responses and additional discussion arising from this process.

PRINT NAME of Interpreter	Signature	Date

Language: _____

☐ The consent form was read to the participant. The person signing below attests that the study as set out in this form was accurately explained to the participant, and any questions have been answered.

PRINT NAME of witness	Signature	Date

Relationship to Participant: _____

Form 1

REVISE RCT170 Plate #001 Visit #000

Patient ID | Patient Initials (F L) | Date (dd/mm/yyyy) 20

SCREENING (Form 1)

1. Inclusion Criteria (please mark the appropriate box with an '✘')

	YES	NO
1. Patient is ≥ 18 years of age	Y ☐	N ☐
2. Receiving invasive mechanical ventilation (endotracheal tube or tracheostomy) in an ICU and at the time of screening, in the opinion of the treating ICU physician, mechanical ventilation is expected to continue at least until the end of the day after tomorrow	Y ☐	N ☐

2. Exclusion Criteria (contraindications)

1. MD considers Pantoprazole or placebo are indicated or contraindicated; reason: _____	Y ☐	N ☐
2. Pantoprazole contraindicated due to specific local product information	Y ☐	N ☐

Australia/New Zealand Sites Only:

- Being treated with HIV protease inhibitors atazanavir (Reyataz) or nelfinavir (Viracept)
- Being treated with high dose methotrexate defined as >300mg/day per chemotherapy
- Documented cirrhosis or severe liver disease (e.g., INR > 5.0 due to liver disease)

Canadian Sites Only:

- Being treated with rilpivirine (Edurant) or atazanavir (Reyataz)

3. Patient in whom a proton pump inhibitor (PPI) or a histamine-2 receptor antagonist (H_2RA) is indicated due to active bleeding or increased bleeding risk, defined as:		
a. Acute gastrointestinal bleeding (ICU physician's clinical opinion)	Y ☐	N ☐
b. Peptic ulcer bleeding within last 8 weeks of screening	Y ☐	N ☐
c. Severe esophagitis	Y ☐	N ☐
d. Current or recent Barrett's esophagus	Y ☐	N ☐
e. Zollinger-Ellison syndrome	Y ☐	N ☐
f. Any previous hospital admission for upper GI bleeding (receiving PPIs for mild dyspepsia or mild gastroesophageal reflux or an uncertain indication are not excluded)	Y ☐	N ☐
4. Invasive mechanical ventilatation for ≥ 72 hours pre-screening (including referring ICU/ER)	Y ☐	N ☐
5. Patient received > 24hours of PPI or H_2RA (this ICU admission including referring ICU)	Y ☐	N ☐
6. Being treated with, or need for, dual antiplatelet therapy (e.g., ASA **and** clopidogrel)	Y ☐	N ☐
7. Admitted for palliative care or physician is not committed to life-sustaining therapies	Y ☐	N ☐
8. Known or suspected pregnancy	Y ☐	N ☐
9. Other (e.g., recent gastric bypass, anaphylaxis requiring H_2RA), specify:	Y ☐	N ☐

3. Eligible Non-Randomized Patients _____

1. Patient declines a priori consent, reason: _____	Y ☐	N ☐
2. Substitute decision maker (SDM) declines a priori consent, reason: _____	Y ☐	N ☐
3. Patient unable to consent, no SDM available and no deferred consent allowed	Y ☐	N ☐
4. MD declined, reason: _____	Y ☐	N ☐
5. Other reason patient/SDM not approached, specify: _____	Y ☐	N ☐
6. Randomized previously in REVISE Trial	Y ☐	N ☐

4. Patient Status (please check ONE box only) ☐ **Included,** proceed to **Randomization** ☐ **Eligible, non-randomized**

Proceed to Randomization

Form 2

REVISE RCT170 Plate #003 Visit #000

Patient ID [ ][ ][ ] 1 [ ][ ][ ] Patient Initials F [ ] L [ ]

CONSENT (Form 2)

1. Consent Encounter

A. Consent timing: ☐ A priori (pre-randomization) ☐ Deferred

B. Consent request by: ☐ Research Coordinator ☐ Site Investigator ☐ ICU Physician

2. Was verbal or written informed consent obtained?

☐ Yes, consent obtained from:

	In ICU	In Hospital	Post Hospital	Date (dd/mm/yyyy)	Consent Method: In-person	Telephone
Patient	☐	☐	☐	[ ][ ]/[ ][ ]/20[ ][ ]	☐	☐
Substitute decision maker (SDM)	☐	☐	☐	[ ][ ]/[ ][ ]/20[ ][ ]	☐	☐
Other, specify: _____	☐	☐	☐	[ ][ ]/[ ][ ]/20[ ][ ]	☐	☐

In New Zealand, discussion of patient wishes with family or friend documented? ☐ Yes ☐ No

☐ No, consent declined by:

	In ICU	In Hospital	Post Hospital	Date (dd/mm/yyyy)	Consent Method: In-person	Telephone
Patient	☐	☐	☐	[ ][ ]/[ ][ ]/20[ ][ ]	☐	☐
Substitute decision maker (SDM)	☐	☐	☐	[ ][ ]/[ ][ ]/20[ ][ ]	☐	☐
Other, specify:	☐	☐	☐	[ ][ ]/[ ][ ]/20[ ][ ]	☐	☐

Reason for decline, specify: ☐ Prefers PPI ☐ Prefers placebo ☐ Distressed SDM ☐ Family discord ☐ Other, specify: _____

☐ No consent, patient lacked capacity to provide consent and no SDM available throughout hospital stay

☐ No consent, patient deceased and was never competent to provide consent, and no SDM available throughout hospital stay

3. Consent obtained then revoked?

☐ No, not applicable

☐ Yes, consent by:

	In ICU	In Hospital	Post Hospital	Date (dd/mm/yyyy)
Patient	☐	☐	☐	[ ][ ]/[ ][ ]/20[ ][ ]
Substitute decision maker (SDM)	☐	☐	☐	[ ][ ]/[ ][ ]/20[ ][ ]
Other, specify: _____	☐	☐	☐	[ ][ ]/[ ][ ]/20[ ][ ]

Details (check ALL that apply):

☐ Allow retention of data collected prior to refusal/revocation
☐ Decline retention of data collected prior to refusal/revocation
☐ Allow data collection after refusal/revocation
☐ Decline data collection after refusal/revocation
☐ Decline further study drug
☐ Other, specify _____

4. If no consent was obtained, has the REC/REB approved the use of this patient's data as provided?

☐ Not applicable, consent obtained

☐ No
- ☐ Yes, in original REC/REB submission → ☐ All data collection
- ☐ Yes, by recent REC/REB correspondence → ☐ Vital Status ONLY
- ☐ Other, specify: _____

REVISE RCT170 Plate #005 Visit #000

Patient ID [ ][ ][ ] 1 [ ][ ][ ]

Patient Initials F [ ] L [ ]

Randomization Date [ ][ ] (dd/mm/yyyy) [ ][ ] 2 0 [ ][ ]

RANDOMIZATION (Form 3) - CANADA

FOR RESEARCH COORDINATOR

1. Pre-Hospital H_2RA or PPI receipt?
(including home, retirement home or nursing home)

H_2RAs: ranitidine (Zantac), cimetidine (Tagamet), famotidine (Pepcid) or nizatidine (Axid)

PPIs: pantoprazole (Pantoloc, Tecta), omeprazole (Losec), lansoprazole (Prevacid), dexlansoprazole, (Dexilant), rabeprazole (Pariet) or esomeprazole (Nexium)

☐ **NO**
Patient will be in **Start/No Start stratum** (no pre-Hospital PPI or H_2RA use)

☐ **YES**
Patient will be in **Continue/Discontinue stratum** (had pre-Hospital PPI or H_2RA use)

2. How was pre-hospital stress ulcer prophylaxis verified? (not all are needed, but check ALL that apply):

- ☐ Chart review including list of home meds
- ☐ Chart review but no list of home meds available
- ☐ Conversation with SDM about home meds
- ☐ Conversation with patient about home meds
- ☐ Conversation with outpatient pharmacy about home meds
- ☐ Hospital pharmacy reconciliation
- ☐ Provincial/state drug database review (e,g., Netcare, Dossier Santé Québec)

3. Date of birth: [ ][ ] [ ][ ] [ ][ ][ ][ ] (dd/mm/yyyy)

FOR RESEARCH PHARMACIST ONLY - Randomization

via web: www.randomize.net

4. Trial assignment (please select one): ☐ Pantoprazole ☐ Placebo

5. Time of randomization (24 hour clock): [ ][ ]:[ ][ ]

6. Study Pharmacist initals: [ ][ ] F L

Form 3

REVISE RCT170 Plate #006 Visit #000

Patient ID 1 | Patient Initials F L | Randomization Date (dd/mm/yyyy) 20

RANDOMIZATION (Form 3) - CANADA

FOR RESEARCH PHARMACIST

1. Pre-Hospital H_2RA or PPI receipt?
(including home, retirement home or nursing home)

H_2RAs: ranitidine (Zantac), cimetidine (Tagamet), famotidine (Pepcid) or nizatidine (Axid)

PPIs: pantoprazole (Pantoloc, Tecta), omeprazole (Losec), lansoprazole (Prevacid), dexlansoprazole, (Dexilant), rabeprazole (Pariet) or esomeprazole (Nexium)

☐ **NO**
Patient will be in **Start/No Start stratum** (no pre-Hospital PPI or H_2RA use)

☐ **YES**
Patient will be in **Continue/Discontinue stratum** (had pre-Hospital PPI or H_2RA use)

2. Date of birth: ☐☐ ☐☐ ☐☐☐☐ (dd/mm/yyyy)

FOR RESEARCH PHARMACIST ONLY - Randomization

via web: www.randomize.net

4. Trial assignment (please select one): ☐ Pantoprazole ☐ Placebo

5. Time of randomization (24 hour clock): ☐☐:☐☐

6. Study Pharmacist initals: ☐☐ F L

Please DO NOT return to the Research Coordinator or s/he will become unblinded.

Thanks for your help!

REVISE RCT170 Plate #008 Visit #000

Patient ID [ ][ ][ ] 1 [ ][ ][ ]

Patient Initials F [ ] L [ ]

STRATIFICATION ERROR FORM (Form 3B)

1. Patient randomized as:

   ☐ **Start/No Start stratum**, as Patient **had NO** Pre-hospital H_2RA or PPI use

   ☐ **Continue/Discontinue stratum,** as Patient **did have** Pre-hospital H_2RA or PPI use

2. Patient should have been randomized to:

   ☐ **Start/No Start stratum**, as Patient **had NO** Pre-hospital H_2RA or PPI use

   ☐ **Continue/Discontinue stratum,** as Patient **did have** Pre-hospital H_2RA or PPI use

3. Comments:

Form 4

REVISE RCT170 Plate #010 Visit #000

Patient ID 1 Patient Initials F L

BASELINE (Form 4)

	dd/mm/yyyy	(24 hour clock)
1. **Study hospital admission date**	20	**Study hospital admission time** :
2. **Study ICU admission date**	20	**Study ICU admission time** :
3. **Intubation date**	20	**Intubation time** (approximate) :

4. **Sex** ☐ Female ☐ Male

5. **APACHE II Score** (24 hrs pre-rand) ☐☐ (Calculated based on 24 hrs prior to randomization including pre-ICU location)

6. **Admission diagnosis code** ☐☐ (if admitted from OR or PARR code should be 48-85) If "other" diagnosis code selected, specify: _____

7. **Location immediately prior to this ICU admission** (check ONE box):

☐ Accident and Emergency Department

☐ Hospital Floor/Ward (including Step-Down Unit)

☐ Operating Theatre /Recovery Room specify:
- ☐ Emergency Surgery
- ☐ Elective Surgery

☐ Other Hospital Emergency, admit date:
☐ Other Hospital ICU, admit date:
☐ Other Hospital Ward, admit date:
→ Other hospital admit date: dd/mm/yyyy ☐☐ ☐☐ 20☐☐

☐ Other, specify: _____

8. **Pre-hospital history of the following** (check ALL that apply):

☐ NONE ☐ Bleeding ulcer ☐ Bleeding varices ☐ Cirrhosis ☐ Hemodialysis ☐ *Clostridioides difficile* infection ☐ *Helicobacter pylori* ☐ COVID-19 confirmed

9. **Patient received medically prescribed PPI or H_2RA prior to randomization?**

☐ No ☐ Yes, specify drug and location:

☐ Unknown pre-hospital (home) medication so presumed no acid suppression

Proton Pump Inhibitor (PPI):

Home	Ward	ICU (pre-randomization)
☐	☐	☐ lansoprazole (Prevacid, lanzol relief, Zoton, Zopral)
☐	☐	☐ dexlansoprazole (Dexilant)
☐	☐	☐ pantoprazole (Pantoloc, Tecta, Panzop relief, Somac Salpraz, Gastenz, Ozpan, Panto, Pantofast, Panthron)
☐	☐	☐ esomeprazole (Nexium, Nexazole, Nexole, Noxicid)
☐	☐	☐ omeprazole (Losec, Omazol relief, Dr Reddy's Omeprazole, Midwest, Omazol IV, Acimax, Meprazole, Omepral, Ozmep, Maxor, Pemzo, Probitor)
☐	☐	☐ rabeprazole (Pariet, Parbezol, Parzole, Razit, Zabep)

Histamine 2 Receptor Antagonists (H_2RA):

Home	Ward	ICU (pre-randomization)
☐	☐	☐ cimetidine (Tagamet, Magicul)
☐	☐	☐ ranitidine (Zantac,Ausran, Ulcaid, Rani2, Peptisoothe)
☐	☐	☐ famotidine (Pepcid, Ausfam, Pepzan)
☐	☐	☐ nizatidine (Axid, Nizac, Tacidine, Tazac)

Other PPI or H_2RA, specify:

☐ ☐ ☐ _____

10. **Drugs that may affect bleeding risk within the last 3 days prior to randomization?**

	Prophylactic Dose	Intermediate Dose	Therapeutic Dose
☐ Unfractionated heparin, specify: →	☐	☐	☐
☐ Low molecular weight heparin, specify: →	☐	☐	☐

☐ None

☐ Warfarin (Coumadin)

☐ Aspirin (ASA), specify: ☐ ≤ 325mg daily ☐ > 325mg daily

☐ Clopidogrel (Plavix)

☐ Non-steroid anti-inflammatory drug (NSAID)

☐ New oral anticoagulants (NOAC) (e.g.,RivaroxibanApixaban, Dabigatran, Edoxaban)

☐ Others (e.g., Dipyridamole (Persantine), Ticlodipine (Ticlid), Tirofiban (Aggrastat), Eptifatide (Integrilin), Direct thrombin inhibitors (Bivalirudin), Prasugrel, Ticagrelor, Cangrelor, specify:

_____

11. **Oral or IV corticosteroids in the week preceding randomization** (e.g., prednisone, hydrocortisone, solumedrol, dexamethasone)**?** ☐ No ☐ Yes, specify: ☐ IV ☐ Oral

REVISE RCT170 Plate #012 Visit #100

Patient ID 1 Patient Initials

COVID-19 - Additional Data (Form 4B - COVID)

(Patients treated for Covid during this REVISE hospital admission)

1. Vaccinated pre-ICU: ☐ No ☐ Unknown ☐ Yes, 1 dose ☐ Yes, 2 doses ☐ Yes, 3 doses

2. COVID-related tests (during this index hospitalization, including pre-ICU admission)

	Date (dd/mm/yyyy)	Results		Not Done
D Dimer Level (highest)	20		ug/L	☐
CRP Level (highest)	20	.	mg/L	☐
Ferritin Level (highest)	20		ug/L	☐

	Not Done	No	Yes	Date (dd/mm/yyyy)	
CT Scan **positive** for PE (first date scanned positive)	☐	☐	☐ →	20	Specify location:
US **positive** for DVT (first date scanned positive)	☐	☐	☐ →	20	Specify location:
US **positive** for DVT (If second DVT identified)	☐	☐	☐ →	20	Specify location:
Bowel Ischemia (radiographic or intraoperative documentation)	☐	☐	☐ →	20	Specify location:

3. COVID-related treatments (during this index hospitalization, including pre-ICU admission).

Please complete whether treatment given as part of a trial or not.

			Start Date (dd/mm/yyyy)	
Tocilizumab	☐ No	☐ Yes →	20	
Sarilumab	☐ No	☐ Yes →	20	
Convalescent plasma	☐ No	☐ Yes →	20	
Oseltamivir or Remdesivir	☐ No	☐ Yes →	20	Oseltamivir ☐ Remdesivir ☐
Dexamethasone or high dose steroid	☐ No	☐ Yes →	20	Dexamethasone ☐ High dose steroid ☐
Statin	☐ No	☐ Yes →	20	
IV Vitamin C	☐ No	☐ Yes →	20	
ACE2 Renin-Angiotensin RAS	☐ No	☐ Yes →	20	
Azithromycin	☐ No	☐ Yes →	20	
ECMO	☐ No	☐ Yes →	20	
Other (e.g., interferon, kinase inhibitors, hydroxychloroquine), specify:	☐ No	☐ Yes →	20	

4. Tracheostomy: ☐ No ☐ Yes → 20

5. Comments: _____

Please note: Coagulation tests and anticoagulation doses are captured on Daily Data Form

Form 6.1 of 2

REVISE RCT170 Plate #030

Study Day

Patient ID 1

Patient Initials F L

Date of Study Day (dd/mm/yyyy) 2 0

DAILY DATA STUDY DAYS 1-14 (Form 6.1 of 2)

1. Advanced life support strategies received today

1. Invasive mechanical ventilation ☐ No ☐ Yes
2. Non-invasive mechanical ventilation (BiPAP): ☐ No ☐ Yes
3. Inotropes or vasopressor infusions ☐ No ☐ Yes
   (e.g., dopamine, norepinephrine, phenylephrine, epinephrine, milrinone, vasopressin)
4. Was renal replacement therapy used today?
   ☐ No ☐ Yes, specify: → ☐ intermittent (IHD) ☐ sustained low efficiency (SLED) ☐ continuous (CRRT) ☐ peritoneal

Time Study Day 1 ONLY

2. Was study drug administered today? ☐ No ☐ Yes ☐☐:☐☐ (24 hr clock)

If a dose of study drug was not received today, please indicate why:

- ☐ Randomized late in the day
- ☐ Discharged from ICU or died
- ☐ Not mechanically ventilated (ICU physician discretion) **If patient re-intubated during this ICU admission, restart REVISE study drug.**
- ☐ No IV access
- ☐ Expected to die, palliative measures only
- ☐ Suspected/proven diagnosis of another exclusion criterion, specify: _____
- ☐ GI bleeding (submit **Bleed Form 9**)
- ☐ Error, missed/probably missed dose (submit **Protocol Deviation Form 12**)
- ☐ Patient declined dose
- ☐ Consent withdrawn, drug stopped (continue data collection)
- ☐ Other, specify: _____

3. Any enteral, parenteral or oral nutrition today? ☐ No ☐ Yes, specify: (check ALL that apply) ☐ Enteral → ☐☐☐☐☐ ☐ Parenteral → ☐☐☐☐☐ ☐ Oral

total daily ml

4. Physiology/Laboratory results today

☐☐☐ hemoglobin (g/L) (lowest) ☐ N/A

☐☐☐☐ platelets (x10 ^{9}/L) (lowest) ☐ N/A

☐☐.☐ INR (highest) ☐ N/A

☐☐☐.☐ PTT (s) (highest) ☐ N/A

creatinine (umol/L) (highest) ☐☐☐☐ ☐ N/A

5. Did the patient receive packed red blood cells today? ☐ No ☐ Yes → ☐☐☐☐ ☐ units in total ☐ ml in total

6. Post randomization, did any of the following outcomes occur today?

Major gastrointestinal bleeding ☐ No ☐ Yes, please complete the **Bleeding Outcome Form 9**
(Complete only one form for each discrete new major bleeding event documented)

Clostridioides difficile infection ☐ No ☐ Yes, please complete the ***Clostridioides Difficile* Outcome Form 10**

Respiratory infection ☐ No ☐ Yes, please complete the **Respiratory Infection Outcome Form 11**
(Complete form with new events only but not necessary on Study Day 1 for prevalent events)

Form 6.2 of 2

REVISE RCT170 Plate #031

Study Day

Patient ID 1

Patient Initials F L

Date of Study Day (dd/mm/yyyy) 2 0

DAILY DATA STUDY DAYS 1-14 (Form 6.2 of 2)

7. Did the patient receive any of the following today (post-randomization)?

1. H_2RA No Yes [e.g., **cimetidine** (Tagamet, Magicul), **famotidine** (Pepcid, Ausfam, Pepzan), **ranitidine** (Zantac, Ausran, Ulcaid, Rani2, Peptisoothe), **nizatidine** (Axid, Nizac, Tacidine, Tazac)]

   Check if H_2RA given for allowable reason (i.e., GI bleeding, patient extubated or consent withdrawn) (If yes and patient mechanically ventilated, submit **Protocol Deviation Form 12** for non-protocolized reason for H_2RA)

2. Open label PPI

   No Yes [e.g., **lansoprazole** (Prevacid, lanzol relief, Zoton, Zopral), **esomeprazole** (Nexium, Nexazole, Nexole, Noxicid), **dexlansoprazole** (Dexilant), **omeprazole** (Losec, Omazol relief, Dr Reddy's Omeprazole, Midwest, Omazol IV, Acimax, Meprazole, Omepral, Ozmep, Maxor, Pemzo, Probitor), **pantoprazole** (Pantoloc, Tecta, Panzop relief, Sòmac, Salpraz, Gastenz, Ozpan, Panto, Pantofast, Panthron), **rabeprazole** (Pariet, Parbezol, Parzole, Razit, Zabep)]

   Check if PPI given for allowable reason (i.e., GI bleeding, patient extubated or consent withdrawn) (If yes and patient mechanically ventilated, submit **Protocol Deviation Form 12** for non-protocolized reason for open-label PPI)

3. Other stress ulcer prophylaxis

   No Yes [e.g., sulcrafate (Carafate), antacid (e.g., Maalox, Gaviscon)]

4. Anticoagulant or antiplatelet agent

	Prophylactic Dose	Intermediate Dose	Therapeutic Dose
Unfractionated heparin, specify: →			
Low molecular weight heparin, specify: →			

None

Warfarin (Coumadin)

Aspirin (ASA), specify: ≤ 325mg daily > 325mg daily

Clopidogrel (Plavix)

Non-steroid anti-inflammatory drug (NSAID)

New oral anticoagulants (NOAC) (e.g.,Rivaroxiban Apixaban, Dabigatran, Edoxaban)

Others [e.g., Dipyridamole (Persantine), Ticlodipine (Ticlid), Tirofiban (Aggrastat), Eptifatide (Integrilin), Direct thrombin inhibitors (Bivalirudin), Prasugrel, Ticagrelor, Cangrelor] specify: _____

5. Oral or IV corticosteroids (e.g., prednisone, hydrocortisone, solumedrol, dexamethasone) No Yes, specify: IV Oral

6. Probiotics

   No Yes If open-label probiotics, specify: _____

8. Was there an adverse event today believed by either the ICU physician or Site Investigator to be directly related to enrolment in the study?

No Yes If yes, please notify the REVISE Methods Center **within 24 hours** of becoming aware of the Adverse Event. An **Adverse Event Directly Related to the Study Form 17 is required** and please ask the ICU physician to sign it and send to the REVISE Methods Center

9. Was today the last day of study daily data collection?

- No
- Yes, patient died, was discharged to the ward, or drug stopped at 90 days (submit **Final Status Form 14**)
- Yes, consent withdrawn for further data collection (submit a **Final Status Form 14**)

Form 7

REVISE RCT170 Plate #033

Study Day

Patient ID 1

Patient Initials F L

Date of Study Day (dd/mm/yyyy) 20

DAILY DATA STUDY DAYS 15-90 (Form 7)

1. Advanced life support strategies received today

1. Invasive mechanical ventilation ☐ No ☐ Yes
2. Non-invasive mechanical ventilation (BiPAP): ☐ No ☐ Yes
3. Inotropes or vasopressor infusions ☐ No ☐ Yes
   (e.g., dopamine, norepinephrine, phenylephrine, epinephrine, milrinone, dobutamine, vasopressin)
4. Was renal replacement therapy used today?
   ☐ No ☐ Yes, specify: → ☐ intermittent (IHD) ☐ sustained low efficiency (SLED) ☐ continuous (CRRT) ☐ peritoneal

2. Laboratory results today:

hemoglobin (g/L) (lowest) ☐ N/A | platelets (x10 ^{9}/L) (lowest) ☐ N/A | INR (highest) ☐ N/A | PTT (s) (highest) ☐ N/A | creatinine (umol/L) (highest) ☐ N/A

3. Was study drug administered today? ☐ No ☐ Yes, specify:

If a dose was not received today, please indicate why and submit a **Protocol Deviation Form 12** if applicable:

- ☐ Discharged from ICU or died
- ☐ Not mechanically ventilated (ICU physician discretion) **If patient re-intubated during this ICU admission, restart REVISE study drug.**
- ☐ No IV access
- ☐ Expected to die, palliative measures only
- ☐ Suspected/proven diagnosis of an other exclusion criterion, specify: _____
- ☐ GI bleeding (submit **Bleed Form 9**)
- ☐ Error, missed/probably missed dose (submit **Protocol Deviation Form 12**)
- ☐ Patient declined dose
- ☐ Consent withdrawn, drug stopped (continue data collection)
- ☐ Other, specify: _____

4. Any enteral, parenteral or oral nutrition today? ☐ No ☐ Yes, specify: (check ALL that apply) ☐ Enteral → ☐☐☐☐☐ ☐ Parenteral → ☐☐☐☐☐ total daily ml ☐ Oral

5. Was anticoagulation received today? ☐ No ☐ Yes, specify → ☐ Intermediate dose ☐ Full therapeutic dose ☐ Prophylactic dose

6. Post randomization, did any of the following outcomes occur today?

Major gastrointestinal bleeding ☐ No ☐ Yes, please complete the **Bleeding Outcome Form 9**
(Complete only one form for each discrete new major bleeding event documented)

Clostridioides difficile infection ☐ No ☐ Yes, please complete the ***Clostridioides Difficile* Outcome Form 10**

Respiratory infection ☐ No ☐ Yes, please complete the **Respiratory Infection Outcome Form 11**
(Complete Form with new events only)

7. Was there an adverse event today believed by either the ICU physician or Site Investigator to be directly related to enrolment in the study?

☐ No ☐ Yes If yes, please notify the REVISE Methods Center **within 24 hours** of becoming aware of the Adverse Event. An **Adverse Event Directly Related to the Study Form 17 is required** and please ask the ICU physician to sign it and send to the REVISE Methods Center

8. Was today the last day of study daily data collection?

- ☐ No
- ☐ Yes, patient died, was discharged to the ward, or drug stopped at 90 days (submit **Final Status Form 14**)
- ☐ Yes, consent withdrawn for further data collection (submit a **Final Status Form 14**)

REVISE RCT170 Plate #035

Study Day

Patient ID 1

Patient Initials F L

Date of Study Day (dd/mm/yyyy) 20

PHARMACY - DAILY DISPENSING RECORD (Form 8)

ALL STUDY PERSONNEL AND CLINICIANS MUST REMAIN BLINDED TO THE PATIENT'S ALLOCATION. PHARMACISTS, PLEASE MAINTAIN A COPY FOR YOUR CONFIDENTIAL RECORDS. Thanks!

1. Please indicate which study drug was dispensed:

☐ **Study Drug (pantoprazole)** **OR** ☐ **Placebo**

Indicate company:

- ☐ Sandoz
- ☐ Fresenius Kabi
- ☐ Takeda
- ☐ Auro Pharma
- ☐ Pharmascience
- ☐ Generic Medical Partners
- ☐ Other, specify: _____

2. Please indicate "yes" if a drug dispensing error was made today that you are aware of:

☒ No ☐ Yes → please submit a **Protocol Deviation (Pharmacy) Form 13** and provide explanation below

3. Comments: _____

Please DO NOT return to the Research Coordinator or s/he will become unblinded. Thanks for your help!

Form 9

REVISE RCT170 Plate #040 Study Day

Patient ID 1 Patient Initials F L Date of Study Day (dd/mm/yyyy) 20

GASTROINTESTINAL BLEEDING OUTCOME (Form 9)

1. Bleeding presentation (check ALL that apply):

- ☐ NG blood
- ☐ NG Coffee ground emesis
- ☐ Melena
- ☐ Hematemesis (vomiting blood)
- ☐ Hematochezia (bright red blood per rectum)
- ☐ Other, specify: _____

2. Bleeding severity (check ALL that apply):

☐ 1. Life threatening bleeding resulting in hypovolemic shock

☐ 2. Clinically important bleeding is overt bleeding and one of the following within 24 hours in the absence of other causes (e.g., sepsis, propofol bolus) →

- ☐ Decrease in Hgb ≥20 g/L
- ☐ PRBC ≥ 2 units
- ☐ Decrease in SBP ≥ 20mmHg or HR increase ≥ 20bpm
- ☐ Initiation of vasopressor (e.g., norepinephrine, epinephrine, vasopressin, dopamine, phenylephrine, dobutamine)
- ☐ Increase of vasopressor
- ☐ Other (specify): _____

☐ 3. Bleeding that requires an invasive intervention specify:

☐ Upper GI **diagnostic** endoscopy, specify findings:
- ☐ gastric ulcer
- ☐ duodenal ulcer
- ☐ esophageal ulcer
- ☐ *Helicobactor pylori*
- ☐ gastritis/erosions
- ☐ duodenitis/erosions
- ☐ esophagitis/erosions
- ☐ gastric varices
- ☐ duodenal varices
- ☐ esophageal varices
- ☐ Portal hypertensive gastropathy
- ☐ Normal
- ☐ Other, specify: _____

☐ Upper GI **therapeutic** endoscopy, specify interventions:
- ☐ injection
- ☐ clips
- ☐ hemospray
- ☐ banding
- ☐ thermal coagulation
- ☐ glue
- ☐ argon plasma coagulation
- ☐ Blakemore/Minnesota tube
- ☐ Other, specify: _____

☐ Colonoscopy
☐ Sigmoidoscopy
☐ Angiogram
☐ Angiogram with embolization/coiling
☐ Surgery, specify: _____
☐ Other, specify: _____

Helicobacter pylori serology positive? ☐ No ☐ Yes

3. Bleed Started: ☐ **unknown** Date (dd/mm/yyyy) 20 TO **Bleed Stopped:** ☐ **unknown** ☐ **bleeding ongoing** Date (dd/mm/yyyy) 20

4. Direct consequences of the bleeding event (check ALL that apply)

☐ 1. Total transfusion (total # units infused) : (confirm # units reported with your hospital blood bank records) RBC FFP platelets cryoprecipitate

☐ 2. Drugs: ☐ PPI ☐ Octreotide ☐ Tranexamic acid ☐ desmopressin (DDAVP)
☐ Other, specify: _____

☐ 3. Major morbidity (e.g., myocardial infarction, stroke), specify: _____

☐ 4. Death ☐ 5. **NONE**

5. Reports sent to the REVISE Methods Center (check ALL that apply)

☐ Endoscopy ☐ Surgical
☐ Radiology ☐ Clinical Notes

☐ **Reports not sent, Investigator review only:**

Reviewing Investigator Name _____ Investigator Signature _____ Date Investigator reviewed (dd/mm/yyyy) 20

Form 11

REVISE RCT170 Plate #060

Study Day ☐☐

Patient ID ☐☐☐ 1 ☐☐☐ Patient Initials ☐☐ Date of Study Day (positive *C Difficile*) ☐☐ ☐☐ 2 0 ☐☐

CLOSTRIDIOIDES DIFFICILE **OUTCOME (Form 10)**

1. Which test performed was positive for *Clostridioides difficile* (Please check ALL that apply)?

- ☐ ELISA (enzyme-linked immunosorbent assay)
- ☐ PCR (polymerase chain reaction)
- ☐ Cell Culture Cytotoxicity Assay
- ☐ LAMP (loop-mediated isothermal amplification)
- ☐ Other, specify: _____

2. *Clinical presentation of Clostridioides difficile* (Please check ALL that apply):

- ☐ Diarrhea ≥ 3 episodes of unformed stools in ≤24 hours
- ☐ Rectal tube in place, stools loose and difficult to quantitate
- ☐ Colonscopic findings demonstrating pseudomembranous colitis
- ☐ Histopathological findings of pseudomembranous colitis
- ☐ Toxic megacolon

3. Treatments implemented for the *Clostridioides difficile* infection?

- ☐ Metronidazole (Flagyl)
- ☐ Vancomycin (Vancocin)
- ☐ Fidaxomicin (Dificid, Dificlir)
- ☐ Colectomy
- ☐ Fecal transplantation
- ☐ Other (e.g., probiotics), specify: _____
- ☐ NONE

4. Other consequences of the *Clostridioides difficile* infection?

- ☐ NONE
- ☐ Ileus
- ☐ Other, specify: _____
- ☐ Hypotension
- ☐ Septic Shock
- ☐ Bowel perforation
- ☐ Death

5. Society for Healthcare Epidemiology of America (SHEA 2018) *Clostridioides Difficile* Infection Severity for Initial Infection (as per clinical impression of ICU physician)

- ☐ **Non-Severe** [defined as white cell count ≤ 15.0 x 10^9/L (or <15,000 mm^3) and creatinine < 1.5 mg/dl (<133umol/L)]
- ☐ **Severe** [defined as white cell count ≥ 15.0 x 10^9/L (or >15,000 mm^3) **OR** creatinine **>** 1.5 mg/dl (<133umol/L)]
- ☐ **Fulminant** (defined as hypotension, shock, ileus or megacolon)

REVISE RCT170 Plate #050 Study Day

Patient ID 1 Patient Initials F L

RESPIRATORY INFECTION OUTCOME (Form 11)

2 Days Prior to Respiratory Infection:
(~ 24-48 hour period Pre-Resp Infection day reported) 20 (dd/mm/yyyy)

☐ N/A, data unavailable pt not in hospital

Highest temp °C ☐☐.☐ ☐N/A ☐PO ☐Ax or Tymp ☐Core/ Rectal

Lowest temp °C ☐☐.☐ ☐N/A ☐PO ☐Ax or Tymp ☐Core/ Rectal

Highest WBC count (10^9/L) ☐☐☐☐.☐ ☐N/A

Lowest WBC count (10^9/L) ☐☐☐☐.☐ ☐N/A

Bands present? ☐No ☐Yes

ARDS present? ☐No ☐Yes

Lowest PaO_2/FIO_2 ☐☐☐☐ ☐N/A

Tracheal secretions: ☐None/minimal ☐Moderate ☐Large

Purulent or mucopurulent? ☐No ☐Yes

New, progressive or persistent CXR infiltrate? (Check ALL that apply) ☐None or no CXR ☐Patchy/diffuse ☐Lobar/bilobar ☐Consolidation ☐Cavitation

Potential Pathogen cultured? ☐No ☐Yes

Nasopharyngeal swab (NPS) positive? ☐No ☐Yes

1 Day Prior to Respiratory Infection:
(~ 24 hour period Pre-Resp Infection day reported) 20 (dd/mm/yyyy)

☐ N/A, data unavailable pt not in hospital

Highest temp °C ☐☐.☐ ☐N/A ☐PO ☐Ax or Tymp ☐Core/ Rectal

Lowest temp °C ☐☐.☐ ☐N/A ☐PO ☐Ax or Tymp ☐Core/ Rectal

Highest WBC count (10^9/L) ☐☐☐☐.☐ ☐N/A

Lowest WBC count (10^9/L) ☐☐☐☐.☐ ☐N/A

Bands present? ☐No ☐Yes

ARDS present? ☐No ☐Yes

Lowest PaO_2/FIO_2 ☐☐☐☐ ☐N/A

Tracheal secretions: ☐None/minimal ☐Moderate ☐Large

Purulent or mucopurulent? ☐No ☐Yes

New, progressive or persistent CXR infiltrate? (Check ALL that apply) ☐None or no CXR ☐Patchy/diffuse ☐Lobar/bilobar ☐Consolidation ☐Cavitation

Potential Pathogen cultured? ☐No ☐Yes

Nasopharyngeal swab (NPS) positive? ☐No ☐Yes

DAY OF RESPIRATORY INFECTION:
20 (dd/mm/yyyy)

Highest temp °C ☐☐.☐ ☐N/A ☐PO ☐Ax or Tymp ☐Core/ Rectal

Lowest temp °C ☐☐.☐ ☐N/A ☐PO ☐Ax or Tymp ☐Core/ Rectal

Highest WBC count (10^9/L) ☐☐☐☐.☐ ☐N/A

Lowest WBC count (10^9/L) ☐☐☐☐.☐ ☐N/A

Bands present? ☐No ☐Yes

ARDS present? ☐No ☐Yes

Lowest PaO_2/FIO_2 ☐☐☐☐ ☐N/A

Tracheal secretions: ☐None/minimal ☐Moderate ☐Large

Purulent or mucopurulent? ☐No ☐Yes

New, progressive or persistent CXR infiltrate? (Check ALL that apply) ☐None or no CXR ☐Patchy/diffuse ☐Lobar/bilobar ☐Consolidation ☐Cavitation

Potential Pathogen cultured? ☐No ☐Yes

Nasopharyngeal swab (NPS) positive? ☐No ☐Yes

24 hours POST Respiratory Infection:
20 (dd/mm/yyyy)

Highest temp °C ☐☐.☐ ☐N/A ☐PO ☐Ax or Tymp ☐Core/ Rectal

Lowest temp °C ☐☐.☐ ☐N/A ☐PO ☐Ax or Tymp ☐Core/ Rectal

Highest WBC count (10^9/L) ☐☐☐☐.☐ ☐N/A

Lowest WBC count (10^9/L) ☐☐☐☐.☐ ☐N/A

Bands present? ☐No ☐Yes

ARDS present? ☐No ☐Yes

Lowest PaO_2/FIO_2 ☐☐☐☐ ☐N/A

Tracheal secretions: ☐None/minimal ☐Moderate ☐Large

Purulent or mucopurulent? ☐No ☐Yes

Calculated REVISE Methods Center CPIS Score: ☐☐

New, progressive or persistent CXR infiltrate? (Check ALL that apply) ☐None or no CXR ☐Patchy/diffuse ☐Lobar/bilobar ☐Consolidation ☐Cavitation

Potential Pathogen cultured? ☐No ☐Yes

Nasopharyngeal swab (NPS) positive? ☐No ☐Yes

Form 5.1

REVISE RCT170 Plate #015 Visit #000

Patient ID 1 Patient Initials

☐ **No cultures performed**

CULTURE REPORT (Form 5.1)

Please list all gram stains and cultures performed in the ICU related to Pulmonary Infections (including from sputum, endotracheal aspirate, bronchoscopy, pleural fluid, nasopharyngeal swab for virus, urine Legionella) and blood culture considered to be related to the pneumonia (i.e., Same organism identified in blood and respiratory specimen).

	Date of Specimen (dd/mm/yyyy)	Result	Organism Code(s) (Please list all today) If more than 3 organisms to report, use additional line.
1.	20	☐ positive ☐ negative	
	Specify Location		
2.	20	☐ positive ☐ negative	
	Specify Location		
3.	20	☐ positive ☐ negative	
	Specify Location		
4.	20	☐ positive ☐ negative	
	Specify Location		
5.	20	☐ positive ☐ negative	
	Specify Location		
6.	20	☐ positive ☐ negative	
	Specify Location		
7.	20	☐ positive ☐ negative	
	Specify Location		

☐ **Please check if additional forms are required for reporting positive cultures**

Form 12

REVISE RCT170 Plate #070

Study Day ☐☐

Patient ID ☐☐☐ 1 ☐☐☐ Patient Initials F ☐ L ☐ Date of Study Day ☐☐ ☐☐ 2 0 ☐☐

PROTOCOL DEVIATION - RESEARCH COORDINATOR REPORT (Form 12)

1. Protocol deviation (check ALL that apply)

- ☐ 1. Randomization of ineligible patient (only submit to local REB upon review with Methods Center and as per local guidelines)
- ☐ 2. Missed dose of study drug
- ☐ 3. Received wrong study drug
- ☐ 4. Open label PPI administered (e.g., not study drug)
- ☐ 5. H_2RA administered
- ☐ 6. Other (specify): _____

2. Explanation: _____

3. Were there any consequences to the patient? ☐ No ☐ Yes, specify: _____

4. Actions taken, specify: _____

REVISE RCT170 Plate #071

Study Day

Patient ID 1

Patient Initials F L

Date of Study Day 2 0

PROTOCOL DEVIATION - PHARMACY REPORT (Form 13)

1. Protocol deviation (check ALL that apply)

- ☐ 1. Missed dose of study drug
- ☐ 2. Dispensed wrong study drug (e.g., pantoprazole given instead of placebo or vice versa)
- ☐ 3. Open label PPI administered (e.g., not study drug)
- ☐ 4. H_2RA administered
- ☐ 5. Other (specify): _____

2. Explanation: _____

3. Were there any consequences to the patient? ☐ No ☐ Yes, specify: _____

4. Actions taken, specify: _____

Form 14

REVISE RCT170 Plate #080

Study Day

Patient ID 1

Patient Initials F L

FINAL STATUS (Form 14)

1. Patient discharged from ICU?

☐ Yes, survived ICU — Date of ICU Discharge (dd/mm/yyyy) 20

☐ No, died in ICU — Date of Death (dd/mm/yyyy) 20

☐ Unknown (e.g., consent revoked), specify: _____

Proximate cause of death in ICU (select one option)

☐ Other, specify: _____

Underlying cause of death in ICU (select up to 3 options)

☐ Other, specify: _____

☐ Other, specify: _____

☐ Other, specify: _____

2. Patient READMITTED to ICU during this index hospital admission?
(NOTE: No need to restart study drug with patient ICU readmission)

☐ No ☐ Yes → Date of ICU Readmission (dd/mm/yyyy) 20 — Date of ICU Discharge (dd/mm/yyyy) 20 — If yes, was readmission for Upper GI bleeding? ☐ No ☐ Yes

Date of ICU Readmission (dd/mm/yyyy) 20 — Date of ICU Discharge (dd/mm/yyyy) 20 — ☐ No ☐ Yes

If Yes, patient readmitted to ICU for upper GI bleeding, please complete **Gastrointestinal Bleeding Outcome Form 9**)

3. Patient discharged from Hospital?

☐ Yes, survived → Date of Hospital Discharge (dd/mm/yyyy) 20

- ☐ Yes, home
- ☐ Yes, acute care facility (non-REVISE site)
- ☐ Yes, long term care facility
- ☐ Yes, rehabilitation center
- ☐ Other, specify: _____

☐ No, died → Date of Death (dd/mm/yyyy) 20

Proximate cause of death in hospital (select one option)

☐ Other, specify: _____

☐ Unknown (e.g., consent revoked), specify: _____

Underlying cause of death in hospital (select up to 3 options)

☐ Other, specify: _____

☐ Other, specify: _____

☐ Other, specify: _____

4. Was this patient confirmed COVID positive anytime from hospital admission up to hospital discharge?

☐ Yes → Date confirmed positive, if applicable (dd/mm/yyyy)

☐ No

5. Vital status at 90 days following randomization?

☐ Alive

- ☐ Home
- ☐ Study hospital
- ☐ Chronic care, long term care facility
- ☐ Other acute care facility (non-REVISE site)
- ☐ Palliative care hospital or facility
- ☐ Inpatient rehabilitation center
- ☐ Other, specify: _____

☐ Deceased

How was the 90 day vital status obtained?

- ☐ Medical record
- ☐ Phone call to other hospital, care facility or family MD
- ☐ Phone call to patient, SDM or family member
- ☐ Other, specify: _____
- ☐ Not obtained, explain: _____

Date of contact (dd/mm/yyyy) Date of Death, if applicable (dd/mm/yyyy)

REVISE RCT170 Plate #095 Visit #000

Patient ID [ ][ ][ ] 1 [ ][ ][ ]

Patient Initials F [ ] L [ ]

COENROLMENT (Form 15)

1. Was patient coenrolled in another study in ICU? ☐ No ☐ Yes, please specify name, design and funding:

Study name:	Design: RCT	Design: observ	Funding: academic	Funding: industry	Funding: local	Informed Consent (1 = A priori, 2 = Deferred, 3 = Waived)	Consent Timing (1 = REVISE 1st, 2 = Concurrent, 3 = REVISE after)	Methods Center Internal Study Code
a. _____	☐	☐	☐	☐	☐	☐	☐	☐☐☐
b. _____	☐	☐	☐	☐	☐	☐	☐	☐☐☐
c. _____	☐	☐	☐	☐	☐	☐	☐	☐☐☐
d. _____	☐	☐	☐	☐	☐	☐	☐	☐☐☐
e. _____	☐	☐	☐	☐	☐	☐	☐	☐☐☐

Form 16

REVISE RCT170 Plate #100

Study Day

Patient ID 1

Patient Initials F L

Date of Study Day 2 0

NOTE TO FILE (Form 16)

REVISE RCT170 Plate #085

Study Day

Patient ID 1

Patient Initials F L

Date of Study Day 20

ADVERSE EVENT - DIRECTLY RELATED TO THE STUDY (Form 17.1 of 3)

1. Onset date and time of Adverse Event: Date (dd/mm/yyyy) 20 / (24 hour clock) :

☐ Unknown

2. Type of Event:
☐ Adverse Drug Reaction (ADR)
☐ Serious Adverse Drug Reaction (SADR)
☐ Suspected Unexpected Serious Adverse Reaction (SUSAR)

3. Was the event attributed to any of the following outcomes (check ALL that apply)

☐ Death
☐ Life threatening (i.e., immediate risk of death)
☐ Prolongation of this hospitalization
☐ Persistent or significant disability or incapacity
☐ Congenital anomaly or birth defect
☐ Medically significant and may require intervention (treatment) to prevent one of the prior outcomes, specify:

_____

_____

☐ Adverse Drug Reaction only, no other conditions judged as serious (ADR)

4. Description of event or diagnosis: _____

_____

_____

5. Relationship to study treatment: (In the opinion of the Attending Physician or Site Investigator)
☐ Possibly Related
☐ Probably Related
☐ Definitely Related

6. Date and time study drug last administered: Date (dd/mm/yyyy) 20 / (24 hour clock) :

7. Action taken regarding the study treatment (check ALL that apply)

☐ None required
☐ Study drug interrupted, specify when resumed — Date (dd/mm/yyyy) 20 / (24 hour clock) :
☐ Study drug permanently discontinued

8. Overall outcome of the event, at time of hospital discharge or death (check one only)

☐ Recovered spontaneously, specify date of resolution: Date (dd/mm/yyyy) 20

☐ Recovered with treatment, specify date of resolution: 20

☐ Recovered with sequelae (specify): _____

☐ Death, specify date and time: (24 hour clock) 20 / :

☐ No resolution (ongoing), specify: _____

☐ Unknown

Form 17.2

REVISE RCT170 Plate #087

Study Day

Patient ID 1

Patient Initials F L

ADVERSE EVENT - DIRECTLY RELATED TO THE STUDY (Form 17.2)

9. Medication Log (within 24 hours of event)

Generic Name: **Dose** **Units** **Frequency** **Route**

1. _____ . _____ _____ _____ _____ _____ **(if other route, specify)**

(dd/mm/yyyy) (dd/mm/yyyy)

Start date 20 End date 20 Ongoing

Indication (to treat event OR pre-event): _____

Generic Name: **Dose** **Units** **Frequency** **Route**

2. _____ . _____ _____ _____ _____ _____ **(if other route, specify)**

(dd/mm/yyyy) (dd/mm/yyyy)

Start date 20 End date 20 Ongoing

Indication (to treat event OR pre-event): _____

Generic Name: **Dose** **Units** **Frequency** **Route**

3. _____ . _____ _____ _____ _____ _____ **(if other route, specify)**

(dd/mm/yyyy) (dd/mm/yyyy)

Start date 20 End date 20 Ongoing

Indication (to treat event OR pre-event): _____

Generic Name: **Dose** **Units** **Frequency** **Route**

4. _____ . _____ _____ _____ _____ _____ **(if other route, specify)**

(dd/mm/yyyy) (dd/mm/yyyy)

Start date 20 End date 20 Ongoing

Indication (to treat event OR pre-event): _____

Generic Name: **Dose** **Units** **Frequency** **Route**

5. _____ . _____ _____ _____ _____ _____ **(if other route, specify)**

(dd/mm/yyyy) (dd/mm/yyyy)

Start date 20 End date 20 Ongoing

Indication (to treat event OR pre-event): _____

☐ **Please check if additional forms are required for reporting Medication Log**

REVISE RCT170 Plate #086

Study Day ☐☐

Patient ID ☐☐☐ 1 ☐☐☐ Patient Initials F ☐ L ☐

ADVERSE EVENT - DIRECTLY RELATED TO THE STUDY (Form 17.3 of 3)

10. Potential confounding factors/relevant medical history: _____

_____

_____

_____

_____

11. Was the study treatment unblinded? ☐ No ☐ Yes, please complete the **Code Break Form 18**

12. Does the Investigator or Site Investigator believe that this event is directly related to the REVISE study drug?

☐ No ☐ Yes, specify reason: _____

_____

_____

13. Reporter Name: _____ **Reporter Signature:** _____

Reporter Designation: _____ **Reporter Telephone:** _____

Date of Report: Date (dd/mm/yyyy) ☐☐ ☐☐ 2 0 ☐☐ **Methods Center Contacted?** ☐ No ☐ Yes

14. I have reviewed this report and agree with its contents

_____ Date (dd/mm/yyyy) ☐☐ ☐☐ 2 0 ☐☐

ICU Physician name **ICU Physician signature**

_____ ☐☐ ☐☐ 2 0 ☐☐

Site Investigator name **Site Investigator signature**

Please fax (+1-905-308-7223) or scan this form immediately to the REVISE Methods Center at REVISE@stjosham.on.ca and call the REVISE Methods Center (+1-905-512-5935)

Reporting checklist for protocol of a clinical trial.

Based on the SPIRIT guidelines.

Instructions to authors

Complete this checklist by entering the page numbers from your manuscript where readers will find each of the items listed below.

Your article may not currently address all the items on the checklist. Please modify your text to include the missing information. If you are certain that an item does not apply, please write "n/a" and provide a short explanation.

Upload your completed checklist as an extra file when you submit to a journal.

In your methods section, say that you used the SPIRITreporting guidelines, and cite them as:

Chan A-W, Tetzlaff JM, Gøtzsche PC, Altman DG, Mann H, Berlin J, Dickersin K, Hróbjartsson A, Schulz KF, Parulekar WR, Krleža-Jerić K, Laupacis A, Moher D. SPIRIT 2013 Explanation and Elaboration: Guidance for protocols of clinical trials. BMJ. 2013;346:e7586

		Reporting Item	Page Number
Administrative information			
Title	#1	Descriptive title identifying the study design, population, interventions, and, if applicable, trial acronym	1
Trial registration	#2a	Trial identifier and registry name. If not yet registered,	2

		name of intended registry	
Trial registration: data set	#2b	All items from the World Health Organization Trial Registration Data Set	2
Protocol version	#3	Date and version identifier	4
Funding	#4	Sources and types of financial, material, and other support	15
Roles and responsibilities: contributorship	#5a	Names, affiliations, and roles of protocol contributors	15
Roles and responsibilities: sponsor contact information	#5b	Name and contact information for the trial sponsor	1
Roles and responsibilities: sponsor and funder	#5c	Role of study sponsor and funders, if any, in study design; collection, management, analysis, and interpretation of data; writing of the report; and the decision to submit the report for publication, including whether they will have ultimate authority over any of these activities	15
Roles and responsibilities: committees	#5d	Composition, roles, and responsibilities of the coordinating centre, steering committee, endpoint adjudication committee, data management team, and other individuals or groups overseeing the trial, if applicable (see Item 21a for data monitoring committee)	9

Introduction

Background and rationale	#6a	Description of research question and justification for undertaking the trial, including summary of relevant studies (published and unpublished) examining benefits and harms for each intervention	4,5
Background and rationale: choice of comparators	#6b	Explanation for choice of comparators	4,5
Objectives	#7	Specific objectives or hypotheses	5
Trial design	#8	Description of trial design including type of trial (eg, parallel group, crossover, factorial, single group), allocation ratio, and framework (eg, superiority, equivalence, non-inferiority, exploratory)	5
Methods: Participants, interventions, and outcomes			
Study setting	#9	Description of study settings (eg, community clinic, academic hospital) and list of countries where data will be collected. Reference to where list of study sites can be obtained	5,11
Eligibility criteria	#10	Inclusion and exclusion criteria for participants. If applicable, eligibility criteria for study centres and individuals who will perform the interventions (eg,	5

		surgeons, psychotherapists)	
Interventions: description	#11a	Interventions for each group with sufficient detail to allow replication, including how and when they will be administered	6
Interventions: modifications	#11b	Criteria for discontinuing or modifying allocated interventions for a given trial participant (eg, drug dose change in response to harms, participant request, or improving / worsening disease)	6
Interventions: adherance	#11c	Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence (eg, drug tablet return; laboratory tests)	6
Interventions: concomitant care	#11d	Relevant concomitant care and interventions that are permitted or prohibited during the trial	6
Outcomes	#12	Primary, secondary, and other outcomes, including the specific measurement variable (eg, systolic blood pressure), analysis metric (eg, change from baseline, final value, time to event), method of aggregation (eg, median, proportion), and time point for each outcome. Explanation of the clinical relevance of chosen efficacy and harm outcomes is strongly recommended	7,8
Participant timeline	#13	Time schedule of enrolment, interventions (including any run-ins and washouts), assessments, and visits for participants. A schematic diagram is highly recommended (see Figure)	5-7

Sample size	#14	Estimated number of participants needed to achieve study objectives and how it was determined, including clinical and statistical assumptions supporting any sample size calculations	9
Recruitment	#15	Strategies for achieving adequate participant enrolment to reach target sample size	5,6
Methods: Assignment of interventions (for controlled trials)			
Allocation: sequence generation	#16a	Method of generating the allocation sequence (eg, computer-generated random numbers), and list of any factors for stratification. To reduce predictability of a random sequence, details of any planned restriction (eg, blocking) should be provided in a separate document that is unavailable to those who enrol participants or assign interventions	6
Allocation concealment mechanism	#16b	Mechanism of implementing the allocation sequence (eg, central telephone; sequentially numbered, opaque, sealed envelopes), describing any steps to conceal the sequence until interventions are assigned	6
Allocation: implementation	#16c	Who will generate the allocation sequence, who will enrol participants, and who will assign participants to interventions	6

Blinding (masking)	#17a	Who will be blinded after assignment to interventions (eg, trial participants, care providers, outcome assessors, data analysts), and how	6
Blinding (masking): emergency unblinding	#17b	If blinded, circumstances under which unblinding is permissible, and procedure for revealing a participant's allocated intervention during the trial	6
Methods: Data collection, management, and analysis			
Data collection plan	#18a	Plans for assessment and collection of outcome, baseline, and other trial data, including any related processes to promote data quality (eg, duplicate measurements, training of assessors) and a description of study instruments (eg, questionnaires, laboratory tests) along with their reliability and validity, if known. Reference to where data collection forms can be found, if not in the protocol	6-9
Data collection plan: retention	#18b	Plans to promote participant retention and complete follow-up, including list of any outcome data to be collected for participants who discontinue or deviate from intervention protocols	9
Data management	#19	Plans for data entry, coding, security, and storage, including any related processes to promote data quality	9

		(eg, double data entry; range checks for data values). Reference to where details of data management procedures can be found, if not in the protocol	
Statistics: outcomes	#20a	Statistical methods for analysing primary and secondary outcomes. Reference to where other details of the statistical analysis plan can be found, if not in the protocol	10
Statistics: additional analyses	#20b	Methods for any additional analyses (eg, subgroup and adjusted analyses)	10
Statistics: analysis population and missing data	#20c	Definition of analysis population relating to protocol non-adherence (eg, as randomised analysis), and any statistical methods to handle missing data (eg, multiple imputation)	10
Methods: Monitoring			
Data monitoring: formal committee	#21a	Composition of data monitoring committee (DMC); summary of its role and reporting structure; statement of whether it is independent from the sponsor and competing interests; and reference to where further details about its charter can be found, if not in the protocol. Alternatively, an explanation of why a DMC is not needed	10
Data monitoring: interim analysis	#21b	Description of any interim analyses and stopping guidelines, including who will have access to these interim results and make the final decision to terminate the trial	10
Harms	#22	Plans for collecting, assessing, reporting, and managing	10

		solicited and spontaneously reported adverse events and other unintended effects of trial interventions or trial conduct	
Auditing	#23	Frequency and procedures for auditing trial conduct, if any, and whether the process will be independent from investigators and the sponsor	9
Ethics and dissemination			
Research ethics approval	#24	Plans for seeking research ethics committee / institutional review board (REC / IRB) approval	5,10
Protocol amendments	#25	Plans for communicating important protocol modifications (eg, changes to eligibility criteria, outcomes, analyses) to relevant parties (eg, investigators, REC / IRBs, trial participants, trial registries, journals, regulators)	10
Consent or assent	#26a	Who will obtain informed consent or assent from potential trial participants or authorised surrogates, and how (see Item 32)	5
Consent or assent: ancillary studies	#26b	Additional consent provisions for collection and use of participant data and biological specimens in ancillary studies, if applicable	10
Confidentiality	#27	How personal information about potential and enrolled participants will be collected, shared, and maintained in order to protect confidentiality before, during, and after the	7

		trial	
Declaration of interests	#28	Financial and other competing interests for principal investigators for the overall trial and each study site	15
Data access	#29	Statement of who will have access to the final trial dataset, and disclosure of contractual agreements that limit such access for investigators	16
Ancillary and post trial care	#30	Provisions, if any, for ancillary and post-trial care, and for compensation to those who suffer harm from trial participation	6
Dissemination policy: trial results	#31a	Plans for investigators and sponsor to communicate trial results to participants, healthcare professionals, the public, and other relevant groups (eg, via publication, reporting in results databases, or other data sharing arrangements), including any publication restrictions	11
Dissemination policy: authorship	#31b	Authorship eligibility guidelines and any intended use of professional writers	11
Dissemination policy: reproducible research	#31c	Plans, if any, for granting public access to the full protocol, participant-level dataset, and statistical code	16
Appendices			
Informed consent materials	#32	Model consent form and other related documentation given to participants and authorised surrogates	Uploaded
Biological specimens	#33	Plans for collection, laboratory evaluation, and storage of	N/A

	biological specimens for genetic or molecular analysis in the current trial and for future use in ancillary studies, if applicable