



UK Protocol

A cluster randomised, crossover, registry-embedded clinical trial of proton pump inhibitors vs. histamine-2 receptor blockers for ulcer prophylaxis therapy in the Intensive Care Unit

Research Ethics Committee reference: 17/LO/1313

Trial Sponsor: Australian and New Zealand Intensive Care Society
Clinical Trials Group

Clinical Trials Registry ref: ANZCTR N 12616000481471

Trial Funder: Health Research Council of New Zealand
Irish Medical Council

IRAS number: 224703

Protocol version: 1.0

Protocol version date: 14/06/2017

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Abbreviations

CMP	Case Mix Programme
CONSORT	Consolidated Standards of Reporting Trials
DMC	Data Monitoring Committee
GCP	Good Clinical Practice
GI	Gastrointestinal
H ₂ RB	Histamine-2 receptor blocker
ICH-GCP	International Conference on Harmonization Guidelines on Good Clinical Practice
ICU	Intensive Care Unit
PI	Principal Investigator
PPI	Proton pump inhibitor
SOP	Standard Operating Procedure
SUP	Stress ulcer prophylaxis

Protocol Summary

Title:	A cluster randomised, crossover, registry-embedded clinical trial of proton pump inhibitors vs. histamine-2 receptor blockers for ulcer prophylaxis therapy in the Intensive Care Unit
Short Title/acronym:	PEPTIC
Sponsor name:	Intensive Care National Audit and Research Centre
Clinical Trials Registry ref:	ANZCTR12616000481471
Design:	Prospective, multicentre, randomised, open-label, cluster crossover, registry-embedded trial
Overall aim:	To compare two approaches to accepted stress ulcer prophylaxis treatment regimens
Primary outcome:	In-hospital all-cause mortality (censored at 90 days)
Secondary outcome:	<ul style="list-style-type: none"> a) proportion of patients with clinically significant upper gastrointestinal bleeding b) proportion of patients with <i>Clostridium difficile</i> infection c) duration of mechanical ventilation d) duration of ICU stay e) duration of hospital stay
Target accrual:	9,300 adults
Inclusion criteria:	<ul style="list-style-type: none"> • >18 years old • Admitted to a participating ICU • Invasively mechanically ventilated with 24 hours of ICU admission
Exclusion criteria:	<ul style="list-style-type: none"> • ICU admission diagnosis of upper gastrointestinal bleeding
Duration of recruitment:	12 months
Duration of participant follow-up:	ICU discharge
Definition of end of trial:	Last participant discharge

1. Background

Around 80% of mechanically ventilated adults in Australian and New Zealand intensive care units (ICUs) are prescribed stress ulcer prophylaxis¹ (SUP). Most patients receive a proton pump inhibitor (PPI) but a sizable minority receive a histamine-2 receptor blocker (H₂RB)^{1,2}. The rationale for using SUP is to prevent morbidity and mortality that might be attributable to occurrence of clinically significant upper gastrointestinal (GI) bleeding. Such bleeding occurs in 2.6% (95%CI, 1.6-3.6 %) of ICU patients in contemporary clinical practice³. In a recent systematic review and meta-analysis comparing PPIs with H₂RBs for ulcer prophylaxis in the ICU, PPIs resulted in a significantly lower risk of overt bleeding than H₂RBs⁴. However, using PPIs instead of H₂RBs also appears to be associated with an increased risk of developing nosocomial pneumonia⁵⁻⁷ and may also be associated with an increased risk of *Clostridium difficile* infection⁵.

Despite the fact that SUP is administered to millions of ICU patients around the world every year, it is uncertain which type is preferable. Moreover, current variability of practice in relation to choice of SUP is largely dependent on clinician preference or unit policy¹. Clinical trials of adequate size to determine whether PPIs or H₂RBs are best for 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 vs. Histamine-2 Receptor Blockers for Ulcer Prophylaxis Therapy in the Intensive Care Unit (PEPTIC) study.

2. Trial Design

The PEPTIC study is a multicentre, randomised, open-label, cluster crossover, registry-embedded trial in mechanically-ventilated adults implemented at the level of the ICU.

2.1 Efficient design

The design of the PEPTIC study combines two novel trial methodologies: cluster crossover randomisation⁸ and collection of outcome data from existing data sources⁹. 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 by using data that are already collected for other purposes.

The cluster crossover design will randomise entire ICUs rather than individual patients. Each ICU will define a cluster and each ICU will crossover to use both of the treatment approaches being tested by the end of the study. Where 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 knowledge¹⁰ but performing a large scale randomised trial relying on multiple existing data sources is a new innovation in clinical research. In addition to being innovative, we submit that this may be the optimal trial design for testing ubiquitous ICU interventions where the necessary data are already being collected for quality assurance and other purposes, and where clinical equipoise exists over two accepted treatment regimens.

2.2 Setting

In this protocol, 'site' refers to the 12 general intensive care units where the trial will be conducted.

2.2.1 Site requirements

- Active participation in the CMP
- Compliance with responsibilities as stated in the PEPTIC Study Site Agreement;
- Compliance with all requirements of the study protocol;
- Compliance with the research governance framework for health and social care and International Conference on Harmonization Guidelines on Good Clinical Practice (ICH-GCP)

2.2.2 Site responsibilities

- Identify two local joint Principal Investigators (PIs) – one critical care consultant and one critical care nurse – to lead the study locally
- Identify a PEPTIC Research Nurse or coordinator responsible for local coordination
- Agree to incorporate the PEPTIC study into routine intensive care clinical practice, ensuring enrolment of all eligible patients
- Agree to ensure adherence with trial protocol and data collection requirements

2.2.3 Site initiation and activation

Prior to a site being activated, the following must be in place:

- a completed site initiation visit (in person or by teleconference)
- all relevant institutional approvals (e.g. confirmation of capacity and capability);
- a fully signed PEPTIC Study Site Agreement; and
- a completed Delegation Log

Once it has been confirmed that all documentation is in place, a site activation e-mail will be issued to the joint- PIs, at which point, the site may start to recruit patients. Once the site has been activated, the PIs are responsible for ensuring:

- adherence to the most recent approved version of the protocol;
- training of relevant site staff in accordance with the trial protocol and GCP requirements;
- appropriate recruitment and care for patients in the study; and
- timely data collection, entry and validation

All local staff involved in the conduct of the trial must be listed on the Delegation Log, highlighting their delegated duties. The log should be copied and sent to the ICNARC PEPTIC team whenever changes are made.

2.3 Population

To be eligible, patients must meet all of the inclusion criteria, and none of the exclusion criteria:

2.3.1 Inclusion criteria

- age 18 years or older
- admitted to a participating ICU
- invasively mechanically ventilated with 24 hours of ICU admission

2.3.2 Exclusion criteria

- ICU admission diagnosis of upper GI bleeding

2.3.3 Co-enrolment

The PEPTIC trial investigators will consider co-enrolment of trial participants onto other interventional studies where there is no possible conflict with the PEPTIC trial aims. Co-enrolment will be on a case-by-case basis.

2.3.4 Screening

Screening of individual patients will not be performed, all eligible patients will be enrolled and identified from the CMP. Screening logs will record any patients that are eligible but not enrolled.

2.4 Consent and randomisation

2.4.1 Opt-out consent

Patients involved in PEPTIC will be receiving a standard treatment which they would receive regardless of the unit's participation in the study. In this manner, the study treatment represents usual care for which specific consent would not usually be sought.

Furthermore, by definition, critically ill patients in ICU are in a serious condition due to their illness and require support for one or more organ functions. Mechanical ventilation is an invasive procedure, often used in parallel with sedative and analgesic drugs. These factors restrict the patient's capacity to consent. It would not be possible to conduct critical care research if confined to patients able to consent.

For these reasons, specific patient consent will not be required. No patient identifiable data will be collected centrally during the course of the PEPTIC study. Patients will be actively approached at an appropriate time by site staff with an information leaflet, which highlights how patients can opt-out of data collection. Posters will also be displayed around participating ICUs, giving patients and their relatives the opportunity to opt out.

2.4.2 Process for opt-out

Patients who choose to opt-out will be noted on a specific log, and their data will not be extracted from the CMP. They will continue to receive SUP treatment, as this forms a standard part of their care.

2.4.3 Randomisation

Study ICUs will be randomised at a minimum of a four at a time in a 1:1 ratio to either:

- Open-label use of PPI
- Open-label use of H₂RB

At the end of the first six-month study period, the sites will crossover for a second six-month period.

2.5 Procedures

2.5.1 Commencing treatment

Units will administer either PPI or H₂RB to all eligible patients according to the unit randomisation. Clinicians are free to use the alternative treatment in situations where that is clearly preferable. Patients who are usually taking a PPI or an H₂RB will switch to the assigned treatment strategy for the duration of their ICU stay unless the treating clinician believes that this is inappropriate.

2.5.2 During treatment

If overt upper GI bleeding occurs, then a PPI will be administered irrespective of treatment allocation. This is in accordance with standard clinical practice.

2.5.3 End of treatment

The decision to discontinue SUP lies with the treating clinician. The duration of the study treatment will be until ICU discharge, death, or until SUP usage is no longer indicated.

All other care will be determined by the clinical team primarily responsible for the participant's care.

2.6 Outcomes

2.6.1 Primary outcomes

- In-hospital all-cause mortality, censored at 90 days

2.6.2 Secondary outcomes

- Proportion of patients with clinically significant upper GI bleeding
- Proportion of patients with *Clostridium difficile* infection
- Duration of mechanical ventilation (for ICUs where this information is available from an existing database)
- ICU length of stay
- Hospital length of stay

2.7 Data collection

To maximise the efficiency of the trial design, data collected for PEPTIC is nested in the CMP. Data extracted from the CMP for participating patients will include:

- Demographics (age, gender)
- Admission (type, source)
- Chronic co-morbidities
- Admission diagnosis
- Illness severity
- Length of stay (ICU, hospital)
- Duration of mechanical ventilation
- In-hospital mortality

Additional patient data collected at each site by research nurses or coordinators will be limited to:

- Patients who develop clinically significant upper GI bleeding
- Patients who develop *Colostridium difficile*
- Details of SUP administered to patients from electronic prescribing records where available, or a monthly audit of the unit where unavailable

This data will be collected on to Excel spreadsheets with no patient identifiable information recorded.

3. Trial closure

3.1 End of trial

The end of the trial will be when the final patient recruited is discharged from the ICU at which point the 'declaration of end of trial' form will be submitted to the REC by ICNARC CTU.

3.2 Archiving trial documents

At the end of the trial, ICNARC CTU will securely archive all centrally held trial-related documents for a minimum of five years, in accordance with ICH-GCP guidelines. Arrangements for confidential destruction of all documents will then be made. The site PIs will be responsible for archiving any trial-related documents, although this is expected to be minimal. Essential documents are those which enable both the conduct of the study and the quality of the data produced to be evaluated and to show whether the site complied with the principles of ICH-GCP and other regulatory requirements.

Guidance on archiving will be provided in the study-specific SOP. All archived documents, both locally and centrally, should be available for inspection upon request.

4. Statistical analysis

4.1 Sample size calculation

With 40 ICUs (international) and assuming a baseline mortality of 15%, our study will have 80% power to detect a 2.7% absolute difference in in-hospital mortality. This sample size is based on an average of 310 admissions per site in each 6-month study period. It incorporates a within-cluster-within-period correlation of 0.035 and within-cluster-between-period correlation of 0.025.

4.2 Statistical analysis plan

Analyses will be conducted on an intention-to-treat basis. Analyses of the primary end point will involve ICU (cluster) summary measures obtained by aggregating the primary endpoint to a rate per ICU per time period and calculating the difference in event rates between the first and second periods for each ICU. These differences will then be entered as the dependent variable into an unweighted linear regression with randomised sequence as the independent variable¹⁴, from which the coefficient of the randomised sequence is then the estimated PPI versus H₂RB difference. Such analyses appropriately control for all clustering effects within ICU and common secular time trends across ICUs. Uncertainty concerning treatment effects will be estimated using standard 95% confidence intervals. For secondary outcomes on a binary scale the same methods will apply, and for outcomes on a continuous scale previously described linear mixed model methods will be applied¹⁵. Sensitivity analyses will be performed for the impact of patients with missing outcome data using multiple imputation methods.

Pre-specified subgroup pairs will be patients who are admitted to the ICU following cardiac surgery vs. patients admitted for any other reason and emergency vs. elective admissions. We will perform the analyses described above for the primary and secondary outcome variables separately for each subgroup. Each analysis will be accompanied by a test for interaction between treatment and subgroup to ascertain whether treatment effect differs significantly between subgroups. Analyses will be performed using the Stata software package (StataCorp, Texas, USA).

5. Trial oversight and ethical compliance

The chief investigator (Dr Stephen Wright) will take overall responsibility for delivery of PEPTIC and oversee progress against timelines/milestones.

5.1 Ethics Approvals

The PEPTIC study will be conducted in accordance with the approved trial protocol, ICH-GCP guidelines, the Data Protection Act (1998), the Mental Capacity Act (2005), as well as the ICNARC CTU research policies and procedures.

The trial has received favourable ethical opinion from London – Bromley Research Ethics committee (Reference 17/LO/1313) and approval from the Health Research Authority approval on 11/10/2017. ICNARC CTU will provide relevant trial documents and other related materials to participating sites.

It is the responsibility of site PIs to obtain necessary local approvals for PEPTIC, including confirmation of capacity and capability. Evidence of capacity and capability at each site must be provided to ICNARC CTU prior to site activation.

5.2 Data protection and participant confidentiality

No identifiable patient data will be required. 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 PEPTIC study patients has been granted by the ICNARC Data Access Advisory Group in accordance with standing protocols. Each patient is identified by a unique number; linkage between each number in the database and a particular patient is maintained by each participating hospital (i.e. data are classified as partially de-identified). Data exported for study analyses will not include any identifiers (i.e. the data included in the PEPTIC study database will be fully de-identified).

Once the extracted data has 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. This data will be combined with the international datasets for final analysis. The dataset will be sent following the Information Commissioner's Office Code of Practice for managing data protection risk. New Zealand is considered to have an 'adequate level of protection' for receiving data from the EU.

5.3 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 Professor Brian Cuthbertson (Chair), Professor Anthony Gordon and Professor Graeme MacLennan. Due to the crossover design, interim analyses of the primary outcome would be difficult to interpret and have low power to detect differences. Accordingly, 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.

5.4 Access to final study dataset

The database will be stored at the Medical Research Institute of New Zealand. Once the primary manuscript has been published, the database will be made open access.

6. Sponsorship and funding

6.1 Sponsorship and indemnity

ICNARC is the UK sponsor for PEPTIC and holds professional indemnity insurance (Market International Insurance Co Ltd) to meet the potential legal liability of the Sponsor and employees for harm to participants arising from the design and management of the research. Indemnity to meet the potential legal liability of investigators/collaborator for harm to participants arising from the conduct of the research is provided by the NHS indemnity scheme or through professional indemnity.

6.2 Funding

The PEPTIC study is endorsed by the Australian and New Zealand Intensive Care Society Clinical Trials Group and is funded by the Health Research Council of New Zealand and the Irish Medical Council. All analyses will be undertaken independent of the funding bodies.

7. Dissemination

The final report will be submitted to XXXXXXXXXXXX. Articles will be prepared for publication in peer-reviewed scientific journals, as well as relevant professional journals. All data will be anonymised.

8. References

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Appendix 1 – Adaptations from original protocol

Section	Changes made
3. Trial Design	<ul style="list-style-type: none">• 3.2 – Site specific requirements / responsibilities added• 3.3 – Co-enrolment details added• 3.4 – Consent processes detailed• 3.5 – Trial procedures expanded
4. Safety monitoring	<ul style="list-style-type: none">• Details amended to those of UK reporting procedures
5. Trial closure	<ul style="list-style-type: none">• UK specific procedures for end of trial and archiving included
7. Trial oversight	<ul style="list-style-type: none">• 7.1 – UK ethics approvals documented• 7.2 – Details of CMP procedures added
8. Sponsorship	<ul style="list-style-type: none">• 8.1 – UK sponsorship details added

Appendix 2 – Protocol version history

Amendment No.	Protocol version no.	Date issued	Author(s) of changes	Details of changes made
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