

A cluster randomised, crossover, registry-embedded clinical trial of proton pump inhibitors versus histamine-2 receptor blockers for ulcer prophylaxis therapy in the intensive care unit (PEPTIC study): study protocol

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Stress ulcer prophylaxis is prescribed to more than 70% of adults who are acutely admitted to an intensive care unit (ICU).¹ Most patients receive a proton pump inhibitor (PPI), but a sizeable minority receive a histamine-2 receptor blocker (H₂RB).^{2,3} The rationale for using stress ulcer prophylaxis is to prevent upper gastrointestinal (GI) bleeding. Such bleeding occurs in 2.6% (95% CI, 1.6–3.6%) of ICU patients in contemporary clinical practice.¹ In a recent systematic review and meta-analysis comparing PPIs with H₂RBs for ulcer prophylaxis in the ICU, PPI use was associated with a significantly lower risk of overt bleeding than H₂RB use.⁴ However, using PPIs instead of H₂RBs also appears to be associated with an increased risk of developing nosocomial pneumonia⁵⁻⁷ and *Clostridium difficile* infection,⁵ and may be associated with increased overall health care cost.⁸

Although stress ulcer prophylaxis is administered to millions of ICU patients around the world every year, it is uncertain which type of ulcer prophylaxis is preferable. Moreover, current variability in practice in relation to choice of stress ulcer prophylaxis is largely dependent on clinician preference or unit policy.³ Clinical trials of adequate size to determine whether PPIs or H₂RBs are the best strategy for stress ulcer prophylaxis have not been performed and are a high priority given the widespread use of these medicines. Here we outline the protocol for the Proton Pump Inhibitors versus Histamine-2 Receptor Blockers for Ulcer Prophylaxis Therapy in the Intensive Care Unit (PEPTIC) study.

Methods

Trial design

The PEPTIC study is a prospective, multicentre, randomised, open-label, cluster crossover, registry-embedded trial comparing two approaches to stress ulcer prophylaxis in mechanically ventilated adults implemented at the level of the ICU. One approach is to use PPIs as the default therapy when stress ulcer prophylaxis is prescribed, and the other

ABSTRACT

Background: The balance of risks and benefits with using proton pump inhibitors (PPIs) versus histamine-2 receptor blockers (H₂RB) for stress ulcer prophylaxis in patients who are invasively ventilated in the intensive care unit (ICU) is uncertain.

Objective: To describe the study protocol and statistical analysis plan for the Proton Pump Inhibitors versus Histamine-2 Receptor Blockers for Ulcer Prophylaxis Therapy in the Intensive Care Unit (PEPTIC) study.

Design, setting and participants: Protocol for a prospective, multicentre, randomised, open-label, cluster crossover, registry-embedded trial to be conducted in 50 ICUs in Australia, Canada, Ireland, New Zealand and the United Kingdom. The PEPTIC study will compare two approaches to stress ulcer prophylaxis in mechanically ventilated adults implemented at the level of the ICU. One approach is to use PPIs as the default therapy and the other approach is to use H₂RBs as the default therapy when stress ulcer prophylaxis is prescribed. Each ICU, by random allocation, will use one approach for 6 months and will then switch to the opposite approach for the next 6 months. The PEPTIC study began recruitment in August 2016 and will complete recruitment in January 2019.

Main outcome measures: The primary end point will be in-hospital mortality. Secondary outcomes include clinically significant upper gastrointestinal bleeding, *Clostridium difficile* infection, ICU length of stay and hospital length of stay.

Results and conclusions: The PEPTIC study will compare the effect on in-hospital mortality of implementing, at the level of the ICU, the use of PPI as the preferred agent for stress ulcer prophylaxis in mechanically ventilated adults in the ICU with using H₂RB as the preferred agent.

Trial registration: Australian and New Zealand Clinical Trials Registry (ANZCTR N12616000481471).

approach is to use H₂RBs as the default therapy when stress ulcer prophylaxis is prescribed. Each ICU, by random allocation, will use one approach for 6 months and will then switch to the opposite approach for the next 6 months. This trial is registered on the Australian and New Zealand Clinical Trials Registry (ANZCTRN 12616000481471).

Rationale for the trial design

The PEPTIC study combines two novel trial design methodologies: cluster randomisation with crossover⁹ and collection of outcome data from existing data sources.¹⁰ This design offers the dual prospect of generating the statistical power necessary to evaluate candidate interventions with small effect sizes and of being much cheaper than a conventional randomised trial because it uses data that are already collected for other purposes.

Entire ICUs are randomly allocated rather than individual patients. We submit that this approach is preferable to individual randomisation because we are testing two approaches to stress ulcer prophylaxis which would logically be implemented at the level of the ICU and would not define the therapy for any given individual. Each ICU will define a cluster and each ICU will cross over to use both of the treatment approaches being tested by the end of the study. The crossover component allows within-ICU comparisons of treatment effects to substantially increase statistical power.^{9,11} When possible, existing registry data sources will be used to collect baseline, intervention and outcome data for the patients admitted to the study ICUs during the trial. Recent academic discourse has highlighted the potential for “big data” to advance medical knowledge,¹² but performing a large scale randomised trial leveraging existing data sources is a relatively new innovation in clinical research.¹³ In addition to being innovative, we submit that this may be the optimal trial design for testing ubiquitous ICU interventions when the necessary data are already being collected for administrative, quality assurance and other purposes; when there is idiosyncratic practice variation;¹⁴

and when clinical equipoise exists for testing two “standard-of-care” treatment regimens.

Setting and randomisation

The PEPTIC study is being conducted in 50 ICUs in Australia, Canada, Ireland, New Zealand and the United Kingdom. Participating ICUs are randomly allocated to the order of receipt of treatments in a 1:1 ratio when ethics and regulatory approvals are in place at each study site, and is stratified by region and time period, with a minimum of four ICUs randomised at each time period.

Population and eligibility

All patients aged 18 years or older who are invasively mechanically ventilated within 24 hours of ICU admission are eligible for the study, except for those patients with an ICU admission diagnosis of upper GI bleeding. Patients who opt out of participating in the study will be excluded from analyses. A flow diagram based on the

Figure 1. Proposed participant flow diagram

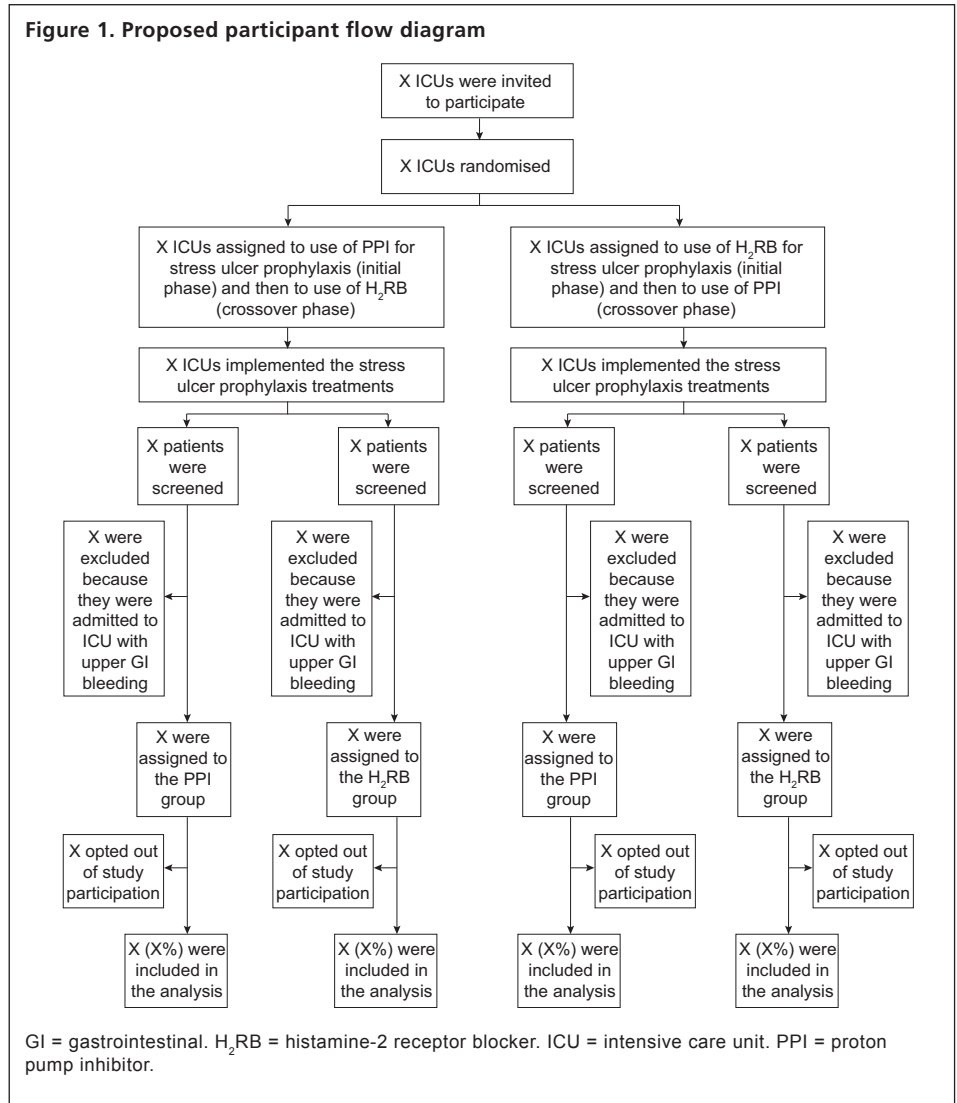


Table 1. Definitions of secondary and tertiary outcomes

Outcome	Definition
Clinically significant upper GI bleeding	Overt upper GI bleeding (eg, haematemesis, melaena or frank blood in the nasogastric tube or upper GI endoscopy) developing as a complication in ICU AND ≥ 1 of the following features within 24 hours of GI bleeding: <ul style="list-style-type: none"> ▪ spontaneous drop of systolic, mean arterial pressure or diastolic blood pressure ≥ 20 mmHg; ▪ start of vasopressor or a 20% increase in vasopressor dose; ▪ decrease in haemoglobin of at least 20 g/L; or ▪ transfusion of ≥ 2 units of packed red blood cells
<i>Clostridium difficile</i> infection	<i>C. difficile</i> toxin-positive or culture-positive stool samples collected during an ICU admission (excluding any patients who had positive tests from specimens collected prior to ICU admission)
ICU length of stay	Time between ICU admission and first ICU discharge (ie, excludes readmission and time spent in a second or subsequent ICU)
Hospital length of stay	The time between ICU admission and index hospital discharge (ie, excludes readmissions and time spent in hospitals other than the index hospital)
Duration of mechanical ventilation*	Total hours of invasive mechanical ventilation during the index ICU admission
Ventilator-associated conditions ¹⁹	Ventilator-associated conditions will be defined as: after a period of stability or improvement on the ventilator (≥ 2 days), the patient has at least one of the following indicators of worsening oxygenation: <ul style="list-style-type: none"> ▪ increase in daily minimum FiO_2 of ≥ 0.20 over the daily minimum FiO_2 in the baseline period, sustained for ≥ 2 days; ▪ increase in daily minimum PEEP values of ≥ 3 cmH₂O over the daily minimum PEEP in the baseline period, sustained for ≥ 2 days (daily minimum defined by lowest FiO_2 or PEEP during a calendar day that is maintained for ≥ 1 h)

FiO_2 = fraction of inspired oxygen. GI = gastrointestinal. ICU = intensive care unit. PEEP = positive end-expiratory pressure. * In the United Kingdom, duration of mechanical ventilation will be defined as the number of calendar days on which advanced respiratory support was received.

Consolidated Standards of Reporting Trials (CONSORT) recommendations for reporting of cluster randomised trials¹⁵ will be presented (Figure 1).

Screening

Screening of individual patients for trial eligibility is not performed. Instead, variables included in existing databases will be used to retrospectively identify patients who fulfil eligibility criteria in each study treatment period. In the 27 participating ICUs from Australia and New Zealand, eligible patients will be identified using data in the Australian and New Zealand Intensive Care Society (ANZICS) Adult Patient Database (APD).¹⁶ In the 14 participating ICUs from the United Kingdom, eligible patients will be identified using the Intensive Care National Audit and Research Centre (ICNARC) Case Mix Programme (CMP) database.¹⁷ In the eight participating ICUs from Canada, eligible patients will be identified through interrogation of an existing provincial clinical information system (eCritical Alberta¹⁸) coupled with a data warehouse and clinical analytics system (eCritical TRACER). In the single participating ICU from Ireland, eligible patients will be identified using data in the ICU's clinical information system.

An information brochure will be provided to adults who have required mechanically ventilation which allows them to opt out of having their data included in the study.

Treatments

Study treatments will be administered on an open label basis. When a clinician chooses to prescribe stress ulcer prophylaxis, the default prescription of either PPI or H₂RB is that allocated to the ICU for the current study treatment period. This default prescription will be used for all patients including those readmitted to ICU during a different study period and transferred from another ICU. However, irrespective of the treatment that is allocated to the ICU, the treating clinician will retain discretion to use either a PPI or a H₂RB in situations in which they consider that a particular treatment is preferable (eg, when the patient has an allergy to one class of drug). Patients who are usually taking a PPI or an H₂RB before hospitalisation or ICU admission will switch to the treatment strategy assigned to the ICU for the duration of their ICU stay, unless the treating clinician believes that this is inappropriate for the particular patient. If upper GI bleeding occurs, then a PPI is administered in accordance with standard clinical practice, irrespective of treatment allocation. The duration of study treatment will be until death, ICU discharge, development

of a clinically significant upper GI bleeding event, or until the treating clinician no longer believes stress ulcer prophylaxis is indicated. No washout is planned between crossover periods. Patients who remain in the ICU through a crossover period will continue to receive the treatment they were originally assigned.

Outcomes

Primary outcome measure

The primary outcome is in-hospital all-cause mortality up to 90 days. In-hospital mortality is recorded in all of the registries that are being used as the primary data source for the PEPTIC study. The rationale for choosing in-hospital mortality as the primary end point for this study is that in-hospital mortality is an important patient-centred endpoint. By providing an estimate of the mortality treatment effect size using PPI versus H₂RB and corresponding 95% confidence intervals, we seek to provide clinicians with a rational basis for weighing the potentially opposing mortality effects attributable to complications that define the various secondary outcome measures outlined below.

Secondary outcome measures

The secondary outcomes (Table 1) are:

- proportion of patients with clinically significant upper GI bleeding;¹
- proportion of patients with *C. difficile* infection;
- ICU length of stay;
- hospital length of stay; and
- duration of mechanical ventilation (for the ICUs where this information is available from an existing database).

Tertiary outcome measure

The proportion of patients with ventilator-associated conditions¹⁹ (for the eight ICUs in Canada) is specified as a tertiary outcome (Table 1).

Data collection

Data will either be extracted from existing databases or obtained by site research coordinators (Figure 2). The existing databases used to obtain data and the data extracted from those databases will vary by jurisdiction

(Table 2). However, in all cases, when a patient is readmitted to ICU during an index hospital admission, this patient will only be included in the study database once, with demographic and illness severity data obtained from the initial ICU admission. Complications such as clinically significant upper GI bleeding events and *C. difficile* infections that develop during ICU readmissions within the index hospital admission will be included in the study database.

In Canada, all baseline data, stress ulcer prophylaxis prescribing data, hospital mortality data, clinically significant GI bleeding events, duration of mechanical ventilation, and ICU and hospital lengths of stay data will be extracted from the eCritical database at trial completion. Data from the eCritical database will be linked using unique health care identifiers with the Alberta Health Services Discharge Abstract Data and Infection Control and Prevention databases to identify participants with *C. difficile* infections.

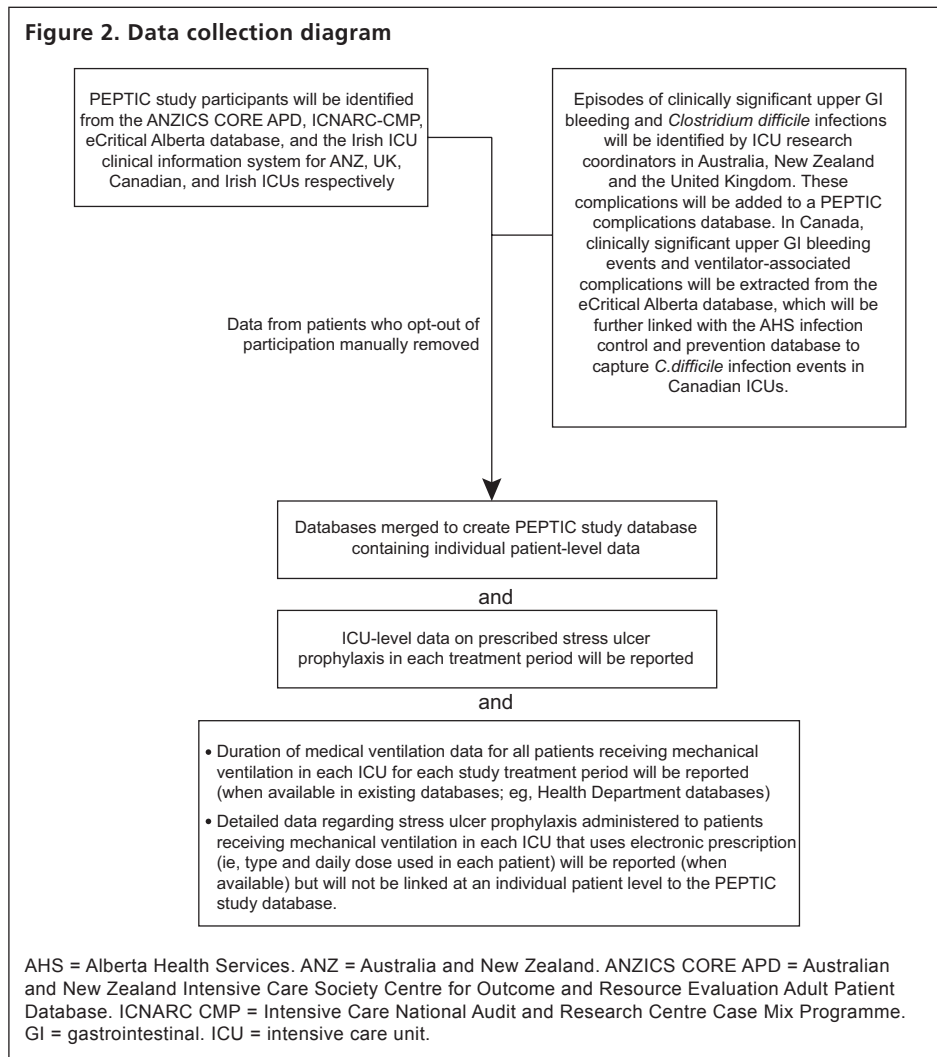


Table 2. Data variables

Data collected from existing databases	<ul style="list-style-type: none"> ▪ Age ▪ Gender ▪ Admission type (elective v emergency) ▪ ICU admission source (ie, ED v ward v theatre v other hospital) ▪ Chronic comorbidities ▪ APACHE III admission diagnosis²⁰ ▪ Illness severity based on the on the APACHE II and III scores and risk of death (all ICUs), ANZ Risk of Death models score (ANZ only),²⁰ and ICNARC risk of death model (United Kingdom only) ▪ ICU length of stay ▪ Hospital length of stay ▪ In-hospital mortality ▪ Duration of mechanical ventilation (Canada, Ireland and the UK only) ▪ Ventilator-associated conditions¹⁹ (Canada only) ▪ Clinically significant upper GI bleeding events (Canada only) ▪ <i>Clostridium difficile</i> infections (Canada and Ireland only) ▪ Dispensing of H₂RBs and PPIs to ICUs in each study period (from hospital pharmacies)
Data collected by site research coordinators	<ul style="list-style-type: none"> ▪ Clinically significant upper GI bleeding events ▪ <i>C. difficile</i> infections ▪ List of patients who opt out of study participation ▪ Monthly audit of stress ulcer prophylaxis use in mechanically ventilated patients (when electronic prescribing records are not available)
Data from electronic prescribing records	<ul style="list-style-type: none"> ▪ Details of stress ulcer prophylaxis administered to all mechanically ventilated patients during each study treatment period

ANZ = Australia and New Zealand. APACHE = Acute Physiology and Chronic Health Evaluation. ED = emergency department. GI = gastrointestinal. H₂RB = histamine-2 receptor blocker. ICNARC = Intensive Care National Audit and Research Centre. ICU = intensive care unit. PPI = proton pump inhibitor.

In Australia and New Zealand, baseline data, hospital mortality data and ICU and hospital length of stay data will be obtained from the ANZICS APD.¹⁶ In Ireland, these data will be obtained from the ICU clinical information system. In the UK, these data, and also the duration of mechanical ventilation, will be obtained from the ICNARC CMP.¹⁷ In Australian, New Zealand and the UK, information about stress ulcer prophylaxis prescribed to mechanically ventilated ICU patients during each of the study periods will be obtained from electronic prescribing records (in centres where these are available). In addition, information on classes of stress ulcer prophylaxis drugs used obtained from medication charts on one day a month for the duration of the study will be collected by research staff, and the total amount of PPI and H₂RB dispensed in each ICU in each study period will be collected where available. Research coordinators will record the ICNARC CMP admission number for UK participants who develop clinically significant upper GI bleeding and/or *C. difficile* infections. In Ireland, all study data will be entered into a research electronic data capture (REDCap) database by research staff.

The final PEPTIC study database will contain data merging all data sources into a single study database.

Power and sample size

With 50 ICUs, and assuming a baseline mortality of 15%, our study will have 80% power to detect a 2.4% absolute difference in in-hospital mortality at a 5% significance. This sample size is based on input parameters estimated from the ANZICS APD administrative data, with an average of 310 admissions per site in each 6-month study period with a variation in number of admissions of 0.50, and incorporates a within-cluster–within-period correlation of 0.035 and within-cluster–between-period correlation of 0.025.¹¹

Overview of planned statistical analyses

Analyses will be conducted on an intention-to-treat basis, meaning that all patients will be analysed according to the randomised treatment of their ICU at the time of their ICU admission, regardless of the treatment received. Descriptive statistics at ICU level will be presented by allocated treatment sequence and for patient characteristics by allocation sequence and observation period. Analyses

of treatment effects will utilise individual level data using generalised estimating equations (GEE) with adjustment for randomisation time period and order of administration of the treatments, with an exchangeable working correlation matrix and robust standard errors using the ICU as the clustering unit, and with derived *P* values and confidence intervals employing the *t* distribution with degrees of freedom correcting for the numbers of model parameters being estimated.¹¹ The primary mortality endpoint will be presented as a risk difference using binary outcomes and an identity link function, and as an odds ratio using the logit link. Should the risk difference model fail to converge, GEE with Gaussian linear regression, identity link and robust standard errors will be employed.²¹ For secondary outcomes on a binary scale, the same methods will apply; for outcomes on a continuous scale, GEE with Gaussian-identity link and robust standard errors will be applied; and for duration/time-to-event variables, we will use Cox regression with robust standard errors to estimate hazard ratios and confidence intervals, with mortality regarded as a competing risk. Sensitivity analyses will be performed for the impact of patients with missing outcome data using multiple imputation methods. Additional sensitivity analyses will adjust for patient-level variables that exhibit imbalance across observation periods.

Subgroup analyses will be performed for individual-level variables — patients who are admitted to the ICU after cardiac surgery versus patients admitted for any other reason; emergency versus elective admissions — and for the ICU-level variable — country. We will perform the analyses described above for the primary and secondary outcome variables assessing subgroup differences using interaction terms between treatment and each subgroup. To test the robustness of the primary analyses, we plan to conduct sensitivity analyses that exclude all patients transferred from another ICU. A detailed statistical analysis plan will be made available on the Wellington ICU website (www.wellingtonicu.com) before unblinding the treatment codes when undertaking the final analysis.

Safety

Ethics approvals

The trial was approved by the Northern B Health and Disability Ethics Committee in New Zealand (15/NTB/52), the Austin Health Human Research Ethics Committee (HREC/15/Austin/144) in Australia, the Research Ethics Board at the University of Alberta, Edmonton, Canada (Pro00074103), the St Vincent's Healthcare Group Ethics and Medical Research Committee in Ireland, and the London–Bromley Research Ethics Committee (17/LO/1313). Additional local

hospital approvals were also obtained as required. In all jurisdictions, ethics approval was granted on the basis of either provision of information with the opportunity to opt out of use of study data or a waiver of consent.

Data monitoring committee

A committee of independent experts in clinical trials, biostatistics and intensive care medicine has been appointed to the Data Monitoring Committee (DMC). The members of the DMC are Brian Cuthbertson (Chair), Anthony Gordon and Graeme MacLennan. The DMC will monitor adverse events as they accrue. No formal interim analyses of the primary outcome have been planned. Given that PPIs and H₂RBs are in widespread use in current practice and their safety profiles are well known, we do not anticipate the trial being stopped for harm. However, the DMC may, at its absolute discretion, request assessment of available trial data at any time.

Adverse events

Study investigators will be actively encouraged to report all adverse reactions to PPIs and H₂RBs that occur during the study. Adverse event reporting will be in line with usual methods for reporting of suspected adverse reactions to licensed medicines. In New Zealand, suspected adverse reactions will be reported to the Centre for Adverse Reaction Monitoring.²² In Australia, adverse reactions will be reported using the Australian Adverse Drug Reaction Reporting System.²³ In Canada, data on suspected adverse events will be captured by the Reporting and Learning System for patient safety in Alberta and to Health Canada through the Canadian Vigilance Adverse Reaction reporting. In Ireland, suspected adverse reactions will be reported to the Health Products Regulatory Authority. In the UK, suspected adverse reactions will be reported to the Medicines and Healthcare Products Regulatory Agency via their yellow card scheme. Details of all reported adverse reactions will be provided to the DMC and will be reported to relevant ethics committees when required.

Confidentiality

The primary data repository for this Australian and New Zealand study is the ANZICS APD, which is an established database including patients admitted to ICUs in Australia and New Zealand.¹⁶ Approval to access the database for the purpose of retrieving data on patients participating in the PEPTIC study has been granted by the ANZICS Centre for Outcome and Resource Evaluation Management Committee in accordance with standing protocols. The ANZICS APD identifies each patient by a unique number. Linkage between each number in the database and a particular patient is maintained by each participating hospital (ie,

data are classified as partially de-identified). Data exported from the ANZICS APD for study analyses will not include any identifiers (ie, the data included in the PEPTIC study database will be fully de-identified). The study data for patients recruited from sites in Ireland will be collected from an ICU Clinical Information System at an individual patient level and incorporated into the main study database at the end of the study.

The primary data repository for the Canadian sites is eCritical Alberta, a provincial clinical information system and established data warehouse and clinical analytics system routinely used for health services research, along with Alberta Health Services administrative databases. Approval to access eCritical Alberta was granted through a provincial executive governance committee, for the purpose of retrieving data on eligible patients admitted to study ICUs during PEPTIC. eCritical will identify each patient through a unique provincial health care number. This unique identifier will be used for linkage of eCritical with Alberta Health Services Discharge Abstract Data and Infection Control and Prevention databases, respectively. Data exported to generate the merged international PEPTIC study database will be de-identified.

For the Irish sites, a log of patient details and corresponding study number will be maintained at the site level. Linkage between each number in the database and a particular patient will be maintained by each participating hospital (ie, data will be partially de-identified). Patients in the PEPTIC database will be identified by study number only.

In the UK, the data repository for this study is the ICNARC CMP, an established database of patients admitted to ICUs. Approval to access the database for the purpose of retrieving data on patients participating in the PEPTIC study will be granted by the ICNARC Data Access Advisory Group in accordance with standing protocols. Each patient is identified by a unique number (site prefix and ICNARC CMP admission number) maintained at each participating hospital; linkage between each number and a particular patient will be carried out by ICNARC who will link data using the CMP admission number (ie, data are classified as partially de-identified). Data exported for study analyses will not include any identifiers (ie, the data included in the PEPTIC study database will be fully de-identified). Once the extracted data have been merged with the complications database for each site, the fully de-identified dataset will be transferred to the Medical Research Institute of New Zealand. These data will be combined with the international datasets for final analysis.

By participating in the trial, sites agreed to provide the researchers with access to their respective registry data for period of the study.

Summary

The PEPTIC study is a multicentre, randomised, open-label, cluster crossover, registry-embedded trial. To our knowledge, it is the first registry-embedded cluster crossover trial ever undertaken and will provide important data regarding the comparative effectiveness of two commonly used approaches to stress ulcer prophylaxis in mechanically ventilated adults in ICUs.

Competing interests

None declared.

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Appendix

This appendix was part of the submitted manuscript and has been peer reviewed. It is posted as supplied by the authors.

The PEPTIC investigators and sites:

Site	Investigators	Co-Investigators
Australia		
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Austin Hospital Department of Intensive Care	Rinaldo Bellomo (MD)	Glenn Eastwood (RN, PhD)
Bendigo Hospital ICU	Jason Fletcher (MD)	Julie Smith (RN) Catherine Boschert (RN)
Canberra Hospital ICU	Frank Van Haren (MD, PhD)	Mary Nourse (RN) Shakira Spiller (RN) Katie Jeffereson (RN)
Concord Hospital ICU	Rosalba Cross (MD)	Helen Wong (RN)
Fiona Stanley Hospital ICU	Edward Litton (MD, MSc)	Annamaria Palermo (RN) Susan Pellicano (RN)
Footscray and Sunshine Hospitals, Western Health ICU	Craig French (MD)	Samantha Bates (RN) Miriam Towns (RN)
Gold Coast University Hospital ICU	David Pearson (MD)	Mandy Tallott (RN) Maimoonbe Gough (RN) Rosemary Willis (RN)
Launceston General Hospital ICU	Matthew Brain (MD)	Sarah Mineall (RN)
Nepean Hospital ICU	Ian Seppelt (MD)	Christina Whitehead (RN) Rebecca Gresham (RN) Kristy Masters (RN)
Northern Health ICU	Angaj Ghosh (MD)	Simone Said (RN)
Rockingham General Hospital	Kartik Atre (MD)	Ravi Sonawane (MD)

ICU		
Royal Hobart Hospital ICU	David Cooper (MD, MSc)	Richard McAllister (RN)
The Royal Melbourne Hospital ICU	Christopher MacIsaac (MD, PhD)	Andrea Jordan (RN) Deborah Barge (RN) Kathleen Byrne (RN)
Royal Perth Intensive Care Department	Steve Webb (MD, PhD)	Sharon Watersn (RN)
Royal Prince Alfred Hospital Intensive Care Services	David Gattas (MD)	Heidi Buhr (RN) Jennifer Coles (RN) James Wun (RN)
St George Hospital ICU	Manoj Saxena (MD)	Deborah Inskip (RN) Jennene Miller (RN)
St Vincent's Hospital Melbourne ICU	John Santamaria (MD)	Roger Smith (RN)
St Vincent's Health Network Sydney Intensive Care Services	Priya Nair (MD) Hergen Buscher (MD)	Claire Reynolds (RN) Nerilee baker (RN, PhD) Karlee McCann (RN)
Wollongong Hospital ICU	Martin Sterba (MD, PhD)	Wenli Geng (RN) Samantha Jakimowicz (RN) Michelle Gales (RN)
Canada		
Alberta	Sean M Bagshaw (PI, MD, MSc)	Dawn Opgenorth (Project Manager, RN)
eCritical Alberta (informatics)	Dan Zuege (MD, MSc) Jo Harris (HBSc, CPHIMS-CA) Malik Agyemang (PhD)	
University of Alberta Hospital General Systems Intensive Care Unit (GSICU)	Derek R Townsend (MD) Sean M Bagshaw (MD, MSc)	Sam Taylor (RN) Catherine Sych (PharmD)
Mazankowski Alberta Heart Institute Cardiovascular Surgery ICU (CVICU)	Sean Van Diepen (MD, MSc) Sean M Bagshaw (MD, MSc)	Desiree Ross (RN) David Diachinsky (RN) Mohamed Omar (PharmD)
University of Alberta Hospital Neurosciences ICU	Demetrios J Kutsogiannis (MD, MSc) Peter G Brindley (MD)	Paul Gerun (RN) Crystal Hancheruk (RN) Spencer Ling (PharmD) Dyan Franco (RN) Pam Lavallee (RN)
Grey Nuns Community	Dominic Carney (MD)	Melissa Ziober (RN)

Hospital (GNH) ICU		Larissa Fedor (PharmD) Krista Dewart (RN)
Misericordia Community (MIS) ICU	Erika MacIntyre (MD) Ella Rokosh (MD)	Patricia O'Toole (RN) Robin Scheelar (PharmD)
Royal Alexandria Hospital (RAH) ICU	Jon Davidow (MD)	Tove LaBlanc (RN) Ken Forgach (PharmD)
Sturgeon Community Hospital (SCH) ICU	Gabriel Suen (MD, MEd)	Glenda Corrigan (RN) Nancy Coyne (RN) Kim Spears (PharmD) Kristina Dover (PharmD) Celine Pelletier (RN)
Red Deer Regional Hospital (RDRH) ICU	Michael Russell (MD)	Carmen Petersen (RN) Gillian Brown (RN) Kerry Oxtoby (RN)
Ireland		
Irish Critical Care- Clinical Trail Network (ICC-CTN)	Alistair Nichol (MD)	Ciara Fahey (PhD) Peter Doran (PhD) Patrick Murray (PhD) Danny McAuley (PhD) John Laffey (PhD)
St Vincent's University Hospital, Dublin, Ireland	Alistair Nichol (MD)	Kathy Brickell (RN) Nicola Hyde (RN) Leanne Hays (PhD)
New Zealand		
Auckland City Hospital Cardiothoracic and Vascular ICU	Shay McGuinness (MD)	Rachael Parke (RN, PhD) Eileen Gilder (RN) Magdalena Butler (RN) Aimee Blakemore (RN) Keri-Anne Cowdrey (RN) Jane Hallion (RN) Stephnie Long (RN)
Middlemore Hospital ICU	Alex Kazemi (MD)	Rima Song (RN) Jefferson Aguila (RN) Vivian Lai (RN)
Nelson Hospital ICU	Alex Browne (MD)	Kylie Fenwick (RN) Petra Crone (RN) Charlotte McNab (RN)
North Shore Hospital ICU	Ywain Lawrey (MD)	Danielle Hacking (RN) Maud Carpenter (RN)
Tauranga Hospital ICU	Troy Browne (MD)	Jennifer Goodson (RN) Shirley Nelson (RN)

Waikato Hospital ICU	Annette Forrest (MD)	Jewel Barlow-Armstrong (RN) Kara Trask (RN) Sarah Rogers (RN) Caitriona Fiske (RN)
Wellington Hospital ICU	Paul Young (MD, PhD)	Anna Hunt (RN) Raulle Sol Cruz (RN) Agnes McKay-Vucago (RN) Eden Lesona (RN) Cassie Lawrence (RN) Harriet Judd (RN) Georgia Hill (BBMedSc) Nick On (MBChB)
United Kingdom		
Basingstoke and North Hampshire Hospital	Richard Partridge (MBBS) Clarisse Carreiras (RN)	McDonald Mupudzi (RN) Denise Griffin (RN)
County Durham and Darling NHS Foundation Trust	Chris Dawson (MBBS) James Limb (BM, BS, BMedSci)	Louise Duncan (RN) Amanda Cowton (RGN)
Dorset County Hospital	Mark Pulletz (MBBS) Sarah Williams (RGN, MRes)	Patricia Williams (RN) Stephanie Dukes Sarah Horton
Freeman Hospital	Stephen Wright (MB ChB) Maite Babio-Galan (RN)	Abigail Harrison Leigh Dunn (RNA)
James Cook University Hospital	Jeremy Henning (MB BCh) Lindsay Garcia (RN)	Keith Hugill (NP, BSc)
North Cumbria University Hospital NHS Trust	Tim Smith (MBBS) Toni Wilson (RGN)	
Northumbria Specialist Emergency Care Hospital	Bryan Yates (MBBS)	Sara Pick
Poole Hospital	Henrik Reschreiter (MD) Julie Camsooksai (RN)	Helena Barcroft-Barnes (RN) Sarah Patch (RN)
Queen Alexandra Hospital	Dave Pogson (MB BCh) Lindsey Cooke	Steve Rose (RGN, BSc)
Queen Elizabeth Hospital Gateshead	Vanessa Linnett Jenny Ritzema	Amanda Mulholland
Royal Hampshire County Hospital	Stephen Wimbush (MB ChB) Nicola Gregerson	Dawn Trodd (RGN) Samantha Hammond Caroline Wrey Brown (RGN) Jane Martin (RGN)
Royal Victoria Infirmary	Stephen Wright (MB ChB)	Ian Clement

	Maite Babio-Galan	
University Hospital of North Tees	Hemal Mohan (MBBS) Michele Clark (RGN, MSc)	
Russells Hall Hospital	Julian Sonksen (MB ChB) Clare Allcock (RN)	